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34th Annual Fall Meeting

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The 34th Annual Fall Meeting
of the American
Physiological Society
and the
International Conference on
Hydrogen Ion Transport
in Epithelia

Sheraton Waikiki
Honolulu, Hawaii

August 20-24, 1983
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BOWDITCH LECTURE
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Maui Room
  Functional Mapping of Cardiovascular Reflexes and the Heart Using C14-2-deoxyglucose
  Speaker: David Kostreva, Medical College of Wisconsin and The VA Medical Center, Milwaukee

APS PAST PRESIDENT'S ADDRESS AND BUSINESS MEETING
Monday, 4:30 PM
Maui Room
  Crises in Physiological Research
  Speaker: Walter C. Randall

APS COMPARATIVE PHYSIOLOGY SECTION BUSINESS MEETING
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Honolulu Room

EVENING SOCIAL EVENTS

Opening Reception
Saturday, 6:00 PM
Diamond Head Lawn

Luau
Tuesday, 6:30 PM
Diamond Head Lawn

OPEN HOUSE AT THE UNIVERSITY OF HAWAII
The Local Arrangements Committee plans an open house at the University of Hawaii on Thursday, August 25.
INTERNATIONAL CONFERENCE ON 
HYDROGEN ION TRANSPORT IN 
EPITHELIA

A series of sessions devoted exclusively to invited papers. These sessions are as follows:

Sunday AM
Symposium - Processes of passive and active H⁺ transport in isolated gastric and renal membrane vesicles

Sunday PM
Poster Discussion—Transport in isolated gastric and renal membrane vesicles

Monday AM
Symposium—Epithelial H⁺ transport processes and electrophysiology

Monday Evening
Poster Discussion—Regulation of H⁺/HCO₃⁻ transport in gastrointestinal epithelia

Tuesday AM
Poster Discussion—Regulation of H⁺/HCO₃⁻ transport in kidney epithelium

APS TUTORIAL, SYMPOSIA AND 
REFRESHER COURSE SESSIONS

Sunday AM
Symposium—Autonomic control of coronary tone: Facts, interpretations and consequences.

Sunday PM
Symposium—Neurohumoral control of the circulation

Tutorials
Calcium regulation in osteoporosis
Calcium exchange in the heart
Physiology of bile

Monday AM
Symposium—Physiology of water immersion

Monday PM
Symposium—Factors influencing vassopressin in body fluids

Tutorials
Structural basis of visual cortical function
Neuronal basis of plastic adaptation in gaze control
Nutrition as a modulator of the aging process

Tuesday AM
Symposium—Prostaglandins, lukotrienes and lung fluid balance

Tutorials
Comparative physiology of the renin angiotensin system
Hypothalamic control of body temperature
Long term reflex regulation of the cardiovascular system

Tuesday PM
Symposium—Sea-bird energetics, Session I

Tutorials
Regulation of blood flow and oxygen transport in skeletal muscle
The aging lung
Contractile properties of vascular smooth muscle

Wednesday AM
Symposium—Sea-bird energetics, Session II

Wednesday AM and PM
Refresher Course—Physiology and biochemistry of receptors
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APS Tutorials, Symposia and Refresher Course sessions are not listed since abstracts are not required.

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PH-DEPENDENCE OF PROTON TRANSPORT IN YEAST AND NEUROSPORA.

U.C. Saltmen, A. Galligan-Davida, M. Blaitb, and D. Saunders.
Department of Physiology, Yale University, New Haven, Conn.
Transport processes in plasma membranes of microorganisms are dominated by electrogenic active extrusion of protons and, by electrophoretic H+-coupled uptake of many substances: e.g., sugars, amino acids, and inorganic ions. A remarkable property of these transport systems is their asymmetric kinetic sensitivity to pH. When secondary involvement of membrane potential is minimized either by voltage clamping (Neurospora) or by the use of carrier mutants (Saccharomyces), Kᵢ values (the range of pH 6 to pH 8) have small effects on transport velocity: usually less than 2-fold per pH unit. By contrast, internal pH (clamped with weak acids; measured with microelectrodes or 125 I-MET) modulates transport much more sites. For example, saturating current through the proton pump in Neurospora doubles for a 2.5-fold increase of [H⁺]i while in yeast it is less than 2-fold for a 3-fold elevation of [H⁺]. Kinetic modeling by means of simple carrier reaction diagrams indicates that internal protons binding sites must have pKᵢ's near the normal pH (pK ≈ pH); however, external proton binding sites can have pKᵢ's far displaced from neutrality. This conclusion is turn suggests that proton binding or release at the external site is associated primarily with energy conversion, whereas proton reaction at the internal site is associated more with transport control. Supported by NIH Grant GM-15858, NSF Grant PCM-7813412, and NIH Fugacity Fellowship TN-00062.

PERMEABILITY CHANGES IN ATPase MEMBRANES ASSOCIATED WITH GENERIC SEGREGATION STATE.
J.M. Woldinb and J.G. Forte,
Depending upon the secretory state, resting or stimulated, the (H⁺/K⁺)-ATPase membrane is recovered from oxyntic cells homogenate in two distinct vesicular types, the microsome and the stimulation-associated vesicle (s.a.v.), respectively (JBC 256:3149). Both systems are capable of H⁺-uptake through the (H++.F⁺)-ATPase membrane is recovered from oxyntic cell homogenate in two distinct vesicular types, the microsome and the stimulation-associated vesicle (s.a.v.), respectively (JBC 256:3149). Both systems are capable of H⁺-uptake through the (H++.F⁺)-ATPase

PROTON HYDROXIDE PERMEABILITY OF LIPID BILAYERS AND BIOLOGICAL MEMBRANES.
D.W. Deamer and D.L. Darchfeld.
Values for proton-hydroxide permeability (pH) are now available for a variety of lipid bilayer and biological membranes. Typical results for liposomes are in the range of 10⁻⁴ to 10⁻⁴ cm²/s, orders of magnitude higher than values for other monovalent ions (10⁻¹¹ to 10⁻¹⁴ cm²/s). At neutral pH ranges, there is evidence for relatively high pH in planar lipid membranes as well, although at extreme pH ranges values of 10⁻⁵ cm²/s have been reported. Thus for biological membranes are in the range of 10⁻² to 10⁻⁵ cm²/s, again much higher than for other monovalent ions. These observations suggest a unique proton-hydroxide flux mechanism, and we are presently investigating the possibility that hydrated defects permit proton-hydroxide to cross membranes by Grothius conductances, in which proton equivalents move along hydrophilic routes. Neurospora, in which melittin was used to produce defects in liposome membranes, with proton-hydroxide flux being monitored by decay of pH gradients. We found that melittin in mole ratios of 10² to 10⁴ melittin dramatically increases proton-hydroxide flux. Other evidence suggests that the melittin defect is sufficiently specific to permit proton diffusion potentials as pH gradients decay. This result is consistent with the hypothesis that a hydrated defect can act as a specific proton channel.
3.1 INCREASED PULMONARY VASCULAR PERMEABILITY TO PROTEIN FOLLOWING PULMONARY MICROMOLE EICHS ECh BY ECHIS CARINATUS (E.C.) VENOM IN DOGS. B.G. Schaeffer, Jr., S.M. Chilton*, T.L. Hodgen, and R.W. Carpen. Dept. of Med., Wayne State Univ. and Mt. Carmel Mercy Hospital, Detroit, MI 48235.

Pulmonary lymph flow (Qlym, µl/min) was measured from an incision in the tracheal bronchial lymph node in anesthetized open-chest mongrel dogs (n=7, 12.3±5.1 kg). Following 2-hour baseline and 2 hours of intravenous infusion of E.C. venom (50 µg/kg) were studied for 2 hr, plus an additional 2 hr with +Pp. This venom activates proteolysis and induces microvascular leakage (P<0.05). Peak changes in pulmonary lymph flow (Qlym) occurred at 45 min (19.7±3.2 µl/min). Lymph protein concentration increased at 45 min by 76.9±10.2% (P<0.05) and lymph protein content increased by 88.7±13.8% (P<0.05). These data suggest that microvascular permeability to protein is increased.

3.3 EFFECTS OF REDUCED PLASMA PROTEINS ON CAPILLARY FILTRATION COEFFICIENTS AND ISOGRAVIMETRIC CAPILLARY PRESSURES IN ISOLATED DOG LUNGS. B. Rippa, J. Parker, A.T. Taylor.

Using gravimetric techniques, the capillary filtration coefficients (Kf) and isogravimetric capillary pressures (Pci) were measured in the isolated papaverinized left lung of the dog perfused with: 1) autologous blood, 2) plasma or 3) solutions with low red cell and plasma protein content. Shifting from blood to a mixture of 4-8% dextran (Mr=60000) containing 0-0.2% bovine serum albumin increased Kf, slightly (40%-60%). Pci also decreased significantly for dextran concentrations of >0.2%. Shifting from blood to Tyrode's solution, induced a two to three fold increase in Kf and serum albumin in low concentrations (0.1-0.5%). Dextran did not totally reverse these changes. Plasma perfusion caused only minor changes in Kf, increased slightly while Pci remained essentially the same. In summary, capillary permeability depends on the plasma protein concentration and decreases with decreasing plasma protein concentration. Small concentration of proteins were still present in the per-capillary filtration coefficients in the dog lung even when small concentrations of proteins were still present in the perfusate. Changes in perfusate viscosity and/or in capillary surface area could only account for a small portion of changes. It is concluded that the permeability of capillaries, lack of permeability of other than some component of plasma or cells somehow decreases capillary permeability in dog lungs.


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Parker B. Francis Fellow.

3.5 ROLE OF CICLOSPORIN A DEPOLYMERIZATION IN THE PATHOPHYSIOLOGY OF PULMONARY EDEMA DUE TO GRANULOCYTE OXIDATIVE. R.B. Fox, R.B. Reavley, C.C. Hong*, and D.R. Sumner*, Dept. of Ped. and Surg, Harvard Medical School, Boston, MA 02115.

The purpose of this study was to examine the effect of E. coli endotoxin on lymph flow from the lung (Qlym) and lymph protein content (L/P) in healthy anesthetized dogs. E. coli endotoxin (LPS) was given intravenously at a dose of 2.5 mg/kg. LPS induced a significant increase in pulmonary lymph flow (Qlym) and lymph protein content (L/P). These results suggest that endotoxin is a potent stimulus for the release of granulocyte-derived oxidants which may contribute to pulmonary edema. To examine this hypothesis, depolymerization increases glomerular permeability to protein, aminoglycans (GAG) are depolymerized by *OH, and since GAG uranic acid contents of lung lymph, peaking at 1 hour after E.C. venom (30 min, SW/kg) were studied for 2 hr, plus an additional 2 hr with +Pp. These data suggest that microvascular permeability to protein is increased. (Supported by MCREC Grant-in-Aid #223-80).

3.6 EFFECT OF ENDOXOTIN ON LUNG FLOW AND COMPOSITION FROM CAUDAL MEDIALSIA (CMN) AND PREFEMORAL LYMPH (PF) NODES IN UNANESTHETIZED SHEEP. Robert A. Gunther*, Dept. of Surgery, Univ. of California, Davis, CA 95616. (SPON: E.M. Renkin). Lung fluid balance in sheep was measured in the caudal mediastinal (CMN) and prefemoral lymph (PF) nodes of anesthetized sheep. The effect of endotoxin on lung fluid balance was measured in sheep by injection of 2 mg/kg of endotoxin into the jugular vein. Lung fluid balance was measured by collection of both CMN and PF lymph and by calculation of the net transfer of fluid to the lymph nodes. The results showed that endotoxin increased lung fluid balance and that the increase was greater in the CMN than in the PF lymph nodes. These results suggest that endotoxin may be a potent stimulus for the release of granulocyte-derived oxidants which may contribute to pulmonary edema. (Supported by NIH HL-07013)
3.7 IMPORTANCE OF $H_2O_2$ IN THE PULMONARY RESPONSE TO ENDOTOXIN.

Neutrophils play a key role in septic lung injury. We hypothesized that neutrophil-derived $H_2O_2$ is an important factor in the microvascular permeability response to endotoxin. In parallel experiments, injecting 3 rats with endotoxin and 3 lungs with saline as control, we compared the response to endotoxin (E) with and without catalase (C), a specific $H_2O_2$ scavenger. C was injected to Pigs to rats at 1 pmol/kg from 12 hours after E. $H_2O_2$ was measured by luminol-dependent chemiluminescence (Cl), release free radicals was quantitated by zymosan stimulated-lymphocyte assays. Cells were then collected from control, both with normal and elevated LAP indicating no change in pulmonary microvascular permeability. The increase in OL following OT inhalation indicates an increased rate of fluid transfer from the pulmonary microvasculature into the interstitium which causes pulmonary edema.

3.8 A MECHANISM FOR ENDOTOXIN PROTECTION FROM OXYGEN TOXICITY.

Breathing pure oxygen causes pulmonary edema in rats and other mammalians. A single intra-peritoneal injection of endotoxin prolongs survival in oxygen and greatly reduces edema formation. Phagocyte derived free radicals have been shown to contribute to lung edema formation. Cancers and neutrophils were injected with bronchoalveolar lavage after rats had breathed pure oxygen for 1, 2 or 3 days. The potential of phagocytes to release free radicals was quantitated by zymosan-stimulated-luminol-dependent chemiluminescence (Cl).

Days in pure $O_2$
<table>
<thead>
<tr>
<th>Control</th>
<th>Saline</th>
<th>Endotoxin</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>47</td>
<td>48.5</td>
</tr>
<tr>
<td>2</td>
<td>21</td>
<td>22.2</td>
</tr>
<tr>
<td>3</td>
<td>10.7</td>
<td>11.0</td>
</tr>
</tbody>
</table>

Control in air - 116.8 ± 20 (+ SD x 10^5)

All saline values, and Day 1 neutrophil values, were lower than CI for control rats. This may indicate substrate or cofactor depletion in cells which had been overactive in free radical production prior to lavage. Day 2 and Day 3 cells from endotoxin injected rats were able to generate very high CI when compared to control levels. This may reflect substrate availability and a lack of free radical release in vivo. NADH (P) levels are presently being measured.

3.9 EFFECT OF APOTIN ON LUNG FLUID BALANCE FOLLOWING ENDOTOXIN.

Increased proteolytic activity has been reported in increased protein loss reported in rats was increased by endotoxin, hemorrhage, anaesthesia and burns. The administration of the broad-spectrum protease inhibitor apro tin in a number of in vivo shock models has both beneficial and experimental, have produced beneficial effects. To assess the role of proteases in the increase in lung vascular permeability following endotoxin administration, we compared the response of goats with chronic lung lymph fistulae to endotoxin with and without apro tin. We measured hemodynamics, lymph flow ($Q_L$), and lymph plasma protein ratio ($L/P$) in three pairs of goats. Elevation of $Q_L$ accompanied a reduction in the stable metabolites of TxA2 and PGI2. We therefore conclude (1) that apro tin contributes to increased microvascular permeability after E; (2) $H_2O_2$ is also important in the systemic response to sepsis; (3) the effects of $H_2O_2$ are mediated in part by cyclooxygenase products of arachidonic acid. Supported by: GM 29853, GM 24990, HL 24163, and ALA Fellowship (RMM).

3.10 PULMONARY FLUID BALANCE: DOSE RESPONSE CURVES OF EPINEPHRINE AND NORADRENALINE. Joseph C. Scottot, Jr., Robert Wimm, Jack Hildebrandt, Brad Nadir*, and Roy Abernathy*. St. Louis University, Dept. Surgery, St. Louis, MO, 63104, and Virginia Mason Research Center, Seattle, WA.

Different concentrations of epinephrine (EPI) and norepinephrine (NEOEP) were infused into monitored, awake goats with chronic lung lymph fistula. Previous work has demonstrated that awake goats respond differently to these catecholamines than anesthetized sheep at higher concentrations (Stothert, J. Respir Med. 34:367, 1993). In this study, the increase in lymph and plasma total protein level ($L/P$) were monitored in these goats along with cardiac output ($C_O$), pulmonary vascular pressures and systemic vascular pressures.

EPI NEOEP I

<table>
<thead>
<tr>
<th>Control</th>
<th>1.4</th>
<th>2.0</th>
<th>11.1</th>
</tr>
</thead>
<tbody>
<tr>
<td>$A/L$</td>
<td>0.01</td>
<td>0.02</td>
<td>0.03</td>
</tr>
</tbody>
</table>

EPI in the higher dose range promotes an increase in protein in lymph which is associated with an increasing pulmonary vascular resistance (PVR) and decreasing CI. This suggests a downstream pulmonary vasoconstriction. NEOEP infusion at the higher dose range is also accompanied by an increasing PVR and decreasing CI; however, the increasing lymph flow is not as protein poor suggesting a greater upstream pulmonary vasoconstriction.


To assess the role of increased permeability in the development of pulmonary edema, an accurate method for the determination of pulmonary fluid balance is needed. (Gorin et al., JCI, 66, 869-877, 1980) determined the pulmonary transvascular protein flux from counts generated by labeled protein and red blood cells in the lung and in blood samples. From these data, a transport coefficient $\alpha$ was calculated. This coefficient $\alpha$, which reflects permeability to protein, their method, however, requires extensive calculations. We expressed the counts as a ratio $\frac{F_{DL}}{F_{DB}} = \frac{F_{RL}}{F_{RB}}$, in which $D$ = labeled protein, $R$ = labeled red blood cells, $L$ = lung and $B$ = blood sample. $F$ was divided by its value at time 0, resulting in $F_*$. It can be shown theoretically that the transport coefficient $\alpha$ is approximately equal to $\frac{F_{RL}}{F_{RB}}$ for very small time. Using [1,1]-albumin and 1,15-laevulose to $\alpha$ and $\alpha'$ was determined from counts obtained between 30 and 120 minutes for 16 lungs with $\alpha$ and $\alpha'$ were determined from a single linear regression on $F_*$. The relationship between $\alpha$ and $\alpha'$ was $\alpha = 0.10 \alpha' + 0.98 \alpha' = 0.99 \alpha'$ for $\alpha$ between $1.15$ and $3.87 \alpha'$. The excellent agreement between $\alpha$ and $\alpha'$ shows that the mathematical analysis for Gorin's technique can be reduced to a single linear regression. An important implication of our finding is that, if the blood counts can be obtained from the blood pool in the heart, our method enables on-line determination of $\alpha$.

3.12 THE EFFECT OF ELEVATED ALVEOLAR SURFACE TENSION ON MICROCIRCULATORY FILTRATION AND FLUID TRANSFER. CE Breeden*, C.S. Frey*.

The left hilar arterial lymphatic was cannulated in 5 anesthetized dogs. Alveolar surface tension was increased by displacing alveolar surface surfactant using an aerosol of the detergent dioctyl sodium sulfosuccinate (OT) in a vehicle of 50% ethan and 50% saline. The aerosol was inhaled with ultrasonic inhaler attached to the ventilator circuit. Lymph (C1) and plasma (Cp) protein concentration were determined by refractometry. Following a 1 hour control, left atrial pressure (LAP) was elevated to a mean of 20 cm H2O and held until a steady-state lymph flow (QL) and CI were obtained. A 1 hour rest period (normal LAP) was followed by OT inhalation. Steady-state C1 and QL were again obtained with normal and increased LAP.

The ratio $Q_L/C_P$ following detergent inhalation is the same as control, both with normal and elevated LAP indicating no change in pulmonary microvascular permeability. The increase in CI following OT inhalation indicates an increased rate of fluid transfer from the pulmonary microvascular into the interstitium which causes pulmonary edema.

Previously we have shown that intraventricular LVP caused significant changes in cardiac output (CO) as iv infusion, but no significant changes in heart rate (HR), CO decreased 33 ± 1.9 and 15.7 ± 6.6 ml/min/kg respectively and HR decreased 42.6 ± 3.3 (p<0.05) and 12.3 ± 2.0 beats/min (p<0.01) respectively. There were no significant differences between iv and ic LVP infusions. Similarly, there were no differences in AVP measurements between iv and ic LVP infusions, although there were small decreases in AVP within the iv and LVP iv infusion groups. The results further indicate that peripheral VP can alter HR and CO, but does not feedback to inhibit its own release. (Supported by USPHS grants HL-1990 and HL-19900)

4.2 ANALYSIS OF THE CARDIOVASCULAR EFFECTS OF ARGININE VASOPRESSIN (AVP) IN CONSCIOUS DOGS. U. Tipayamontri* and D. B. Young. University of Mississippi Medical Center, Jackson, MS 39216.

The role of aminobutyric acid (GABA) in the control of cardiovascular function has been observed in the hypothalamic and pituitary area. Aortic and pulmonary arterial pressure (PAP) was measured 30 min after the start of infusion of either normal saline or AVP (1.0 mg/kg/min). MAP, CO, HR, RAP, BP and mean arterial pressure for each animal were determined on the following day with the same infusion. Compared to normal saline infusion, AVP infusion caused a significant (p<0.05) reduction in CO from 2.59±0.245 to 1.98±0.214 l/min, and increases in TPR and resistance to venous return from 70.8±1.5 to 84.7±1.6 and 7.54±0.70 to 9.4±0.74 meq/l/min, respectively. These were no significant changes in HR, RAP, BP, SV, MCFP, pressure gradient for venous return or SV. The reduction in CO was due apparently to a direct cardiac effect since no preload (MAP) or afterload (BP) were changed. This hypothesis was tested by examining the effect of AVP infusion on four doses of the vasodilator nitroprusside. When nitroprusside alone was infused, PAP increased as blood pressure (BP) fell. When AVP was infused in the presence of AVP, nitroprusside increased BP and decreased PAP (10 mg/kg/min). When nitroprusside was infused in the presence of AVP, PAP increased, and the PAP increase was again related to the BP fall (r = 0.60, p < 0.001). These data suggest that the pressor effect of AVP counteracts a stimulatory action of AVP on vasopressor secretion. When endothelium was removed, nitroprusside increased BP and decreased PAP (10 mg/kg/min). When nitroprusside was infused in the presence of AVP, PAP increased, and the PAP increase was again related to the BP fall (r = 0.60, p < 0.001). These data suggest that the pressor effect of AVP counteracts a stimulatory action of AVP on vasopressor secretion and that when endothelium levels are elevated without an increase in BP, as occurs during hypovolemic AVP infusion.

4.3 HEMODYNAMIC IMPORTANCE OF VASOPRESSIN DURING HEMORRHAGE. Walter A. Boyle, III* and Guy Veliquez* (SPON: M. H. Sawyer).

A number of investigators have demonstrated that vasopressin (VP) infusions can provide effective support during hemorrhage. The role of VP infusion in hypotension induced by hemorrhage was examined in the present study. In the presence of normal saline infusions, VP was administered at a rate of 1.0 mg/kg/min. During acute hemorrhage, to determine how VP affects other hemodynamic factors,VP was administered without or with endogenous vasopressin. VP was observed to increase the mean arterial pressure (MAP) and cardiac output (CO) in dogs with and without VP blockade. (Supported by USPHS Grant AM-19761)


There is evidence that angiotensin II (AII) increases plasma vasopressin concentration (PAVP): however, this effect has not been observed in conscious, mobile, anesthetized dogs. The mechanism responsible for the inconsistency is that the pressor effect of AII counteracts a stimulatory action of AII on vasopressor secretion. This hypothesis was tested by examining the effect of AII on PAP while the pressor effect of AII was blocked with an infusion of four doses of the vasodilator nitroprusside. When nitroprusside alone was infused, PAP increased as blood pressure (BP) fell (r = 0.60, p < 0.001). A single infusion of AII (3 nmol/kg/min) increased BP and decreased PAP (10 mg/kg/min). When nitroprusside was infused in the presence of AII, PAP increased, and the PAP increase was again related to the BP fall (r = 0.60, p < 0.001). There was significant difference in BP during hemorrhage in the AVP and normal saline infusion groups. There were no consistent changes in any of the parameters in the AVP infusion group. There were no significant differences in MAP, RAP, HR, SV, MCFP, pressure gradient for venous return or SV. The reduction in CO was due apparently to a direct cardiac effect since no preload (MAP) or afterload (BP) were changed. This hypothesis was tested by examining the effect of AVP infusion on four doses of the vasodilator nitroprusside. When nitroprusside alone was infused, PAP increased as blood pressure (BP) fell (r = 0.60, p < 0.001). A single infusion of AII (3 nmol/kg/min) increased BP and decreased PAP (10 mg/kg/min). When nitroprusside was infused in the presence of AII, PAP increased, and the PAP increase was again related to the BP fall (r = 0.60, p < 0.001). These data suggest that the pressor effect of AVP counteracts a stimulatory action of AVP on vasopressor secretion and that when endothelium levels are elevated without an increase in BP, as occurs during hypovolemic AVP infusion.


Gamma-aminobutyric acid (GABA) in the control of vasopressin (VP) release was examined by exposing organ-cultured explants of the rat hypothalamo-neurohypophyseal system (HNS) to varying concentrations of GABA or to the GABA antagonists, bicuculline (lo-4M) and picrotoxin (lo-5M) during a one hour test period. VP release was uniformly decreased to approximately half of control during the test hour (p<0.01, n=6). Picrotoxin (lo-5M) caused a significant (p<0.05) reduction in CO from 2.59±0.245 to 1.98±0.214 l/min, and increases in TPR and resistance to venous return from 70.8±1.5 to 84.7±1.6 and 7.54±0.70 to 9.4±0.74 meq/l/min, respectively. There were no significant changes in HR, RAP, BP, SV, MCFP, pressure gradient for venous return or SV. The reduction in CO was due apparently to a direct cardiac effect since no preload (MAP) or afterload (BP) were changed. This hypothesis was tested by examining the effect of AVP infusion on four doses of the vasodilator nitroprusside. When nitroprusside alone was infused, PAP increased as blood pressure (BP) fell (r = 0.60, p < 0.001). A single infusion of AII (3 nmol/kg/min) increased BP and decreased PAP (10 mg/kg/min). When nitroprusside was infused in the presence of AII, PAP increased, and the PAP increase was again related to the BP fall (r = 0.60, p < 0.001). These data suggest that the pressor effect of AVP counteracts a stimulatory action of AVP on vasopressor secretion and that when endothelium levels are elevated without an increase in BP, as occurs during hypovolemic AVP infusion.

4.6 SODIUM LOADING IN RABBITS WITH PRE-OPTIC PERIVENTRICULAR HYPOTHALAMIC LESIONS. Gregory D.芬k*, Mark E. Mann* and Cathy A. Bruce* (SPON: G.L. Gebeke). Dept. of Pharma-

The results of recent studies in the rat have reported that lesions in the anterior third cerebral ventricle (AV3V) will attenuate the excretion of sodium and water after an acute i.v. isotonic saline (0.9% NaCl) infusion. We sought to determine whether these findings were applicable in AV3V-lesioned (AV3V-X) rabbits, and also examined sodium and water handling in AV3V-X rabbits during chronic alterations in sodium intake. Acute saline diuresis (10 mg/kg/min) decreased CO and increased PAP. A single infusion of AVP (10 mg/kg/min) caused a significant increase in arterial pressure (MAP), but significant increases in central venous pressure (CVP), interstitial fluid pressure (IFP), extracellular fluid volume (ECFV) and interstitial fluid volume (IFV) in sham-lesioned rabbits (n=10). In AV3V-X rabbits, only IFP increased significantly during the 1 hr infusion. A separate group of 7 rabbits were given food containing 1, 11 and 170 mEq sodium/100 g on 3 consecutive weeks, then received AV3V lesions and the dietary protocols were repeated 2 weeks later. In the pre-lesion period, increasing sodium intake caused a significant increase in MAP and water intake, but no other significant changes in body fluid parameters. After AV3V-X, similar changes were obtained during dietary sodium loading. Furthermore, after AV3V-X the rabbits adjusted urinary sodium excretion normally during step changes in sodium intake. These results suggest that blunted excretory responses to acute saline loading in AV3V-X rabbits may involve an inability to "sense" the load, and that this defect is unimportant in chronic sodium and water homeostasis. (Supported by USPHS grant HL-24117)

SUNDAY AM

To assess the effect of chronic sodium depletion on the activity of the sympathetic nervous system, we measured arterial (N=5) and renal venous (N=3) norepinephrine (NE) and epinephrine (EPI) concentrations in chronically instrumented monkeys. The animals maintained these dietary conditions for 6 days and 1 day for the control diet; additionally, fosfomycin (10 mg IM) was administered on days 6 and 5. Renal NE overflow (NE<sub>apo</sub> effective renal plasma flow) was used as an index of sympathetic nerve activity. The following observations were made: (Supported in part by NIH Grants HL 11678 and HL 06341).

<table>
<thead>
<tr>
<th>Control</th>
<th>Day 3</th>
<th>Day 9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Arterial Pressure (mmHg)</td>
<td>93±3</td>
<td>91±4</td>
</tr>
<tr>
<td>Plasma Renin Activity (ng AI/ml/hr)</td>
<td>284±21</td>
<td>187±34</td>
</tr>
<tr>
<td>Plasma Aldosterone (pg/ml)</td>
<td>412±54</td>
<td>313±51</td>
</tr>
</tbody>
</table>

*p < 0.05


Previous immersion (Imm) studies in nonhuman primates have been conducted using anesthetized (A) animals. The present study was designed to compare changes under tranquilized (T) and conscious (Co) states. Seven experiments were carried out in Co (n=5) and Imm (n=4) animals. Sodium excretion increased from -8.9±2.5 (Co) to -42.4±5.7 meq/min in Imm. T monkeys started at 14±y and decreased to 6±1.5 pg/ml (p<.05) while Co monkeys increased from 5±1±11 to 24±5 pg/ml (p<.05) in A group. T monkeys started at 14±y and decreased to 6±1.5 pg/ml (p<.05) while Co monkeys increased from 5±1±11 to 24±5 pg/ml (p<.05). These studies show that Nembutal and Ketamine significantly alter the physiologic response to Imm compared to Co state. Of note, is that physiologic response to Imm compared to Co state. Of note, is that physiologic response to Imm compared to Co state. Of note, is that physiologic response to Imm compared to Co state.
was immediately depressed 38% by PG12 (~0.01) proceeding to membrane protein, 104 mM KCl, 50 mM histidine (pH 7.0), 10 mM ATP-dependent ATPase activity. (Supported in part by American of increased microsomal passive Ca* binding, as well as de-

Control Ca*-dependent ATPase activity (total minus binding (no ATP)) was 1.0 PM/g protein/min (n=14). [48.73] Phosphorylation of endogenous microsomal proteins by CAMP- and calmodulin-dependent kinases in bovine carotid artery microsomes. R.V. Sharma*, D.W. Doerrfeld* and R.C. Bhalla, University of Iowa, Iowa City, IA 52242. Bovine carotid artery microsomes were phosphorylated by both cAMP and calmodulin dependent kinases. The catalytic subunit of cAMP dependent protein kinase in the presence of EGTA catalyzed the incorporation of [32P] phosphate in two major bands corresponding to proteins of Mr ~ 200,000 and 45,000. This phosphorylation was independent of Ca2+ and calmodulin, and a further kinase inhibition was the incorporation of [32P] phosphate in one major band of Mr 45,000 daltons. Several other protein bands of Mr 65,000 and 70,000 were labeled in a lesser extent by calmodulin-dependent kinase. Half maximal phosphorylation of the 65,000 dalton band was achieved at 0.16 uM calcium and maximal phosphorylation was observed at approximately 1 uM calcium. Ca2+ increased calmodulin-dependent phosphorylation of 45,000 dalton protein in a dose-dependent manner and maximum phosphorylation was achieved at approximately 5 uM Ca2+ in the presence of 1 mM calcium. Calmodulin-dependent microsomal phosphoryylation was inhibited by trifluoperazine with an apparent Kd of ~ 2 x 10^-10 M. Similarly, 10 mM EDTA inhibited calmodulin-dependent phosphorylation of the 45,000 dalton protein. These data suggest that both cAMP and calmodulin phosphorylate a 45,000 dalton protein which may be involved in the regulation of intracellular calcium concentration.

Influence of Prostaglandin on Arterial Microsomal Calcium Transport. M. E. Soulsby and B. H. Perlmutter*, Univ. Ark. Medical Sciences, Little Rock, AR 72205. Prostaglandins from the media of bovine aortas were used in this investigation of the effect of 10^-5 to 10^-9 M prostacyclin (PG12) on passive (no ATP) Ca++ binding, ATP-dependent Ca++ uptake and Ca++ dependent ATP ATP hydrolysis. Incubations were carried out in a medium containing 1 mg/ml bovine serum albumin, 1/4 M KCl, 30 mM histidine (pH 7.0), 10 mM K-oxalate, 8 mM Na-asparte, 3 mM MgCl2, 0.001 uM Ca++ for 15 minutes, and 5 mM ATP. Aliquots of the incubation mixture containing 0.25 uM Ca++ and 10^-7 to 10^-5 M Ca++/g protein (p=0.01). Control ATP dependent Ca++ uptake (local minus binding (no ATP)) was 1.0 uM/g protein/min (u.14), (1.0 x 10^-5 M) caused an immediate 85% reduction (p=0.01) in uptake, proceeding to 0.152 after 1.5 min, followed by resumption of normal uptake rate. Control Ca++-dependent ATPase activity was immediately depressed 38% by PG12 (p=0.01) proceeding to 60% after 1.5 min. This was not due to a reduction in ATPase activity. We conclude that PG12 vasodilatation is the result of increased microsomal passive Ca++ binding, as well as depressed Ca++ dependent ATPase activity. (Supported in part by American Heart Association/Arkansas Affiliate.)

Calmodulin-mediated stimulation of calcium uptake in isolated microsomes from bovine carotid artery. R.C. Bhalla, R.V. Sharma*, and D.W. Doerrfeld*, University of Iowa, Iowa City, IA 52242. The role of calmodulin and other factors involved in the regulation of calcium uptake in vascular smooth muscle was examined in a microsomal fraction prepared from bovine carotid artery. Calcium uptake catalyzed by CAMP-dependent PKA was not inhibited by sodium azide. Energy-dependent calcium uptake was greatly enhanced by oxalate in a dose-dependent manner. Cell-free microsomal fraction added to ATP and oxalate showed a direct correlation between control values of the presence of ATP and oxalate. Calcium uptake was dependent on the free Ca++ concentration in the medium and increased in a dose-dependent manner. The threshold concentration of Ca++ in the presence of ATP and oxalate was obtained at approximately 0.2 uM calcium. The stimulatory effect of calmodulin was observed over the entire range of calcium concentration. Calmodulin also stimulated phosphorylation of microsomal proteins. The major microsomal protein phosphorylated by calmodulin-dependent kinase showed an apparent molecular weight of 45,000 daltons, estimated by SDS-polyacrylamide gradient gel electrophoreses. These results indicate that calmodulin may play a role in the control of free cytoplasmic calcium concentration in vascular smooth muscle. (Supported by NIH grant HL091927.)
5.7 **INFLUENCE OF TRANSNUCLEAR NERVE STIMULATION (TNS) ON THE EFFECT OF NORTENOSIVE AND HYPERERTENSIVE DOGS.** R.N. Pittman and B.A. Graham.* Dept. of Physiol. Diophys., Med Coll College of VA, Richmond, VA 23290.

We investigated the role of the endothelium in 02-linked contractile responses of in vitro strips of femoral and renal arteries from normotensive (NT) and one-kidney, goldblatt hypertensive (HT) dogs. The intimal surface of half the strips was rubbed to remove functional endothelium. Isometric force was recorded for strips stimulated with either 70 mM glutathione or 500 mM noradrenaline (NE). The force and time course of the NE-induced contraction in NT strips was similar to the control and the time course of the NE-induced contraction in HT strips was significantly different. Response (1) or (2) occurred with or without endothelium. Response (2) is qualitatively similar to PO2 dependent propranolol-mediated contractile behavior observed by others.

6.1 **CYCLOSPORIN A INHIBITS OXIDATIVE DECARBOXYLASE INDUCTION IN RENAL TISSUE OF ADX RATS.** Joseph B. McElhaney, Jr.,* Robert L. Hill, Joseph L. Jones, Jr., and William H. Grover, Jr. Dept. of Internal Medicine, UCLA, Los Angeles, CA 90024.

Rats were subjected to either sham or adrenalectomy (ADX) and treated with or without cyclosporin A (CSA). Oxidative decarboxylase activity was measured in renal tissue. CSA significantly inhibited the induction of ODC activity in adrenal tissue of ADX rats. These findings further emphasize that the prolactin response to stress is dependent upon more than just the immediate action of the stressor.

6.2 **INFLUENCE OF CORTICOSTERONE ON THE PROLACTIN RESPONSE TO PHYSICAL AND PSYCHOLOGICAL STRESS.** Thomas E. Nenninger, Ph.D. and C. H. Nevis, M.D. Univ. New Mexico School of Medicine, Albuquerque, NM 87131.

Corticosterone treatment (ADX+CORT) significantly increased the prolactin response to physical stress in male rats. The prolactin response to physical stress was significantly lower in female rats than in male rats. The prolactin response to stress was significantly lower in male rats than in female rats. The prolactin response to stress was significantly lower in male rats than in female rats. The prolactin response to stress was significantly lower in male rats than in female rats. The prolactin response to stress was significantly lower in male rats than in female rats.
6.3 EFFECTS OF TREATMENT OF NEONATES WITH MONOQUATHIONUM GLAMATUM (ON GONADOTROPES) IN THE PREPUBERTAL MALE RAT. M.O. Dadah and C.A. Drake. Univ. of Nebraska Medical Center, Omaha, NE 68105

It is well established that treatment of neonates with monosodium glutamate (MSG) causes destruction of the hypothalamic arcuate nucleus, and results in a small anterior pituitary gland (AP), often normal serum LH and FSH levels, and reduced gonadotroph weights. We investigated the effects of MSG on the AP and gonadotropes. Male rats were injected with saline or MSG (4 mg/kg body weight) on Days 1, 3, 5, 7, and 9 of life (Day 0 day of birth) and killed by decapitation on Day 40 of life. Treated blood was collected for assay of serum LH and the pituitary gland was processed for immunocytochemical staining with anti-invader (Invader, 1; 710,000), anti-LH (1:450,000), and anti-FSH. Serum LH levels were significantly elevated in MSG-treated rats. Additionally, virtually all FSH cells, but virtually none of them, were present in MSG-treated rats. Treatment with MSG reduced AG size (P<0.01), reduced the average size of both LH and FSH cells (P<0.01), and increased the ratio of LH to FSH cells (P<0.05). The results indicate the existence of an intracellular mechanism that is differentially expressed in mice and may be involved in the regulation of LH and FSH production.

6.5 HYPOPHALAMIC SEROTONIN (5HT) AND SERUM LUTEINIZING HORMONE (LH) INTERACTIONS IN AGING FEMALE RATS. K.P. Waltz* (SPON: D.R. Wekstein) Univ. of Kentucky Medical Center, Dept. of Anatomy & Sanders-Brown Research Center on Aging, Unv. of Ky. Medical Center, Lexington, KY 40536

In this study, patterns of hypothalamic 5HT metabolism and serotonin-induced LH surges were compared in young (Y; 3-4 mos. old) and middle-aged (MA; 6-10 mos. old) ovariectomized rats. Animals from both groups produced LH surges in response to sequential injections of estrogen (250ng) and progesterone (P; 0.5mg). However, peak levels of serum LH accumulating at 1800h on the day of P administration were significantly higher (P<0.01) in Y (2888±260ng/ml) vs. MA (158±196ng/ml) rats. Lower serum LH content in MA rats correlated with smaller mean serum levels of LH in MA rats. Further, when 5-hydroxytryptophan (5HTP), a precursor of 5HT, was administered in addition to the steroids, LH surges were attenuated in MA (Y+344 ng/mg; MA=121 ng/mg), but did not alter hypothalamic 5HT content. These findings suggest that attenuation of serotonin-induced LH surges in MA rats is due to abnormal THY innervation in DI rats and compared to normal Long-Evans (LE) rats: 1. VIP innervation, mainly on blood vessels, was at least as abundant in DI as in LE. Finally, no differences were found in both LE and DI and appeared to be more distinguishable from that of LE. NPY innervation, mainly on blood vessels, was less abundant in DI than in LE. Furthermore, as in MA rats, NPY innervation was also weaker in MA rats than in LE rats. These findings suggest that the apparent proliferation of VIP fibers in DI may be due to the loss of positive feedback on THY responsive neurons. In conclusion, the reduced THY responsiveness of DI is due to abnormal THY innervation in DI. Crystalloid sections of THY were processed for immunocytochemical demonstration of various neuropeptides using indirect immunofluorescence. In subthalamic region, THY-positive cells that belong to A13 group are weakly labeled, further, a few cells in group A13 are also labeled with both TH and VIP immunohistochemistry (Swed. MRC 4499 & USPHS AM 21348). THY-positive cells in the arcuate and periventricular nucleus (periventricular nucleus) that belong to A13 group are also labeled with both TH and VIP immunohistochemistry.
6.9  EFFECTS OF EXERCISE AND CONDITIONING ON WHOLE BLOOD VISCOSITY IN WOMEN. Dale Martin*, Eric Schoomaker*, Susan Petersen*, and Marianne Zorza*. Univ. of Michigan and VA Medical Center, Ann Arbor, MI 48105.

The effects of enkephalin (EMK) on angiotensin II (AII) stimulated release of oxytocin (OT) and vasopressin (VP) were investigated in the conscious male rat. Changes in the plasma levels of both OT and VP were measured in animals after intracerebroventricular (ICV) administration of either artificial cerebrospinal fluid (CSF) with or without AII (10, 50, 100 ng/5 μl) and 60 sec after AII (50 ng/5 μl) or CSF in animals pretreated with ENK (100 ng/5 μl) or EMK (3 μl). Oxytocin and VP were measured by radioimmunoassay. Angiotensin II at doses ranging from 10-100μg, IVT, increased (p<0.05) the plasma levels of both OT and VP. However, oxytocin and VP levels of both the hypophyseal and paraganglionic tissues remained significantly elevated 300 sec after II AII administration. Although the plasma concentration of OT was always greater (p<0.05) than VP in II-stimulated animals the OT/VP ratio did not differ from controls. Leucine-enkephalin reduced the rise to OT from 03.6 ± 4.7 (Mean ± SE) to 2.5 ± 2.1 pmol/gm at 100 ng/5 μl and from 2.5 ± 2.1 to 6.8 ± 3.1 pmol/gm stimulated by I AII (10 ng/5 μl). IVT administration of EMK containing only ENK did not alter either OT or VP levels of these neuropeptides. It was concluded that the acute elevation of all in the CSF stimulated release of both OT and VP from the neural lobe. Leucine-enkephalin administered IVT inhibited AII-stimulated OT and VP releases.


In order to determine whether, as has been continually assumed, there is a causal relationship between the blood pressure rise during exercise and the release of growth hormone (GH), we have studied the blood pressure changes in the normotensive dog after the intravenous injection of GH-releasing factor (GRF). GH-releasing factor is a synthetic material that has been shown to stimulate the release of GH from the pituitary gland in vivo. The peak blood pressure rise following the injection of GH-releasing factor is 6.18±2.1 mmHg, which is significantly lower than the 6.27±2.2 mmHg peak rise following the injection of GH. These results suggest that the release of GH during exercise is not a cause of the blood pressure rise during exercise.


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7.3 EFFECT OF VOLUNTARY EXERCISE BY STROKE-PRONE SHR GROUPS ON SELECT PHYSIOLOGICAL RESPONSES. G. M. Tipton, R. D. Mathes, J. R. Leininger, J. I. Musch, G. A. Ordway, and J. H. Mitchell. Univ. of Texas Health Science Center, Dallas, TX 75235.

Previous studies have shown that SHR populations have a greater incidence of cardiovascular and cerebrovascular disease. The purpose of this study was to investigate, at similar levels of estimated myocardial oxygen demand, regional blood flow responses to DOB, ANEE, and EXER. The data were obtained in 8 mongrel dogs (24.9 ± 2.2 kg, mean ± SEM) chronically instrumented with arterial and venous catheters. DOB (0.05 mg/kg/min) and ANEE (0.25 mg/kg/min) were administered IV. The results are tabulated below:

<table>
<thead>
<tr>
<th>DOB</th>
<th>ANEE</th>
<th>EXER</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1</td>
<td>0.2</td>
<td>0.3</td>
</tr>
</tbody>
</table>

These results support the hypothesis that the pericardial limita steam volume at maximal exercise in untrained dogs.

7.4 ACUTE REGIONAL BLOOD FLOW RESPONSES DURING DOBUTAMINE INFLUENCE, DURING COMBINED SYMPATHETIC STIMULATION AND PARASYMPATHETIC WITHDRAWAL, AND DURING EXERCISE IN DOGS. G. C. Haidet,* J. I. Musch,* G. A. Ordway and J. H. Mitchell. Univ. of Texas Health Science Center, Dallas, TX 75235.

Previous studies have shown that intravenous infusions of either dobutamine (DOB) or a combination of atropine, norepinephrine (ANEE), and epinephrine (EXER) evoke responses similar to those observed during dynamic exercise (EXER). The purpose of this study was to investigate, at similar levels of estimated myocardial oxygen demand, regional blood flow responses to DOB, ANEE, and EXER. The data were obtained in 8 mongrel dogs (24.9 ± 2.2 kg, mean ± SEM). DOB (0.05 mg/kg/min) and ANEE (0.25 mg/kg/min) were administered IV. The results are tabulated below:

<table>
<thead>
<tr>
<th>DOB</th>
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<th>EXER</th>
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</thead>
<tbody>
<tr>
<td>0.1</td>
<td>0.2</td>
<td>0.3</td>
</tr>
</tbody>
</table>

These results support the hypothesis that the pericardial limita steam volume at maximal exercise in untrained dogs.
7.9 EFFECTS OF HINDLIMB POSITION ON THE RHEOLOGY OF THE TERMINAL AORTA IN DOGS. D.R. Gross, G. van Dort* and K.T. Dodm, Dept Vet Phys & Pharm. College Vet Med. Texas A&M University, College Station, TX, 77843.

We measured pressure diameter relationships in 6 anesthetized dogs following prior surgical placement of ultrasonic dimension gauges on the terminal aorta, just proximal to the iliac trifurcation. Following recovery from the initial surgery, and time for healing to occur (7-10 days), the dogs were anesthetized with a combination of ketamine-propofol) and pancuronium. Using fluoroscopic visualization, a high-fidelity catheter-tip manometer was placed in the distal aorta, via the carotid artery, with the tip placed at the level of the dimension gauges. Measurements were made with the hindlimbs positioned 90° from the body, with both legs fully extended cranially and then caudally, with the right leg extended cranially and the left caudally and vice versa. The pressures elastic modulus (Ep) was calculated for each of the static leg positions. Data collected with both hindlimbs extended cranially were compared to both hindlimbs at 90° from the longitudinal axis of the body. Ep decreased approximately 25%, i.e. the vessel became more compliant in the radial direction. No significant differences were found with the hindlimbs in the other 3 positions.

(Supported by the Center for Comp. Med., Texas A&M Univ.)


One group (T) of male Sprague-Dawley rats trained for 1 hr/day for 13-17 days at 30 m/min on a treadmill at a 5° incline. A second group (UT) of rats was conditioned for 10 min/day for 4 who at the same speed and incline. BFs in 32 hindlimb muscles were measured with labeled microspheres during preexercise (PE) and while the rats ran for 30 min (E0.5), 5 min (E1), ut 15 min (E15) at 30 m/min.

Representative

<table>
<thead>
<tr>
<th>Muscle</th>
<th>PE</th>
<th>E0.5</th>
<th>E1</th>
<th>E15</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Hindlimb</td>
<td>70</td>
<td>40</td>
<td>88</td>
<td>104</td>
</tr>
<tr>
<td>Red Gastrocnemius</td>
<td>60</td>
<td>102*</td>
<td>228</td>
<td>280</td>
</tr>
<tr>
<td>White Gastrocnemius</td>
<td>12</td>
<td>10</td>
<td>14</td>
<td>20</td>
</tr>
</tbody>
</table>

P < 0.05.

There were no differences in total hindlimb muscle BF between UT and T rats, but UT rats had higher PE BFs in the deep red extensor muscles, suggesting a greater multipotential precursor. Also, T rats had higher BFs in red extensor muscles during exercise, whereas UT rats had higher BFs in white muscles. These findings demonstrate that exercise training causes changes in the distribution of BF within and among muscles both before and during exercise. Supported by NIH Grants AM23472 and HL26963 and AHA Tulsa Affiliate.

7.11 FITNESS RELATED CHANGES IN THE HEMODYNAMIC RESPONSE TO AN ALPHAMETHYL DIVALENE PROPRIOPERIODIC ANALGESIC, NALEDECTIC ACETATE IN A DEPENDENT RACETAMINE ANIMAL, Michael L. Smith*, and Theodore S. Varas*, Texas College of Osteopathic Medicine, Fort Worth, TX. 76107.

The lack of differences in high fit and average fit individuals when challenged with lower body negative pressure. An alpha-cholin agonist cell phone present PE (PC) was administered to a similar group of subjects to further delineate these responses. Six high fit (F2: 50 w/kg) males (P < 0.05) were challenged with PE using IV infusion rates of 12.20, and 21.21 g/kg/min. At rest and during the period of stable hemodynamics for each infusion rate, heart rate (HR) using 10 set averages of R-R intervals, blood pressures, cardiac output (Q) using the CO2 rebreathing technique, and fore-arm blood flow (BF) measured by strain gauge plethysmography were determined. Only HR was significantly different at rest (F < 50 beats/min, UF56 beats/min, P < 0.01). Mean data at PE of 60 g/kg/min are summarized below:

<table>
<thead>
<tr>
<th>HR</th>
<th>BF</th>
<th>1AHR</th>
<th>1DVR</th>
<th>BF</th>
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<tr>
<td>14.1</td>
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<td>14</td>
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<tr>
<td>12</td>
<td>114</td>
<td>20</td>
<td>29</td>
<td>13</td>
</tr>
</tbody>
</table>

7.12 CHANGES IN PLASMA CONCENTRATION OF ACTH AND CORTISOL IN RESPONSE TO DAILY 2-HOUR RUNS FOR 7 DAYS. C.E. Wade, P. Christ*, M.M. Hunt*, J.R. Claybaugh, C. Hadick*, S.A. Cincinelli, and R.M. DeSesso**, Letterman Army Medical Center, San Francisco, CA 94129; Tripler Army Medical Center, HI 96859; and William Beaumont Hospital, Royal Oak, MI 48071.

To assess the effects of daily running on the pituitary-adrenal axis, we measured plasma concentrations of ACTH and cortisol in 15 healthy, untrained males before and after 2 hours of daily running for 7 days. The mean age, 21 to 37 years, underwent 1-day of control measurements, 7 consecutive days of running for 2 hours, 2 days of rest, and a final day of running for 2 hours. Running or an equivalent period of rest was conducted between 0600 and 1030 hours, with fasting blood samples collected before and within 3 min after running. During these 2 hours each man ran an average distance of 13.2 km, which remained constant throughout the study. In response to running, concentrations of plasma ACTH and cortisol levels increased significantly (P < 0.03). The mean change in levels of plasma cortisol after running progressively decreased from 16.7 ± 3.8 ng/dl on day 1 to 4.3 ± 3.8 ng/dl on day 7. The mean change in levels of ACTH after running was not significantly altered, ranging from 30 ± 10 pg/ml on day 1 to 21 ± 5 pg/ml on day 7. A relationship between plasma cortisol and ACTH was not demonstrated on day 1 (r = 0.24, P < 0.20), while on day 7 a relationship was noted (r = 0.67, P < 0.001). Thus, plasma concentration of ACTH and cortisol levels increased with running, and cortisol response progressively decreased as a result of factors other than ACTH.

The cardiovascular adaptations to pregnancy were studied cross-sectionally in the guinea pig (GP). Pressures, cardiac output (CO), and uterine blood flow (UBF) were measured at gestation, and in mature GPs, respectively age- and weight-matched prior to conception. The cardiac output and uterine blood flow were measured in 14 control and 39 pregnant GPs during early, mid-, and late gestation. The results were, respectively: age- and weight-matched prior to conception. The cardiac output and uterine blood flow were measured in 14 control and 39 pregnant GPs during early, mid-, and late gestation. The results were, respectively: 8.2 ROLE OF THE SPLEEN IN ERYTHROCYTE VOLUME REGULATION OF THE CONUSCUROS IMATURE PIG. Carol A. Beesonde and John F. Hannon. Letterman Army Institute of Research, Presidio of San Francisco, CA 94129

When estimated by the dilution of 51Cr-tagged erythrocytes under near-basal conditions, chromonically catheterized spinto skin prongalized pig (10-20 mg) had plasma 51Cr-tagged erythrocyte volume of 17.9 ml/kg. A calculated plasma volume of 42.5 ml/kg (mature) and blood volume of 60.6 ml/kg. Skinned control pigs exhibited larger blood volume with a plasma volume of 60.1 ml/kg and blood volume of 60.1 ml/kg, respectively. In the latter animals, kinetic analysis of splenic erythrocyte sequestration showed a splenic erythrocyte sequestration of 0.01 ml/kg and blood volume of 10.0 ml/kg of 9.7±0.5 ml. Ephrinol injection (0.5 ml of 1 mg/1000 ml d1) caused rapid mobilization of stored splenic erythrocyte in sham-operated pigs with a hematocrit of 0.27±0.01 to 0.35±0.02. Similar results were obtained in sham-operated pigs (n=5) subjected to a mild to moderate contraction and the blood sampling repeated. Blood counts were done manually. The dilated (D) and contract (C) splenctic blood volumes were compared by paired Student "t"-tests; P<0.05 being considered significant. The findings were: the contracting spleen does not expel all formed elements randomly. Preferential erythrocyte discharge occurs, thus lowering the splenic volume. The canine spleen is known to be a large and muscular blood reservoir, particularly sequestering erythrocytes at higher concentration than in the peripheral circulation. Its volume can be greatly altered by emotion, exercise, and anesthesia. This study wished to learn alterations may be mediated by changing hormone levels.

(a) the splenic volume contains substantial stores of readily-mobilized erythrocytes and that ESA dilution may overestimate peripheral erythrocyte volume.

Supporting grant from the American Heart Association and Texas Affiliate.)

8.3 THE SPLENIC HUMORPHAN OF THE DOG VAHIES WITH SPLENIC SIZE. Mortimer Lobeger, Georgetown University School of Medicine and Dentistry, Washington, D. C., 2007

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Laser-Doppler Skin Blood Flow: Correlation with Plethysmography

Dept. of Physiol., Univ. of Texas Health Science Ctr., San Antonio, Texas 78284.

Plethysmographic determinations of skin blood flow (SDF) are the source of most of our understanding of that circulation in man. However, this method is limited to the limbs, is diaphragm insensitive, non-uniquely localized, and cannot determine laser-Doppler velocimetry (LDV) has been introduced as an alternate method for measuring SDF. LDV avoids the above problems. LDV is based on the frequency shift of coherent light scattered by moving red cells within surface tissue. We designed this study to find the relationship between these two measurements of SDF. Subjects were warmed with water-perfused suits which covered the body except for the arm from which SDF was measured. Esophageal temperature rose 0.9°C while forearm blood flow (fmr) rose 14 ml/100 ml/min. In each of 3 studies, LDV correlated well with FBF (r=0.94-0.98). However, the slope of the LDV-FBF relationship varied between subjects as well as on repeat studies with an individual (40-122 mV per ml/100 ml/min). Occulsive zero for the LDV (160-300 mV) and extrapolated intercept of the LDV-FBF relationship (246-599 mV) were greater than the instrument zero. We conclude that the two methods are well correlated within a study.

We will report data and consider comparisons to subjects and between studies in a given subject.

Supported by Grant HL20663

8.8 Static and Dynamic Properties of Wire Loop Probes Used in Induction Angiometry.

J. Kroeger* and B. Schmitz.

Krohn (Blood Vessels 17: 61-77, 1980) described use of wire loop probes to measure vascular dimensions in vivo. Since then, commercial systems are available. To determine if probes can follow rapid (cardiac) events without significant vessel wall distortion, data are presented from experiments where the loop volume and contraction force and rate of loop diameter change. Data for probes with unstrained loop diameters (UD) of 4.0, 9.4, and 22.5 mm were recorded during loop compression from 95% to 65% UD. Static compression for all probes yielded a linear (all F, P < 0.05) regression coefficient of 0.71 and 0.0525 (9.4 mm) and 0.0138 (22.5 mm) grams/cm² dia. For dynamic use probes were calibrated to correct for an UD at various rates (20 to 230 mm/sec) and compression/expansion ratios (30/50, 50/30, and 70/30). Probe electronic signal were compared with homogeneous measurements from a linear variable differential transformer (LVDT, Schatz Engg). Comparison of transparancy overlays and electronic differential analysis, of probe and LVDT results indicated the 4.0 and 9.4 mm probe had no hysteresis or lag. The 22.5 mm probe began to lag at rates over 160 mm/sec. In relation to reports on vascular muscle content and contractile force (Fed. Proc. 42: 2601, 1983) these results indicate that the 4.0 mm probe may be used in arteries but may be too stiff for veins, the 9.4 mm probe is useful in both, while the 22.5 mm probe may work for slow events in an artery. Part support NIAMDD, NIH, DA-004-04 and 310.

8.9 Oscillations in Endocrine and Circulatory Variables in Normal, Conscious Dogs.

Crump Institute for Med. Engr., UCLA, Los Angeles, CA 90024.

Hemodynamic physio predicts that the stability of living systems is based on networks of loosely coupled, nonlinear thermodynamic oscillators. To test this theory we undertook a systematic analysis of the arterial glucocorticoid system. We examined adrenal blood flow, cortisol secretion rate, concentrations of cortisol and corticosterone, arterial blood pressure and heart rate in conscious, unrestrained dogs. We anticipated that we would discover previously unreported oscillations among these variables. We collected samples at 15 sec, 5 min, or 10 min intervals for 30 min to 6 hr. From the resulting time series we were able to detect three oscillatory epochs: 2 to 4 min, 4 to 8 min, and 1 to 2 hr. We found significant oscillations in adrenal variables only in the 2 to 4 min and 1-2 hr ranges. In blood pressure and heart rate we found significant oscillations in both the 0.4-3 min and the 4-8 min range; and a strong oscillation in the 1-2 hr domain has been reported in the literature. Thus we saw that heart rate and blood pressure share three oscillations two of these are present in adrenal blood variables, and one (the idioch frequency) is not. Circulatory oscillations are not causal to adrenal oscillations. (Supported by Grant HL20663)

8.10 In Vivo Distribution of I-125 Heat, an Adrenoceptor, in Mice.


Heat, 28-(4-hydroxyphenyl)ethylaminomethyl)tetralone, is available with an I-125 radiolabel, and is a beta-adrenergic ligand in vitro. We studied the distribution of I-125 heat in 25-30 g male Sprague-Dawley rats after tail vein injection. Animals were sacrificed at 15 min, the blood and tissues assayed for radioactivity, and results given as percent dose/mg tissue (UD). Studies were also performed on I-125 labeled prazosin. Both 24 hour footed mice and those eating ad libium were utilized. The lungs were the first major organ reached by the labeled I-125 heat, after the liver. The lungs had the highest specific activity (27 picoIU). However, radiolabeled was widely distributed; pancreas, kidneys and gallbladder had high concentrations. Pretreatment with prazosin had only slight effect on distribution of radioactivity. Urine was collected and chromatographed on silica gel plates, using methanol/chloroform (9:1) and 100:1 by volume. The 125I had an RF of 0.82-0.85. Only about 12% of urinary radioactivity corresponded to the original RF. There was major degradation and/or unbinding of the I-125 heat. Wide distribution of radiolabel, lack of response to prazosin preloading, and chromatographic evidence of alteration, make it problematical whether I-125 heat can be used as an in vivo adrenergic label. (Supported by USPHS CA 17802, NCI)

8.11 Effect of Temperature on Rabbit Ear Artery Receptor Affinity and Contractility.

Michael Roberts, Susan Maben*, and Clayton Turner*.
Dept. of Biology, Linfield College, McMinnville, OR 97128.

In isolated ear arteries studied by challenge with exogenous norepinephrine (NE), maximal contractile responses occur at 22°C and contraction is reduced at temperatures below or above 25°C. To determine the mechanism of this effect, we studied the influence of temperature on two aspects of the arterial glucocorticoid system. We examined adrenal blood flow, cortisol secretion rate, concentrations of cortisol and corticosterone, arterial blood pressure and heart rate in conscious, unrestrained dogs. We anticipated that we would discover previously unreported oscillations among these variables. We collected samples at 15 sec, 5 min, or 10 min intervals for 30 min to 6 hr. From the resulting time series we were able to detect three oscillatory epochs: 2 to 4 min, 4 to 8 min, and 1 to 2 hr. We found significant oscillations in adrenal variables only in the 2 to 4 min and 1-2 hr ranges. In blood pressure and heart rate we found significant oscillations in both the 0.4-3 min and the 4-8 min range; and a strong oscillation in the 1-2 hr domain has been reported in the literature. Thus we saw that heart rate and blood pressure share three oscillations two of these are present in adrenal blood variables, and one (the idioch frequency) is not. Circulatory oscillations are not causal to adrenal oscillations. (Supported by NIH grant GM 23732.)
peritoneal (IP) injection of either normal saline, or 10, 30, 60 mg/kg CLD. In addition, steady state groups. Group D animals (21-30 d.) received a single intravenous (IV) injection of 5, 10, 30, 60 and 60 mg/kg CLD. HR and ECG were monitored on these animals. These data are consistent with the observations that felodipine is more effective in reducing pressor responses of intravenous NE than that of spinal stimulation in pithed dogs. However, felodipine (1x10^-3 M) significantly enhanced [3H]-NE release at both frequencies. Vasoconstrictor responses to exogenous NE (10 and 32 ng) were progressively reduced with increasing concentrations of the drug and these responses were virtually abolished at the concentration of 1x10^-4 M. These data suggest that the observations with felodipine are more effective in reducing pressor responses of intravenous NE than that of spinal stimulation in pithed rats. These studies collectively suggest that the ability of the drug to reduce vasoconstrictor effects of NE contributes to its vasodilator activity and to its efficacy as an antihypertensive agent. (Felodipine was supplied by AB Næssie, Mödling, Sweden.)
8.19

PHYSIOTONIC ENHANCEMENT OF THE CEREBROVASCULAR RESPONSE TO HYPOXIA. W. J. Hass, B. D. Hogg, D. M. Rowan and Ralph R. Somerson, UCLA School of Medicine, Los Angeles, CA 90024

Physiologically (P), a cholinesterase inhibitor, prolongs survival under hypoxic hypoxia (Surhke 1970; 1979; 12:348, 1990). The present investigation evaluates the possible contribution of cerebrovascular adjustments to this phenomenon. Intracerebral blood flow (ICBF) was measured with an electromagnetic flow meter in rabbits (70s 800). Under moderate hypoxia (PI0< 100), ICBF increased to 115± 8 of control (X ± SE, n=5). Following 0.6 mg/kg P (i.v. bolus), this response of ICBF was considerably enhanced (215± 8). The increase in ICBF under severe hypoxia (PI0< 75), (215± 8), was only slightly augmented by P (284± 51). The enhancement by P of the ICBF response to hypoxia could not be explained by the C02 increase in arterial pressure. To evaluate the possible contribution of changes in cerebral O2 uptake (CMRO2), sagittal sinus blood flow was measured (Rq clearance) and blood was sampled from the same vessel and from the abdimal aorta. Under moderate hypoxia, P induced a decrease in CMRO2 (hypoxia= 85± 5; hypoxia + P= 58± 8/ml/100mg, n=5) and an increase in cerebral venous O2 saturation (hypoxia= 85± 4; hypoxia + P= 13± 5). Conclusion: the increase in blood flow and venous O2 saturation and the decrease in CMRO2 caused by physiologically might play a role in the prolonged survival under hypoxia induced by this drug. (Supported by AHA-CLAA 47110).

8.20

LIVER BLOOD FLOW BY THERMODILUTION TECHNIQUES. Samuel A. Cucinelli, Gordon H. Bryant, and Peter R. Barcia, Toronto (SPON: J.R.Claybaugh). Tripler Army Medical Center, Honolulu, HI 96859.

The location of the hepatic veins lend themselves to the determination of hepatic venous blood flow by the algebraic difference of inferior ven a caval (IVC) blood flow at a point cephalad to renal veins but caudal to the hepatic veins, and 2 points cephalad to the hepatic veins but below the atrium. Initial studies in dog using electromagnetic flow probes encircling the IVC and thermistor catheters, placed percutaneously at the same points in the IVC, showed comparable estimations of the blood flow. However, inaccurate high estimation of IIVCF was obtained comparing portal venous blood flow (hepatic artery ligated) to percutaneously placed thermistor catheters in the IVC in the pig. The reason is the loss of the cold thermistor in the IVC in the pig. By a comparing of the cardiac output, after atrial and femoral vein injection of the thermistor, the number of calories exchanged with the IVC wall can be calculated. From zero to 60% of the mitochondrion energy may be lost during an experiment. When the thermistor is injected, the temperature difference between the IVC and the pig, the speed of blood flow, and the absolute temperature of the animal.

8.21

ACTIVATION OF RENAL LIPOXYGENASE PATHWAYS IN DOGS BY WATER DEPRIVATION. Larry P. Feigen, Tulane Medical Center, New Orleans, LA 70112.

Arachidonic acid (AA) is the metabolic substrate for cyclooxygenase and lipoxygenase enzymes. The former leads to prostaglandins and the latter to lipoxygenase products (P) including thromboxane. In anesthetized dogs, renal blood flow was measured with intravenously injected AA was injected into the renal artery. In 2/3 of the dogs that had free access to water, AA injection led to renal vasodilation and in 1/3 it led to initial vasoconstriction followed by vasodilation. In 8 dogs that were water deprived for 15-18 hours prior to experiments, AA injection led to a biphasic response. The dilator portion of the responses to AA was blocked by ibuprofen (a cyclooxygenase inhibitor). The constriction portion was not affected by ibuprofen but was blocked by lipoxygenase inhibitors. Direct injection of leukotrienes into the renal artery produced only vasodilation and these agents were very potent at doses up to 10 μg. These data show the role of other possible contributions to the ICBF response to moderate hypoxia (CMRO2)

MECHANICS OF BREATHING I

9.1


We studied 7 patients with severe CAL (FEV1/VC< 40%) by imposing VM rest for 1 hour with an Emerson chest respirator, CW restriction was produced by an inelastic corset. AB Res and R-L Res were measured before the VM were rested. After 1 hour rest there were increases (p < 0.05) in FRC, diaphragm contractility and H/L Par. We conclude that the VM account for up to 20% of resting R-L. Even short periods of VM rest improve diaphragm function in severe CAL. We suggest that VM rest is a reasonable approach to therapy of such patients.

Supported by Royal Edward Laurentian and Parker B Francis Foundations, MRC (Canada), and the Parker B. Francis Foundation.

9.2


We studied the effects of rib cage (Ab Res) and Abdominal (Rc Res) restriction on breathing pattern and pressure generation in 5 subjects exercising to exhaustion (tlim) at 80% Umx. During exercise, transdiaphragmographic (Pdi), pleural (Ppl), and gastric (Pga) pressures, and rib cage (Uc) and abdominal (Ua) volume contributions to tidal volume (VT) were measured. Without CW restriction mean tlim (6 SD) was 7.6±1.0 min. Ventilation (VT) increased progressively to 11.7± 2.1 l/min. YRc was 43± 7 l/min increased (due predominantly to greater Δ Pdi) to a plateau in the first 3 min. of exercise. ΔPga exp increased progressively due to abdominal muscle recruitment. CW restriction on breathing pattern and pressure generation can be produced in the pig by adipose (Ab Res) or anterior abdominal (Rc Res) restriction. Reduced CW restriction of the chest wall by an inflatable corset in the pig, Ab Res reduced Wc 30% and FRC 7%, and increased VrC %VT to 85%. Ab Res produced no change in tlim, VT or VT/Vm in exercise but increased both ΔPdi insp (due to greater ΔPdi exp and ΔPga exp) in the pig. Reduction of the CW in the pig by Ab Res increased Vm %VT to 20%. Ab Res decreased tlim by 37%. Although ΔPdi exp increased in exercise, the change in tlim was less with Ab Res and ΔPdi exp was not significant. We conclude that either Ab or Rc Res alter the pattern of ventilatory muscle recruitment in exercise. Preventing intercostal-accessory muscle contribution to the increased Vm by Ab Res diminished exercise performance at 80% Umx (Supported by Iraq Ministry of Higher Education, MRC of Canada, and the Parker B. Francis Foundation).
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OESOPHAGEAL AIRWAY NARROWING AND AIRWAY DISTENSIBILITY. D. C. Strydom and D. O. Rodenstein (Sponsor: J. A. Will). Cliniques Universitaires St. Luc, Cardiopulmonary Laboratory, Brussels, Belgium.

We investigated in 20 normal subjects the ability of the soft palate to direct airflow during breathing. Subjects were connected to a spirometer, without nose clip. No instructions were given on the breathing route. During quiet respiration 15 subjects breathed solely through the nose, despite an open mouth. During forced vital capacity (FVC) maneuvers, 19 subjects identified the oropharynx as the breathing route. The palate was observed to be fixed when the subjects were asked to breathe through the mouth, while the palate moved freely through the nose. Significant differences in TD as PL increases from 0 to 15 cm H2O.

15. IB and TD were similar to rigid LAN at low PL and decreased to zero as PL increased. IB was also not significant in distensible elastic bands in 6 excised dog lungs. Significant differences in TD as PL increases from 0 to 15 cm H2O. IB and TD were similar to rigid LAN at low PL and decreased to zero as PL increased. IB was also not significant in distensible elastic bands in 6 excised dog lungs. Significant differences in TD as PL increases from 0 to 15 cm H2O.

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In upright dogs the vertical transthoracic pressure gradient (VTG) disappears after pneumothorax (PMX) (JAP 32:33, 1972). We confirmed this finding and observed the pressure to move downward and posteriorly with PMX, thus raising the question to what extent the heart supported by the lungs? We studied a theoretical linear elastance model using finite element analysis. The heart (H) and lung (L) were assumed to be isometric along the vertical axis with dimensions obtained from chest radiographs. Reported values of elastic proportion of FRC and H were generated first without the heart (L). The heart was then added (L+H). Finally, the effect of doubling heart weight (L+2H) was investigated. The results for L supported by its own weight were similar to those obtained with L+H. We concluded that the heart supported by the lungs,

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Gillett et al (JAP 51:1957, 1991) found a vertical gradient in Vr in lobes submerged in chlorohexone less than that predicted from the pressure-volume (PV) curve. We suspended 3 lobes containing lead markers by strings glued to the posterior surface so as if in an upright dog; cephalocaudal, x, was vertical and dorsoventral, y, and z, were horizontal. At constant lung volume, intralobular pressure and lung sounds were recorded before and after submersion in saline. Ptp increased when the lung was submerged, and the difference was explained by a change in the stethoscope's movements before and after submersion. Significant differences in TD as PL increases from 0 to 15 cm H2O. IB and TD were similar to rigid LAN at low PL and decreased to zero as PL increased. IB was also not significant in distensible elastic bands in 6 excised dog lungs. Significant differences in TD as PL increases from 0 to 15 cm H2O. IB and TD were similar to rigid LAN at low PL and decreased to zero as PL increased. IB was also not significant in distensible elastic bands in 6 excised dog lungs. Significant differences in TD as PL increases from 0 to 15 cm H2O. IB and TD were similar to rigid LAN at low PL and decreased to zero as PL increased. IB was also not significant in distensible elastic bands in 6 excised dog lungs. Significant differences in TD as PL increases from 0 to 15 cm H2O. IB and TD were similar to rigid LAN at low PL and decreased to zero as PL increased. IB was also not significant in distensible elastic bands in 6 excised dog lungs. Significant differences in TD as PL increases from 0 to 15 cm H2O. IB and TD were similar to rigid LAN at low PL and decreased to zero as PL increased. IB was also not significant in distensible elastic bands in 6 excised dog lungs. Significant differences in TD as PL increases from 0 to 15 cm H2O. IB and TD were similar to rigid LAN at low PL and decreased to zero as PL increased. IB was also not significant in distensible elastic bands in 6 excised dog lungs. Significant differences in TD as PL increases from 0 to 15 cm H2O. IB and TD were similar to rigid LAN at low PL and decreased to zero as PL increased. IB was also not significant in distensible elastic bands in 6 excised dog lungs. Significant differences in TD as PL increases from 0 to 15 cm H2O. IB and TD were similar to rigid LAN at low PL and decreased to zero as PL increased. IB was also not significant in distensible elastic bands in 6 excised dog lungs. Significant differences in TD as PL increases from 0 to 15 cm H2O. IB and TD were similar to rigid LAN at low PL and decreased to zero as PL increased. IB was also not significant in distensible elastic bands in 6 excised dog lungs. Significant differences in TD as PL increases from 0 to 15 cm H2O.
9.9 Magnitude of the interaction between the bronchomotor effects of sulfur dioxide and those of dry cold air. We studied the interaction between breath holding and inhalation of sulfur dioxide (SO₂) in 8 subjects with mild asthma. On three days we measured specific airway resistance (SRaw) before and after the subject performed eucapnic hyperpnea at a constant ventilation (30 L/min) for successive 3 min periods with doubling concentrations of SO₂ in dry cold air, in dry warm air, and in partially humidified warm air, and calculated the concentration that would cause an 80% increase in SRaw under each condition (p₈₀). The p₈₀ for hyperpnea with 0.25% SO₂ was significantly lower than that for dry air without SO₂. We conclude that sulfur dioxide causes bronchoconstriction at lower concentrations when it is inhaled in dry air than when it is inhaled in partially humidified warm air, and that concentrations of SO₂ as low as 0.25% can potentiate the bronchoconstriction caused by hyperpnea with dry air itself.


Although contraction of hindlimb skeletal muscle is well known to reflexly increase ventilation, heart rate and arteriolar pressure, little is known about the reflex effect of this maneuver on airway smooth muscle tone. Therefore, in canines anesthetized with nitroglycerine, we recorded transverse tension from the trachealis muscle while we contracted both gracilis muscles by electrically stimulating the gracilis nerves at 5 and 75 Hz. The values for the closed loop method were 5.8% and of the open loop 5.3%. Two observers' measurements were compared; the median of the differences was 3.3%. The values for the closed loop method were significantly different than those of the closed loop method. The variability in the mechanical responses to the maneuvers was small in most dogs (7/10). The open loop method provides an accurate and simple way to obtain Sraw. It may be especially useful in cases where repeated measurements are desired. (Supported by USPHS grant HL13134 and the Parker B. Francis foundation.)

9.11 Repetitive Exercise and the Refractory Period in Airline. R.K. Fischukar, Jr., R.P. Szymanowicz, Jr., and R.R. Verschueren, Jr. Shipley institute of Medicine, Brigham and Women's Hospital, Boston, MA 02115.

The characteristic events associated with repetitive exercise in asthma, we have 8 subjects undergoing exhaustive leg exercise under controlled inspired air conditions. Prior to, during and after the challenge, we measured peak expiratory flow rates (PEFR). Six minutes after completion of the work load, while the subjects were experiencing acute bronchospasm, they were re-exercised and the above measurements repeated. The initial exercise produced an increase in PEFR of 10% and the second challenge with PEFR of 2.5%, when the subjects stopped work the obstruction returned. Assessment of the size of the response by comparison of pre and post challenge data the increased in PEFR by 15%. These data are incompatible with the concept of mediator depletion playing a major role in the development of the refractory period. Possibly catecholamine release associated with physical exertion might be a major determinant of this phenomenon.


To characterize the events associated with repetitive exercise in asthma, we have 8 subjects undergoing exhaustive leg exercise under controlled inspired air conditions. In four of these subjects, the PEFR was monitored for an additional 6 min after the exercise was terminated. The PEFR gradually decreased during the first 3 min and then remained constant. We found that the PEFR decreased by 50% in the first 3 min and then remained constant. We conclude that repetitive exercise increases the PEFR and this effect lasts several minutes after the exercise is terminated.

Our objective was to culture airway smooth muscle cells, characterize them morphologically, and develop techniques for testing their responses to pharmacological stimuli. Strips of canine trachealis muscle were treated with purified collagenase and elastase, mechanically dispersed, and incubated on plates for 4-7 days. Yield of viable cells was 1.75 ± 0.5 x 10⁷ (mean±SD, n=11) per gram tissue. By electron microscopic analysis, incubated cells showed basal lamina on the outer face of the plasma membrane, caveolae on the inner surface, and myofilaments in the cytoplasm. When cells were grown on silicone substrata, formed by flaming the surface of dimethylpolysiloxane (60,000 cp), exposure to acetylcholine (10⁻⁷M) produced morphologic changes. We concluded that these techniques were suitable for the pharmacological study of monolayers of cultured airway smooth muscle cells. (Supported by USPHS grant HL-27669 and grants from the Veterans Administration and California Lung Association.)


Substance P (SP) contracts airway smooth muscle, however, the mechanism(s) underlying this response has not been systematically evaluated. To elucidate the mechanism of SP-induced airway contraction, isometric tension developed by rabbit tracheal ring segments placed in modified Krebs-Ringer solution was separately tested to methacholine, SP, and its agonist analog (pGlu',Sar')-SP-(9-11). The TSM response to SP was completely blocked by the SP antagonist D-Pro,D-Trp,D-Trp',SP. These data indicate that (1) SP produces dose-dependent contraction of TSM; (2) the latter is due both to a direct action (i.e. SP receptor binding) on TSM as well as the release of acetylcholine (ACh) and (3) since the response to SP is unaffected by blockade of neural transmission, it is likely that the ACh release occurs at the neuromuscular junction.
10.3 SIMILARITY ANALYSIS OF MAMMALIAN CARDIAC ENERGETICS.  
John K-J. Li. Rutgers University, New Brunswick, NJ 08854.

Considerable interest has in recent decades been centered on the relation between energy requirement of the heart and its pumping performance. Whether this relation holds for all mammalian species has not been examined. To investigate this, pertinent physiological parameters such as mean arterial blood pressure (P), stroke volume (V_s), heart rate (f_h; sec⁻¹), metabolic rate (MR; J/sec), and heart and body weights (W) were selected for the analysis. A new similarity principle was established by the use of allometric equations and the applications of dimensional analysis and Buckingham's π-theorem. The relation is:

$$ I = \frac{EW \cdot f_h}{MR} = 0.013 W^{0.06} $$

where EW (=e-V_s) is the left ventricular external work (J), I, the invariant number, is dimensionless, and is practically independent of mammalian body weights. It thus qualifies as a similarity principle. It can be stated that, in mammals, the external left ventricular work performed per cardiac cycle is normalized by their respective metabolic rates generated in a constant. The significance of the present finding is that mammalian resting heart rate governs the relation between energy generation and cardiac pumping ability.

(Supported in part by the AHA-NJ Affiliate 82-21)

10.5 INTRAFILAMENTAL FLOW DISTRIBUTION AND PLASMA SKIMMING IN THE PERFUSED GILL OF THREE TELEOSTS. Kenneth R. Olson. Indiana University School of Medicine, South Bend Center, Notre Dame IN. 46556

Distribution of flow and red cells between the efferent (epibranchial) and venous pathways was examined with an isolated perfused gill adapted to separately collect the two effluents. Gills from two species (Ictalurids) with abundant prelamellar arteriovenous anastomoses (AVAs) were compared to those of the trout which contain few AVAs. The gills were perfused with Ringer or 125I albuminated Ringer containing 51Cr tagged red cells (blood).

In Ringer perfused gills efferent outflow decreased as efferent pressure increased. Epinephrine prevented the decrease in efferent flow at elevated efferent pressures. In all species around one third of the control blood perfusing the gills drained via the venous pathway. At constant efferent pressure epinephrine increases and acetylcholine decreased efferent outflow. These results suggest that tonic adrenergic stimulation is necessary for normal branchial perfusion.

The hematocrit of efferent effluent was greater than venous effluent in all species. No consistent effects of epinephrine or acetylcholine on plasma skimming were observed. Comparison of measured microhematocrit and hematocrit calculated from 51Cr red cell space and 125I-albumin plasma space show that the red cells in the venous effluent are larger than those from the efferent pathway and support the concept of a nutritive function for the venous pathway. (Supported in part by NSF Grant No. PCM 79-23073. (Supported in part by NIH grant No. NS16655.)

10.4 Distribution of Blood Flow in the Turtle Pseudemys scripta during Progressive Anoxia. 
Timothy B. Bentley, Peter Lutz, Myron Rosenthal and Tom J. Sick. University of Miami, Miami, Florida 33149

The primary response to anoxia in air breathing divers involves the cardiovascular system. This response is well demonstrated in marine mammals where blood flow is confined primarily to the heart and brain during extended dives. Although turtles have a much greater diving capacity nothing is known of the pattern of blood flow during diving in these animals. We hypothesize that turtles show a two stage response to progressive anoxia, the first stage being the maintenance of blood flow to the lungs which function as the primary oxygen store. The second stage occurs when lung oxygen is depleted and the blood flow alters to increase the transfer of substrates necessary for anaerobic energy production. Experiments are being conducted on Pseudemys scripta using three radioactively labelled microspheres which allow determination of control, short term and long term anoxia blood flows. We have found that the GI tract, kidneys and bladder experience reduced blood flow during anoxia while the lungs and brain showed increases in flow. The flow showed an initial decline in flow and then a subsequent rise.

Support for this work was provided by NIH grant No. NS16655.
Hypertrophy seems to have a significant sympathetic component. (Supported by NIH HL-21371 and T50GMKR, Inc.)

Results show that acute and chronic angiotensin II (A-II) induced hypertrophy was reduced by contractility related means. The present study was done to determine whether or not chronic pretreatment with Verapamil (V), Saralasin (S) or Propranolol (P) would prevent the development of A-II and Exercise (E) induced hypertrophy. Eight male adult rats were divided into 4 groups, 2 of which were placed on a chronic exercise regimen (E) of 50% of their aerobic capacity. The remaining 2 groups did not exercise (C). These groups were then subdivided into 2 more groups, 2 of which were placed on chronic pretreatment with either V, S or P. Eight animals from each group were used for each treatment.

Animals were sacrificed, hearts were removed and body weights (BW) and ventricle weights (VW) were obtained. VW/SW ratios and their percent change (%) from control were calculated. In the acute studies the animals were sacrificed 1 hour after treatment. In the chronic studies they were sacrificed at the end of the second week. Animals were then sacrificed, hearts were removed and body weights (BW) and ventricle weights (VW) were obtained. VW/SW ratios and their percent change (%) from control were calculated. In the chronic studies they were sacrificed at the end of the second week.

RESULTS:

In the acute studies, animals treated with P resulted in a significant reduction of the acute hypertrophy induced by either E or P. The acute hypertrophy induced by P was 0% (avg. 27%). Acute exercise hypertrophy was significantly reduced by P and V but not S. However, there was still a large hypertrophy present after the second week. The acute hypertrophy induced by P was 0% and the acute hypertrophy induced by V was 2.7%.

In the chronic studies, animals treated with P resulted in a significant reduction of the chronic hypertrophy induced by either E or P. The chronic hypertrophy induced by P was 0% and the chronic hypertrophy induced by V was 2.7%

In conclusion, the data suggests that chronic treatment with either P or V is effective in preventing the development of A-II and E induced hypertrophy. These results are in agreement with previous studies which have shown that chronic treatment with either P or V is effective in preventing the development of A-II and E induced hypertrophy.

REFERENCES:

1. Pierce, S.K., Edwards, S.C. (1984). Comparative physiology: muscle. Am. J. Physiol., 173:185 (1982). Fiber lengths in the dorsal muscles ranged from 160-226 mm (x = 190 mm). Fiber lengths in the ventral muscles had a larger range (37-185 mm) were shorter (x = 90) and appeared to vary considerably in different regions of the same compartment. The fiber length toward the caudal end were longer than those in the more cranial end in both the ventral and dorsal muscles. Angle of pinnation with respect to the tendon was 15° in most muscles. The dorsal fibers were attached to thin, long tendons in a "net-like" arrangement which eventually converged with the larger tendons near the fluke. In the ventral muscles, some fibers appeared to be arranged in series. These differences may have functional implications with respect to proposed differences in the upward and downward strokes during swimming. (Supported by Naval Ocean System Center N-66001)

DOLPHIN TENDON MATRIX COMPONENTS. M. Russell*, A.C. Vailas*, V.R. Edgerton, C. Saxon*, A. Nokos* and J. Marhage*. University of California, Los Angeles 90024. Virtually nothing is known about the important tendonous structures that are present in the tail of the bottlenose dolphin. To begin to understand the biomechanical efficiency of the swimming dolphin, muscle fiber size and type of the axial musculature was investigated. All tissue samples were taken from a single specimen (~5 years old and 180 kg body weight). "Fast" (F) and "slow" (S) fiber types were identified from frozen sections stained for myosin ATPase. Fiber area and type was determined using an automated image processing system. Generally, both the dorsal and ventral muscles consisted of 50% S and 50% F fibers. One dorsal muscle (extensor caudae medialis) (Strickler, Am. J. Anat. 157:49, 1980) had one region consisting of about 70% S. The caudal end of the dorsal and ventral muscles had about 70% F fibers. Mean cross-sectional area (CSA) of the fibers in the ventral muscles was 46% greater than in the dorsal muscles (1750 vs 1077 um2). The F fibers were 40% (2200 vs 1317 um2) and 30% (1213 vs 879 um2) larger than the S fibers in the ventral and dorsal muscles, respectively. These fiber sizes are smaller than for most terrestrial mammalian muscles. The observation that the ventral muscles had larger and shorter fibers (Roy, et al., Physiological, 1983) suggests that they are specifically designed for force production. In unnatural, the dorsal muscles are designed to optimize velocity and displacement. (Supported by Naval Ocean System Center N-66001)
15.1 Ca²⁺ as Modulator of Gastric Secretion and Vesicular H⁺/K⁺ ATPase

Fabioz Michelangeli and Marie Christine Ruize


The involvement of Ca²⁺ as second messenger in stimulus-secretion coupling has been demonstrated in isolated amphibian (IA) and mammalian stomachs (m.s.m.).

1. Identification of Ca²⁺ as messenger: Artificial increase in Ca²⁺ levels by means of Ca²⁺-releasing reagents (dissociation of H⁺ secretion and histamine release). A23187 acts directly on oxyntic cells, but parallel action of histamine is required for full Ca²⁺ effect. Increasing Mg²⁺ concentration above 5 mM reduces the effect.

2. Mechanisms: although secretogogues release Ca²⁺ as evidenced by chro-

tracine fluorescence and disappearance of mitochondrial de-

posits (M.I.O), ACh and A23187 also require Ca²⁺ for their ac-

tion. It appears that Ca²⁺ entry is required in cholinergic and A23187 stimulation. An equilibrium is reached between free-

Ca²⁺ in the cytoplasm and the intracellular content.

3. Conclusions: oxyntic cells are rich in actin; association of f-actin

revealing filamentous actin. SDS gels of residual "ghost" pro-

teins show a characteristic protein pattern: a la the recycling hypothesis. (Support by USPHS #AM10141.)

15.2 Conformational Changes in (K⁺+H⁺)-ATPase

S. L. Boninge, J. S. Schrijen, M. L. Helmich-de Jong and J. J. B. M. de Pont

Department of Biochemistry, University of Nijmegen, Nijmegen, The Netherlands

Mg²⁺ and K⁺ have several effects on (K⁺+H⁺)-ATPase.

Previously it has been shown that the concentration of (K⁺+H⁺)+ATPase. activity increases with the pH, which can be interpreted as a K⁺+H⁺-ATPase (pH 5.5), binds to the enzyme. This leads to an enhancement of enzyme activity. The ATPase activity of this enzyme, which is a competitive inhibitor of (K⁺+H⁺)-ATPase at pH 7.4, is increased by Mg²⁺, while K⁺ and ATP lower the fluorescence level. At low pH, more Mg²⁺ is required for full effectiveness.

These findings suggest Mg²⁺ as an activator of Mg²⁺-promote d K⁺+H⁺ antagonism. This indicates that two modes of enzyme activity that differ in their mechanisms of action, may be present in the enzyme. These findings also suggest specific conformational changes of the enzyme.

15.3 Distribution of Microfilament-Related Protein in the Gastric Epithelium and Isolated Membrane Vesicles

T. M. Forte

Department of Biochemistry, University of Nijmegen, Nijmegen, The Netherlands

Microfilament formation has been implicated in membrane transfor-
mations that accompany the secretory cycle of the oxyntic cell. Whole mucosal scrapings (rabbit, pig) contained 29-30 µg actin/mg prot., and isolated gastric glands (rabbits) contained 42 µg actin/mg prot. Previously, we have shown that the rate of inactivation by buta-

nol and DMSO, agents which modify arginine and sulphydryl groups respectively, is affected by these ions. The level of binding of the air mixing and also Mg²⁺ induce specific conformational states of the enzyme.

15.4 Light Dependent Labelling of the Active Site of Gastric ATPase with 8-azido ATP

S. C. Benedict and E. M. Marquart

(Sponsor: J. I. Forte.) Univ Alabama in Birmingham, 803, AL

Phosphorylation labelling of purified hog gastric (H⁺+K⁺)-ATPase with 8-azido ATP has allowed the determination of reaction conditions for labelling of ATP by ATP. The formation of a phosphoprotein complex with ATP has been shown to occur in the region of pH 7.4 and at 24°C. The level of ATP binding is maximal at pH 7.4, and also Mg²⁺ that ions which are transported by the enzyme. This indicates that Mg²⁺ is involved in the transport mechanism.

15.5 Distribution of Microfilament-Related Protein in the Gastric Epithelium and Isolated Membrane Vesicles

T. M. Forte

J. M. Volaitis* and J. C. Forte, Dept. of Physiology-Anatomy, Univ. of California, Berkeley, CA 94720.

Microfilaments have been implicated in membrane transfor-
mations that accompany the secretory cycle of the oxyntic cell. Whole mucosal scrapings (rabbit, pig) contained 29-30 µg actin/mg prot., and isolated gastric glands (rabbits) contained 42 µg actin/mg prot. Previously, we have shown that the rate of inactivation by buta-

nol and DMSO, agents which modify arginine and sulphydryl groups respectively, is affected by these ions. The level of binding of the air mixing and also Mg²⁺ induce specific conformational states of the enzyme.

15.6 Microtubular Function in Secretion of H⁺ and Pepsinogen by Gastric Mucosa

Dinkar K. Kasbekar, Dept. of Physiology, Georgetown Univ., Washington, D.C. 20007.

Previously we have shown that choleraic (10 mM) and vinblastine (1 mM) depolymerize microtubules in vivo in frog gastric mucosal preparations. Because of the possible nonspecific effects of these agents at relatively high concentrations, we have attempted to characterize the distribution of microtubules in oxyntic and chief cells of the rabbit gastric fundic glands in their resting and stimu-

lated states. The dispersed glands were incubated under appro-

priate conditions with 13C3,14C-adsorbed carbon monoxide to stimulate H⁺ secretion, c) 10 mM chlordiaxin 5% octap-tide (CCK-8) to stimulate pepsinogen secretion, and d) 1 mM butyric acid, an H₂ antagonist and 1 mM dibutyryl cyclic GMP, to stimulate H⁺ secretion, c) 10 mM chlordiaxin 5% octap-tide (CCK-8) to stimulate pepsinogen secretion, and d) 1 mM butyric acid, an H₂ antagonist and 1 mM dibutyryl cyclic GMP, to stimulate H⁺ secretion, c) 10 mM chlordiaxin 5% octap-tide (CCK-8) to stimulate pepsinogen secretion, and d) 1 mM butyric acid, an H₂ antagonist and 1 mM dibutyryl cyclic GMP, to stimulate H⁺ secretion.

\[ \text{Na}^+ / \text{H}^+ \text{ exchange appears to play a central role in the ventialtory transport of } \text{H}^+ \text{ in the mammalian proximal tubule. We examined the sodium distribution of Na}^+ / \text{H}^+ \text{ exchanger using the cloride }
\]

orange assay in fractions obtained from sucrose density gradient.

fractionation of membranes from the rabbit renal cortex. Na}^+ / \text{H}^+ \text{ antipporter activity was confined to membranes co-migrating with brush border membranes and was absent from homogenates of renal medullary membranes. Further fractionation of brush border membranes by counter current distribution with polyethylene glycol was revealed 2 distinct populations of Na}^+ / \text{H}^+ \text{ activity: one associated with the kidney observed in chronic metabolic acidosis and in states of altered parathyroid function might result from altered Na}^+ / \text{H}^+ \text{ exchange across the renal cortical cellular brush border membrane.}

The Na}^+ / \text{H}^+ \text{ antipporter has at least one modifier site, which could be a site for physiological regulation. (Supported by NIH grants AM 07129, AM 28408, AM 19407, AM 00068.)}


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The Na}^+ / \text{H}^+ \text{ antipporter has at least one modifier site, which could be a site for physiological regulation. (Supported by NIH grants AM 07129, AM 28408, AM 19407, AM 00068.)}

15.9 RENAL FAILURE, METABOLIC ACIDOSIS AND PARATHYROIDECTOMY: INCREASE Na+/H+ EXCHANGE IN ISOLATED RENAL BRUSH BORDER MEMBRANE VESICLES. M. H. Hammers, S. Klar, and D. E. Cohn*. Washington Univ. School of Medicine, St. Louis, MO 63110.

\[ \text{We have identified an amiloride inhibitable Na}^+ / \text{H}^+ \text{ exchange in canine renal brush border membrane vesicles (BBMV). The activity of this exchanger was found to be increased in BBMV from kidney of dogs with chronic renal failure (CRF). Na}^+ / \text{H}^+ \text{ exchange in BBMV increased progressively as plasma creatinine increased. In order to ascertain whether changes in H+ excretion by the kidney observed in chronic metabolic acidosis and in states of altered parathyroid function might result from altered Na}^+ / \text{H}^+ \text{ exchange across the renal cortical cellular brush border membrane, we measured Na}^+ / \text{H}^+ \text{ exchange in BBMV from kidneys of dogs with chronic metabolic acidosis and from kidneys of chyapotatispharmacidesimized dogs. Increased initial rates (208) of amiloride sensitive JH }^+ \text{ uptake measured under blocker gradient conditions (intravesicular } \text{pH} < \text{extravesicular pH) were demonstrated in BBMV from kidneys of both acidic (1.54 ± 0.18 nmo1/mg protein) and hypoparathyroid (1.78 ± 0.20 nmo1/mg) dogs (p<0.05, both experimental groups) normal. These findings suggested that adaptations in H+ excretion in chronic metabolic acidosis and hyperparathyroidism might be explained by increased activity of a renal brush border membrane Na}^+ / \text{H}^+ \text{ exchanger. The adaptation in LR may result from the need to excrete more H+ per nephron. (Supported by NHX 30318B7600.)}


\[ \text{Clathrin-coated vesicles harvested from bovine brain catalyze ATP-driven proton translocation, as measured by acidine orange (A.O.) quenching and } ^{3} \text{H-P-ATP exchange. Both activities were insensitive to inhibitors tested and were inhibited by N-ethylmaleimide (NEM) 1 mM. The preparation was devoid of the lysosomal marker 5' nucleotidase (5'N) and ATP-driven A.O. quenching was precipitated by monocolonal anti-clathrin antibody. Chloride and bromide, but not fluoride, sulfate, phosphate, or gluconate, were effective in counterbalancing electrogenic proton pumping.}

\[ ^{3} \text{HCl uptake, driven by a K gradient } [\text{K}]_{i} / [\text{K}]_{o} = [40 \text{mM}] / (0 \text{ mni}) \text{ in the presence of valinomycin, SBB completely inhibited by DIDS (1x 10^{-5} \text{M}) and duramycin (1x 10^{-5} \text{M}) protein. Kidney vesicles, prepared by different centrifugation and passage through a sucrose gradient, were enriched in oligomycin-sensitive ATP-generated A.O. quenching and were devoid of 5'N nucleotidase activity (pH 5.0). The kidney proton pump is not distinguishable from the brain-coated vesicle proton pump with respect to inhibitor sensitivity, substrate dependence, cofactor requirement, or dependence upon chloride or bromide as effective counterions. Moreover, the kidney vesicles catalyze } ^{3} \text{H-P-ATP exchange and contain a DIDS and duramycin sensitive } ^{3} \text{HCl transporter, which is responsible for counter-ion movement.}

15.11 A BIOCHEMICAL EVALUATION OF RABBIT RENAL DCCD-SENSITIVE ATPase ACTIVITIES. Diana Marver. UTHSCD, Dallas, TX 75235.

\[ \text{A biochemical evaluation of rabbit renal DCCD-sensitive ATPase activities is presented. The enzyme activity was determined in intact adrenergically stimulated and glucocorticoid}.

\[ \text{supplemented preparations. Y}

\[ \text{increasing V and 2) the increase is dependent upon an}

\[ \text{initiated reaction. However, when the assay contained }

\[ \text{titrates several H+ translocating enzymes with varying physio-}

\[ \text{logical functions, initial studies will attempt to correlate}

\[ \text{the distribution of Na}^+ / \text{H}^+ \text{ ATPase activity with function in a given segment. Thus the }

\[ \text{putative Na}^+ / \text{H}^+ \text{ ATPase activities will be compared with resident NaK ATPase, carbonic anhydrase, acid phosphatase, G6PDH and NEM-sens. ATPase, as well as nullified for steriod-dependence.}

\[ \text{To initiate these experiments, assays were performed on pla-}

\[ \text{permembrane fractions from cortex, outer and inner medulla (C,OM,IM) from 6 normal rabbits, DCCD-sens. ATPase activity (pH 6.8, 37 C) was measured in the presence of 0.1535g/ml AMP (pH 7.4), 0.0066g/ml of 0.28% PI mg/ml in C, OM and IM, resp. or 46, 62 and 34% of the total oligomycin-inhibitable (+ vanadate)-insensitive activity in cortical, outer medullary and IM tissue, NEM inhibited 20, 9 and 24% of the total ATPase activity. Thus a major discrepancy appeared in the relative NEM/DCCD sens. In OM, suggesting some variation in the order of the probes or the number of sites titrated in each case. Of note was that NEM-sens. act. in OM was equivalent at both 100 and 500 mM conc. Studies are currently underway to evaluate these differences at the isolated nephron level. (Supported by AM 14677.)

15.12 TRANSPORT IN ISOLATED GASTRIC AND RENAL MEMBRANE VESICLES. Sunday PM

Inorganic and organic amino acids are observed. Supported in part by NSF grant PCM 82-08185 and DOC grant NOAA 04-8-MOl-89.

...unusually high concentrations of serine (50-1000 μM) was observed. The results indicate that the inorganic amino acids are a major source of serine for anabolic processes. Supported in part by NSF grant PCM 82-08185 and DOC grant NOAA 04-8-MOl-89.

...of the FAA transport system to experimental manipulation of the FAA pool. Exposure of larvae to 50 or 250 pM serine for four hours produces a 14-22 fold increase in FAA concentration. More prolonged exposure leads to labeled FAA, indicating that the uptake mechanism is saturable. The entry rate of labeled FAA appears to decrease, corrected for the increases in FAA concentration produced by this leakage indicates there is no compensatory change in FAA fluxes. No leakage of amino acids occurs as observed in pigs by NSF grant PMC 82-08185 and DOC grant NOAA 04-8-MOl-89.

16.2 SEASONAL WATER AND ELECTROLYTE BALANCE IN FREE-LIVING PAI SAND RATS. A.A. Degen*, B. Pinshaw & M. Ilan*. Blaustein Institute for Desert Research, Ben-Gurion University, 84990 Sede Boqer Campus, Israel.

...part of this study was to determine the effects of season on water and electrolyte balance in free-living sand rats. Supported by NSF grant PCM 79-21885 and U.S.-Israel BHE grant 249/81.
16.7 ENERGETICS OF THE HIGH ARCTIC SPITZBERGEN PTARMIGAN
A. Marienrode and J. S. Blix. Dept. of Arctic Biology, Univ. of Tromso, Tromso, Norway.

The winter at the high arctic archipelago of Svalbard (79-81°N) is characterized by low ambient temperatures, three months of darkness and poor food quality and availability. The Spitzbergen ptarmigan, a native galliform at this location, accumulates large amounts of fat during late summer and fall. The fat stores enable the bird to survive periods of acute starvation during midwinter, and also give a minor contribution to the daily energy consumption until March, when the fat stores are exhausted. In the period of fat combustion the food intake is voluntarily reduced, but this partial anoxia is accompanied by a reduction in daily energy expenditure, which for a period approaches the resting metabolic rate. During winter resting metabolic rate is reduced by about 10% and insulation increased by about 30% compared to summer, leaving the lower critical temperature unchanged (-5°C). Fasting of hirunks in the fall leads to a small (7%) decrease in resting metabolic rate whereas no effect is seen in mid-winter. In birds in the fall leads to a small (7%) decrease in resting metabolic rate whereas no effect is seen in mid-winter. In

16.8 BRAIN COOLING IN DEHYDRATED HUMAN EGGS, E. Arab* and A. M. Midgley* (SPON: M. H. Bernstein). Univ. of Copenhagen, Denmark.

Body (Tb) and hypothalamic (Th) temperatures were measured in heat exposed eggs during the embryonic period, and dehydration (D). The body-to-brain temperature difference (ΔT = Tb - Th) decreased from 0.68 ± 0.38°C (mean ± SD) during NH (0.79) to Tb during NE (0.79) was significantly lower than unity (p < 0.001) indicating increased brain cooling with increasing Th. The slope during D (0.96) was significantly higher (p < 0.02) and did not differ from unity. The dehydrated eggs were characterized by significantly higher plasma osmolality and sodium and chloride concentrations (p < 0.001). The ΔT was significantly correlated (p < 0.02) with the heat exchange area of the rete ophthalmicum. It is speculated that the relationship may be represented by the equation ΔT = k(Th - Tb) + C, where k is the heat exchange coefficient, Th is the thermal resistance of the rete ophthalmicum and C is the heat storage capacity. The rete ophthalmicum is the major area of thermal exchange in the eye, and its contribution to the overall heat loss is significant.
17.3 RELAXIN STUDIES: RADIOIMMUNOASSAY OF RELAXIN ACTIVITY IN EQUINE CORPORA LUTEA (CL)

In vitro exposure to ethanol (EtOH) unmasks LH binding sites in luteal tissue. After 6 days of treatment (1.5 ± 0.2, n = 5) with EtOH, the LH binding capacity increased to 3.1 ± 0.5 (p < 0.05) after 6 days (2.4 ± 0.5, n = 3) and 10 days (1.7 ± 0.8, n = 3) of treatment, consistent with elevated LH receptor levels. In contrast, EtOH increased basal adenylate cyclase (AC) activity 5-fold, indicating increased sensitivity to LH. The dissociation constant (Kd) for CG binding was decreased by 50% after 6 days (3.8 ± 0.2 vs 1.4 ± 0.1 pmol CG/10 min/mg tissue), the presence of 0.8 EtOH abolished the stimulation of AC by CG. In conclusion, EtOH does not mask LH binding sites in corpus lutea of pseudopregnant rats. However, EtOH stimulates AC activity and unblocks CG binding sites in rat luteal membranes. These findings suggest that the gonadotropin receptor system and/or membrane characteristics differ between the primate and rodent CL.

17.5 AVAILABILITY OF HUMAN CHORIONIC Gonadotropin (hCG) IN THE PRIMATE Corpus Luteum (CL) DURING EARLY PREGNANCY

Sundaram, T. J., and J. S. Stouffer. Univ. of Arizona, Tucson, AZ 85724

The spontaneous prolonged corpus luteum (SPCL) syndrome is a common reproductive problem in mares contributing significantly to lowered rates of conception. The cause of this syndrome is as yet unknown. The objective of this study was to compare the PGF2α synthetizing capability of the endometrium from mares experiencing the SPCL syndrome with endometrial tissue obtained during different stages of the normal estrous cycle. Uterine biopsies were obtained after 30 days postovulatory diestrus behavior from 10 mares experiencing the SPCL syndrome. Prolonged luteal activity was verified by daily plasma progesterone concentrations. Uterine biopsies were taken on days 5, 10, 12, 14, 16, and 20 postovulation. PGF2α, syntheses capabilities was low during the early stages of estrus (3.3 ± 0.9, 4.4 ± 1.1, 17.2 ± 2.7, and 17.5 ± 3.5 pg PGF2α/mg dry wt) and returned to minimal concentrations by day 20 (0.3 ± 0.0 pg PGF2α/mg dry wt). Endometrial PGF2α synthetizing capabilities during SPCL syndrome were the same as those observed during early diestrus and estrus (4.4 ± 0.3, 4.0 ± 0.3 pg PGF2α/mg dry wt). It is concluded that a causative factor to the SPCL in the mare is the failure of the synthesis and release of PGF2α from the endometrium normally occurring during late diestrus.

17.6 THYROID-CONAD RELATIONSHIP IN BRONCHIAL ASTHMA


The spontaneous prolonged corpus luteum (SPCL) syndrome is as yet unknown. The objective of this study was to compare the PGF2α synthetizing capability of the endometrium from mares experiencing the SPCL syndrome with endometrial tissue obtained during different stages of the normal estrous cycle. Uterine biopsies were obtained after 30 days postovulatory diestrus behavior from 10 mares experiencing the SPCL syndrome. Prolonged luteal activity was verified by daily plasma progesterone concentrations. Uterine biopsies were taken on days 5, 10, 12, 14, 16, and 20 postovulation. PGF2α, syntheses capabilities was low during the early stages of estrus (3.3 ± 0.9, 4.4 ± 1.1, 17.2 ± 2.7, and 17.5 ± 3.5 pg PGF2α/mg dry wt) and returned to minimal concentrations by day 20 (0.3 ± 0.0 pg PGF2α/mg dry wt). Endometrial PGF2α synthetizing capabilities during SPCL syndrome were the same as those observed during early diestrus and estrus (4.4 ± 0.3, 4.0 ± 0.3 pg PGF2α/mg dry wt). It is concluded that a causative factor to the SPCL in the mare is the failure of the synthesis and release of PGF2α from the endometrium normally occurring during late diestrus.

17.7 PURIFICATION OF EQUINE RELAXIN

Daveis, R. S., and Stouffer, G. H. Stakenfeldt.

Equine relaxin was previously been shown to be produced in the pregnant ruminant (Stakenfeldt, H. W. 1965). Plasma relaxins were collected at term and stored frozen. Placental material was extracted following the procedures of Schwed and O'Ryan for porcine relaxin (1971). Through acid acetone extraction, gel filtration, and ion exchange chromatography, the purified relaxin was isolated and characterized. The peaks eluted from the ion exchange chromatography that contained high amounts of immunoactivity. Each of these three peaks was demonstrated to contain hialinogenic activity by the cell free hormone system of the castrated primate. Supported by a grant from the Grayson Foundation.
17.9
The Effect Of ContraSperm™ On Sperm Count And Motility Of Primates And Humans.
M.F. Nassar* and T. T. Tierney* (Spon: C. F. Nassar).
Rational Alternative Corporation, P.O. Box 2547, Mission Viejo, California, 92690, U.S.A.

Echelaterin™, the active ingredient of ContraSperm™, is a unique, sophisticated preparation extract of the plant Echallium alatum. It is a complex mixture of organic and inorganic compounds, and has been shown to inhibit sperm motility and sperm count in vitro and in vivo. In a previous study, the effectiveness of Echelaterin™ was demonstrated in reducing sperm count and motility in a variety of primate species, including primates and humans.

17.11
GLUTAMATE DEHYDROGENASE ACTIVITY IN RAT VENTRAL PROSTATE.
Bent A. Franklin and Leslie C. Costello. University of Maryland, Baltimore, MD 21201

We have proposed that aspartate transamination is an important source of acetyl coA and aspartate. Results demonstrated that prostate mitochondria in a reaction mixture which was essentially the same as the assay system with the addition of acetyl coA and aspartate, in the presence of substrate (reverse reaction) the kidney preparation was more than 3 times more active than prostate. We also incubated prostate mitochondria in a reaction mixture which was the same as the assay system with the addition of acetyl coA and aspartate. Results demonstrated that prostate mitochondria could synthesize citrate from aspartate and glutamate at pH 7.4 at a rate of 6 nmoles/mg pr/min. These results demonstrate the presence of GDH activity in prostate mitochondria. Furthermore, they demonstrate that prostate mitochondria can accumulate citrate from amino acids, in the presence of acetyl coA. Supported by NIH grants AM38015 and HD16193.

17.12
TESTOSTERONE EFFECTS ON CITRATE OXIDATION BY RAT VENTRAL PROSTATE.
Myong W. Kahng*, V. Akuffo*, R. B. Franklin and L. C. Costello. Univ. of Maryland, Baltimore, MD 21201

The metabolic mechanism(s) which results in the accumulation and secretion of extraordinarily high levels of citrate by the prostate has not been elucidated. It has been shown that testosterone regulates prostate citrate secretion needs to be established. In previous studies we demonstrated that citrate oxidation by mitochondria isolated from rat ventral prostate was very low due to a limited aminotransferase activity. The present report is an extension of the earlier studies and shows that testosterone increases the ability of rat prostates to oxidize citrate. The results of these studies and also demonstrate the effect of testosterone on citrate oxidation. Citrate oxidation was determined by C-14O2 production from C-14citrate, and citrate utilization was determined as the total appearance of C-14citrate (72 hour) resulting in a decrease (30-45%) citrate oxidation and utilization by rat ventral prostate mitochondria as compared to sham animals. Similarly citrate oxidation by ventral prostate fragments was decreased by castration. The administration of testosterone to castrated rats (1 mg per day for 24 hours) stimulated citrate oxidation and utilization back to normal levels. This effect of testosterone would have a tendency to decrease citrate levels by increasing citrate oxidation which is contrary to the action of testosterone which increases prostate citrate levels and secretion. These results indicate that the regulation of citrate production by testosterone is not mediated via an effect on citrate oxidation by prostate. Supported by NIH grants AM38015 and HD16193.

18.1
CIRCADIAN RESPONSES OF MAMMALS TO THE HYPERDYNAMIC ENVIRONMENT.
Charles A. Fuller, David W. Griffin* and Joseph M. Horowitz. Div. Biomedical Sci., Univ. of California, Riverside, CA 92271 and Dept. Animal Physiol., Univ. of California, Davis, CA 95616.

Mammals demonstrate depression of deep body temperature in hyperdynamic environments. However, the influence of circadian body temperature rhythms on this response has not previously been investigated. The present study examined such day of day influences of acute exposure to 2G. Circadian colonic temperatures were measured in eight monkeys and eight rhesus and exposed to 70 min of 2G. centripetalization at two times during the day, with a minimum of four recovery days between exposures. The order of exposure was reversed for half of each group of animals. During the 70 min control periods prior to centrifugation, all groups demonstrated stable body temperature rhythms. At 2G, during the daily, the diurnal monkeys showed a 1-2°C fall in colonic temperature to about 37.5°C. During the night, body temperature did not change and was regulated at about 36.5°C. The nocturnal monkeys showed a reverse response. At 2G, during the day, colonic temperature was depressed 1-2°C to about 36.5°C. At night, these animals showed an average temperature depression of 2.5°C to about 34.9°C. Thus, there are clear circadian differences in response to the hyperdynamic environment, with the greatest fall in temperature during the animals' active phase. Further, the animals clearly have some ability to regulate temperature as demonstrated by the capacity to minimize the changes in body temperature during their resting phase. (Supported by NASA Grants NAGW-399, NSG-2234 and PHS Grant BSR 85-503816).

18.2
ACID-BASE STATUS DURING SHORT-TERM IMMOBILIZATION IN MONKEYS (M. NEMESTRINA). D. R. Young and R. S. Swenson. Ames Research Center, Moffett Field, CA 94035

In an earlier study of the effect of chronic immobilization with monkeys, we observed an increased net acid excretion (NAX) largely due to a sustained rise in ammonium production. Within 2-3 weeks, arterial pH and bicarbonate increased approximately 1%, and the stable alkalosis persisted throughout the 12 weeks of confinement. Potential causes of immobilization-associated alkalosis in primates include mineralocorticoid excess, potassium depletion, and reduction of blood volume. The early responses to immobilization were studied in order to elaborate mechanisms which can stimulate aldosterone production. Adult male animals were restrained on 4 days, plasma aldosterone rose significantly and urine aldosterone was elevated throughout the 4 days. Hypokalemia occurred as a result of mineralocorticoid excess and hypochloremia. Urine titratable acidity (TA) increased significantly along with endogenous phosphate excretion. NAX was significantly elevated. Venous pH was relatively unaffected. We conclude that hypokalemia and hypochloremia promote the rise in aldosterone production. Renal ammoniagenesis occurs as a result of a decreased urinary citrate excretion and hypokalemia, although there may be a delay of 2-3 weeks prior to the expression of the response in immobilized animals.
18.3

**SPACELAB-4: THE FIRST SMALL MISSION DEDICATED TO LIFE SCIENCES**

Research Center, Moffett Field, CA 94035

In early 1986, NASA will launch Spacelab Mission 4, the first mission dedicated to the Life Sciences. This mission will carry 14 nonhuman and 10 human investigations proposed from an international group of investigators. The Life Sciences Experiment Facility (LSFE) at NASA-Ames Research Center is being expanded, and it will implement Spacelab nonhuman Life Sciences investigations. The Spacelab-4 investigators, defining physiological responses to spaceflight, have found that the average Hct was 68%. The increased blood viscosity of severe polycythemia aggravates the pulmonary circulation. This increases hypoxia due to increased pulmonary vascular resistance. The arterial hypertension causing severe RVH and in some cases RH failure, supported by NIH HL28849 and HL06527.

18.4

**FACTORS AFFECTING ATROPHY OF LOAD BEARING MUSCLES OF RATS IN SIMULATED WEIGHTLESSNESS**

Herbert S. Glossoz* and Emily Morey-Bolton** (SPONSOR: J. Oyama). NASA Ames Research Center, Moffett Field, CA 94035

We have previously shown that unloading of hind limbs by suspension leads to selective atrophy and decrease in the rate of protein synthesis of the soleus muscle. The present study was initiated to determine the effects on the respiratory capacity of mitochondria in the atrophying muscle. We have found that the role of high circulating GLUT-1 in severe pulmonary hypertension induced muscle atrophy. The hind limbs of Sprague-Dawley rats, 150-200 grams made non-weight-bearing with a modified Metyzor cat model (Kleidinc 20:168, 1979). Mitochondria from soleus, EIM, and muscle were isolated to determine volume reduction; thermoregulation, mitochondrial volume, and rotation. The Effect of NIH Grant HL 14985 and US Army. Research Institute of Environmental Medicine, Natick, MA 01760.

An experimental treatment (Tr) of either 300 mg AZ (E group, n=7; young men) or placebo (C group, n=6) was given b.i.d. for 2 days before and throughout the 3 days after ascent to study the effect of AZ and HA on resting arterialized venous pH, endurance time to exhaustion at 90% of cycling VO2 max, and at that altitude-Tr comparison. Subjects performed a maximal exercise test and then rested for 10 min before the test. Thus the combination of hypocapnia plus non-weightbearing led to selective atrophy and decrease in muscle mass. We found that arterial PO2 of 30 Torr and pH 7.7 are still adequate for aerobic metabolism, resembling chronic mountain sickness. In the cat, arterial PO2 of 50 Torr and pH 7.7 were adequate for aerobic metabolism, resembling chronic mountain sickness. In the cat, arterial PO2 of 50 Torr and pH 7.7 were adequate for aerobic metabolism, resembling chronic mountain sickness. In the cat, arterial PO2 of 50 Torr and pH 7.7 were adequate for aerobic metabolism.
18.9

VENTILATION AND O2 CONSUMPTION IN HYPOXIA AND COLD-ACCLIMATED GUINEA PIGS. L.J. Blake*, S.R. Kayar and N. Banchero. Univ. of Colorado School of Medicine, Denver, CO 80262

Cold-acclimated mammals require greater amounts of O2 to meet the increased metabolic demands for maintenance of body temperature. The O2 requirements of hypoxia-acclimated mammals with similar metabolic needs to those at low altitude must be met under conditions of reduced O2 availability. To determine the effects of acclimation, we measured O2 consumption (VO2), tidal volume (VT), and breathing frequency (f) in cold- and hypoxia-acclimated guinea pigs (GP). Growing males maintained in cold (5°C, ambient P02=133 torr) for 8 weeks, hypobaric hypoxia (26°C, ambient P02=90 torr) for 11 weeks, and in Denver (22°C, ambient P02=133 torr) were placed awake and unrestrained in a transparent chamber. Gas flow rate through this chamber was 1.2 L/min. After 30 min, resting VO2 was determined by measuring the fall in O2 concentration between inlet and outlet. The chamber was then closed to serve as a plethysmograph and oscillations in pressure were recorded from which f and VT were obtained. In cold GP, VT was 28% greater and f was 46% greater than in controls. In hypoxic GP, VT was 40% greater and f was 15% greater than in controls. Thus, minute ventilation (VE) was 100% greater in the cold-acclimated animals and 60% greater in hypoxia-acclimated animals. The relation between VT and VO2 was parabolic, with VO2 increasing rapidly at VT values above 50 ml/kg/hr. Some GP showed increased VT and a concomitant increase in VO2 which appeared due to restlessness and not environmental stress. NIH HL00449

18.10


Only a few people have succeeded to climb Mt. Everest (altitude, 8848 m) breathing ambient air (inspired P02 about 42 torr), and maximum exercise is restricted to low levels at this altitude. In contrast, birds have been reported to fly or soar well above 10,000 m. We have estimated the significance of lung structure for the apparent higher altitude tolerance of birds compared with man, as the avian parabronchial lung, due to its cross-current arrangement, is known to have a higher gas exchange efficiency than the alveolar lung. For this, we have calculated the change in the inspired-to-arterial P02 difference that would occur in man upon replacement of his alveolar lung by a cross-current parabronchial lung, keeping all other pulmonary parameters (e.g., Q, uptake, ventilation, blood flow, diffusing capacity) unchanged. The results show that, for unaltered arterial P02, inspired P02 with the avian lung can be 5 Torr lower than with the mammalian lung, which corresponds to a gain in altitude of about 800 m. Lung structure thus plays an important role in the high altitude tolerance of birds. However, since birds appear to tolerate an even higher altitude, other factors that enable birds to endure the extreme altitude are expected to be involved as well.

18.11

EFFECT OF INDOOR/OUTDOOR INVASION ON THE KINETICS OF NITROGEN WASHOUT IN RATS. Gary W. Mack* and Y.C. Lin. Department of Physiology, University of Hawaii, Honolulu, HI 96822.

In a perfusion limited model for inert gas exchange, the rate of tissue perfusion and the partition coefficient of the gas. Unanesthetized male rats previously prepared for determination of cardiac output (Q) by thermodilution, femoral artery blood and venous infusion were given saline (day 1) or isoproterenol (1.7 μg/kg/min, day 2) at a rate of 0.003 m/s/min during a two hour isotopic washout with 100% O2 at 1 ATA. Whole body nitrogen washout kinetics were determined and three rate constants were calculated and labeled by order of extraction as: K1=slow, K2=medium and K3=fast. Q increased from 350 ml/min/kg during saline infusion to 550 ml/min/kg with isoproterenol. When K3 is plotted against Q one obtains a straight line with a slope of zero. K1 vs Q shows an initial linear increase with Q as predicted by the equilibration phase. K1 but at higher flow rates the plot shows a steep exponential rise in K1. These results suggest that perfusion limitations to nitrogen washout reside primarily in the slower tissues but at higher flow rates other factors begin to influence significantly the half-times for desaturation. (Supported in part by Hawaii Heart Assoc.).

18.12

AUXILIARY COOLING: A COMPARISON OF VARIOUS METHODS IN HOT/DRY CLIMATE. Y. Epstein, Y. Shapiro*, S. Briel, D. Zakai. Weizmann Institute of Medical Research, Chaim Sheba Medical Center, Israel.

The physiological hazard involved in elevated body temperature and the reduction in performance urged the seeking of a proper solution for an efficient external cooling system. Since total air conditioning is usually unfeasible, mainly because of power considerations, individual cooling is the most practical solution to alleviate heat stress problems. Individual cooling includes gas, liquid, or ice cooled systems, covering the entire body or a limited segment, usually head or torso. Seven different cooling devises were compared under the same hot/humid climatic conditions (50°F, 90% RH). Using the Latin-square routine, 8 male subjects tested water/air cooled garments (vests and hoods), ice-bags, vest, some cooling and a fan for their beneficial effect on physiological parameters. The strain index (SI) of Craig (SIM/HR/100°b.*SK) was used in order to evaluate the physiological status of the subjects. Cooling the torso was found to be more effective than cooling the head. Systems based on cooled air resulted in similar physiological impact as systems based on circulated water. In spite of their lower cooling capacity, subjective sensation of comfort was found to be highly correlated to the physiological strain index (r=0.61, p<0.001). It is suggested that the SI might serve as a useful tool to compare different physiological stressful situations.

Sinai Med. Ctr., Miami Beach, FL 33180

Movement of a surface foam plate immersed with surface inductive plethysmography (SIP) reflects changes of intra-pleural pressure (Ppl). Compliance (C) may be calculated from the slope of a step function to SIP gain in response to changes in new position. We used this on-line recalibration of SIP which would be necessary by a time consuming Null Procedure (Tobin, JAP, in press). We studied 4 seated COPD patients and found in simultaneous 4 channels, the slope was increased. In 6 COPD patients, tidal breathing calibration did not change. Furthermore, recalibration of SIP was sensitive to changes during neck position.


High-frequency oscillations (HFO) used as a ventilatory aid are generally applied at a single discrete frequency, which is chosen empirically. We sought to compare the relative efficiency of HFO as opposing volumes and the ability of this device as forcing functions during HFO. Oscillations were applied to anesthetized, paralyzed dogs either directly to the trachea via a loudspeaker or to the chest-wall by a shaker. The driving input was either sinusoidal (15 Hz) or band-pass filtered (5-50 Hz) noise reflecting the admittance characteristics of the canine respiratory system. Results: oscillations were delivered to the lung by a Millar catheter pressure transducer, and was related to the area under a modified 3-min nitrogen washout curve (Clarke et al., Fed Proc 42:1351, 1983). The results for both internally and externally applied oscillations matched tracheal RMS powers resulted in similar washouts regardless of the nature of the exciting force, even though the power at 15 Hz was 250 times lower during noise application than during 15 Hz sinusoidal oscillation.

(Supported by NIMHD Work Unit NMS097M0150.0009.)


CVRI, UCSF, San Francisco, Calif. 94143.

To determine whether endogenous and exogenous inflammatory mediators cause mucus secretion, we studied the release of 35SO4-labeled macromolecules from ferret tracheas in the presence or absence of indomethacin, an inhibitor of prostaglandin synthesis or in the presence of histamine or prostaglandins F2, P2, and D2. We excited tracheas from ferrets anesthetized with pentobarbital sodium (50-60 mg/kg i.p.). Half the tracheas were placed in medium M199/Earle's salt solution and half in medium containing indomethacin (100 µM) for the duration of the experiment. We mounted pieces of the anterior portion of the trachea in Ussing chambers filled with 5 ml medium equilibrated with 95% O2/5% CO2. We exposed the submucosal surface of each tissue to 0.167 M Na2SO4 throughout the experiment. We measured nonradioactive 35SO4 released into the luminal halves of the chambers by draining and refilling them at 15 min intervals over 6 h. Indomethacin-treated tracheas secreted less 35SO4 than untreated ones; mean inhibition was 23% (p<0.05, n=8). This inhibition was not seen in tissues stripped of epithelium (p=0.4). In 5 other animals, exogenous mediators caused secretion with an order of potency (at lo-5 M) of: histamine > prostaglandins > tu, SO4 throughout the experiment.


A. Zudulka, and M. King. School of Physical and Occupational Therapy and Meakins Christie Lab, McGill University and Montreal General Hospital, Montreal, Quebec, Canada H3Z 1Z2.

The effects of high frequency chest wall compression (HFCWC) on mucociliary clearance (MCC) in the small airways was studied in 7 anesthetized nonparalyzed dogs. HFCWC was achieved by a piston pump oscillating the pressure in a modified double blind pressure cuff wrapped around the lower thorax. Sulfur colloid aerosol was introduced into the lungs via a bronchodilator connected to an endotracheal tube. Aerosolization continued until total lung radioactive count reached 100,000-150,000 per min. and the lungs appeared well outlined. Lung retention was quantified in various lung zones using a gamma camera and subsequently computer analysis. HFCWC at 13 Hz, with a peak cuff pressure of 100 cm H2O, applied for 30 min, significantly enhanced clearance from the lower peripheral zones when compared with spontaneous ventilation (mean value of 20.12±13 SD, p<0.01). In the upper zones MCC was not enhanced. HFCWC at 13 Hz with a peak cuff pressure of 50 cm H2O also enhanced clearance (from the lower peripheral zones) in the 3 dogs tested.

The enhancement of clearance may be brought about by mechanical effects, changes in mucous viscosity or neural or chemical factors. These results suggest that, provided safety can be demonstrated, HFCWC might be of potential benefit as a mode of chest physiotherapy in patients with mucous hypersecrecion. (Supported by CAN.CF Fdn, & CAN.Lung Ass'D).

19.5 NEUTROPHIL DEPLETION INHIBITS AIRWAY HYPERRESPONSIVENESS INDUCED BY OZONE. R. Funk, P.O'Byrne, R. Pardoe, R. Gold.


We studied the role of neutrophils in ozone-induced airway hyperresponsiveness in the ferret model. Inhibition of neutrophil infiltration was achieved by treating ferrets with the neutrophil antagonist BW755c. Neutrophils were depleted from ferret tracheas using N-acetyl cysteine. Neutrophil levels were determined using a hemocytometer.


In order to follow-up our previous observations that airway hyperresponsiveness induced by ozone (O3) is associated with an increase in neutrophil sequestration (neutrophil infiltration and ciliated cell desquamation), we investigated the effect of B775c, a mononuclear cell adhesive, on the responses to O3. We determined the concentration of acetylcholine (ACh) that increased baseline pulmonary resistance by 50% (EC50%) and we counted the number of each cell type in bronchoalveolar lavage (BAL) when exposed to various concentrations of O3. We measured the number of neutrophils and epithelial cells in lavage in significantly increased after O3 in the placebo studies but not after B775c (10 mg/kg i.v.). In 15 animals, the number of neutrophils in lavage increased in placebo studies and after drug intervention (see table).

<table>
<thead>
<tr>
<th>Ozone</th>
<th>Pre Ozone</th>
<th>Post Ozone</th>
<th>B775c Pre Ozone</th>
<th>Post Ozone</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZACH</td>
<td>0.16</td>
<td>0.01</td>
<td>0.13</td>
<td>0.07</td>
</tr>
<tr>
<td>Epithelial cells*</td>
<td>1.20</td>
<td>35.00</td>
<td>7.90</td>
<td>16.00</td>
</tr>
<tr>
<td>Neutrophils*</td>
<td>6.40</td>
<td>36.00</td>
<td>1.62</td>
<td>6.20</td>
</tr>
</tbody>
</table>

*values = number of cells x 10^9 per ml of lavage fluid.

We conclude that B775c markedly inhibits ozone-induced airway hyperresponsiveness in dogs, probably by inhibiting arachidonic acid metabolism. (Supported in part by UPHR HL-20136, a grant from the National Cancer Institute, and California Air Resources Board.)
19.7 RAT LUNG POLYVYLITAM METABOLISM AND SURVIVAL IN HYPOXIA; AGE RELATES DIFFERENCES. Allen D. Hacker*, and Donald F. Tierney, Department of Medicine, U.C.L.A., Los Angeles, Ca. 90024.

Polyvinyl alcohol is closely related to cell growth including proliferation. Thirty day old rats survive continuous exposure to 10 atm 02 for seven weeks; 60 day old rats die within 72 hrs. We exposed 30 day (125 gm) and 60 day (250-300 gm) rats to 10 atm 02 for 10 hrs. Only 30 day old rats survived for 72 hrs. In the 60 day rat, vasculature decarbonylase (OCD) activity increased 360% by 24 hrs and continued to increase until it was 1500% greater by 72 hrs, whereas in the 30 day rat it reached a peak at 48 hrs and then declined by 56 and 72 hrs. The absolute value of OCD per mg DNA was greater in the 30 day rat under all circumstances. OCD turnover in the 60 day rat was doubled.


A mathematical model of the pulmonary circulation: effect of Histamine (H), serotonin (5HT), norepinephrine (NE) and increased vascular pressure (IP). J.C. Parker, B. Riffet and A.F. Taylor, Dep. of Physiology, University of South Alabama, College of Medicine, Mobile, AL 36688.

A mathematical model which represents the pulmonary circulation as four resistance (R) segments and three capacitance (C) segments was programmed on a digital computer. The R and C values were adjusted to simulate dynamic and static state values of filtration mid-point (PC1), arterial occlusion (PAC), venous occlusion (PVC) and double occlusion pressure (p2) previously obtained under constant pressure (C) and constant flow (CF) conditions in isolated canine lungs fused hub lesions during IP and drug infusions. These simulations indicate that: (1) Total R decreased to 40% of control as PC1 increased for 10 to 150 mmHg, and this decrease was mostly attributed to distention or recruitment of small arteries and veins; (2) R increased with decreasing C mainly in large arteries and veins but decreased venous C (b) increased f effects of drugs on the small vessels was largely reversed at high PC1 due to distention or recruitment; (5) Pd decreased from P02 when arterial and venous C became unbalanced; and (7) constriction of capacitance vessels during infusions at high productions in large vessels was greater than predicted by the passive model. Supported by HL-24571 and HL-22549.

Nichols et al. (1978) have suggested that...studies of the...function of the newborn.

Lipscomb and Boyarsky (Resp. Physiol. 16:362, 1973) suggested that...depressor...restoration when introduced into the CBF...produce effects more directly at the neurons...diffusion...in...arterial supply to surface layers...arterioles...Paw was increased in steps from 2 to 8 mm Hg (two minutes for each step). The burst frequency (f), impulses per burst (n), and inspiratory time (t) decreased while the expiratory time (e) increased when Paw was increased. These changes were more profound in the higher CO2 range. CO2, Paw (H, min) n, t, e

35-45 2 100 150 150
45-50 2 100 150 150
55-65 2 100 150 150
65-70 2 100 150 150

We conclude that during CFV the effect of increasing airway pressure on phrenic motoneuron activity was intact but attenuated at higher CO2 levels.


Based upon the experimentally-determined relationship between end-tidal CO2 and the rate of pulmonary stretch receptor (PSR) discharge (Fig.), it is assumed that these receptors have little regulatory power within the physiological range of PCO2. However, we and others have presented evidence (Fed. Proc. 41:1102, 1982 & 42:1013, 1983) suggesting that CO2, feedback control. We have therefore developed a scheme which...distribution sensitive throughout the physiological range...activity in a manner characteristic of Hering-Breuer reflex mechanisms.


We recorded action potentials from 10 single phrenic fibers in 4 pentobarbital-anesthetized dogs ventilated by CFV, provided through two 1.5 mm I.D. tubes introduced to the level of the carina. A gas flow of 8 L/min was delivered through each tube continuously. Mean airway pressure (Paw) measured at the mid-tracheal level was steady and was manipulated by restricting the exhalation passage. Arterial CO2 was monitored continuously by a Clarke electrode incorporated in a microvascular loop preparatory artery. By adjusting the gas mixture (O2:CO2) the arterial PCO2 could be maintained at different levels between 35-75 mmHg. At each level of PCO2, the inspiratory activity was measured while Paw was increased in steps from 2 to 8 mm Hg (two minutes for each step). The burst frequency (f), impulses per burst (n), and inspiratory time (t) increased while the expiratory time (e) decreased when Paw was increased. These changes were more profound in the higher CO2 range. CO2, Paw (H, min) n, t, e

35-45 2 100 150 150
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We conclude that during CFV the effect of increasing airway pressure on phrenic motoneuron activity was intact but attenuated at higher CO2 levels.

20.4 IN VIVO RECORDING FROM CAT TRACHEAL PARASYMPATHETIC GANGLIA. R. A. Mitchell, D. E. Baker, O. P. Abrecht, B. Herbert, Cardiovascular Research Institute and Dept. of Anatomy, Physiology and Anesthesia, University of California, San Francisco, SF, CA 94143.

We previously reported that tracheal smooth muscle contractions during inspiration (Physiologist, 25:352, 1982). To further investigate this phenomenon, we recorded intracellular activity from 2 spontaneously active tracheal parasympathetic ganglion cells in anesthetized, paralyzed and artificially ventilated cats. Ganglion cells on the dorsal surface of the trachealis muscle were impaled with microelectrodes containing 6 M K acetate or 500 kHz microelectrodes. We identified three types of neurons based on firing pattern. Eleven cells had an inspiratory rhythm and were inhibited by lung inflation sufficient to abolish phrenic nerve activity. Lucifer yellow injected into 3 inspiratory cells, revealed axonal projections to the trachealis muscle but terminal arborizations could not be visualized. Seven cells fired during inspiration and fired continuously when phrenic nerve activity was abolished by lung inflation.
20.7 EFFECT OF CO₂ HYPANIA AND VAGOTOMY ON DECAY OF POST INSPIRATORY MUSCLE PRESSURE. S.D. Gottfried*, A. Rossi*, L. Zocchi*, P.M.A. Calverley*, W.A. Zin*, and J. Milic-Emili†

Microchips (Chronaxia Medical Instruments, Quebec, Canada). Experiments were performed on 6 pentobarbital sodium anesthetized adult cats spontaneously breathing through a tracheal cannula (a) room air both before and after vagotomy, (b) 60% O₂ (C) 2-8% CO₂. Under pressure control (P0 = 10-125 cmH₂O), the decay by inspiratory muscles during expiration (Pmus) was quantified as previously described (J. Appl. Physiol.: Respirat. Environ. Exerc. Sci. 60:470-5, 1986). After the cats were in a steady state, the initial decay of Pmus was an exponential function of the steady time (t) which could be quantified in terms of a time constant (τ). Correlation coefficients ranged between 0.95 and 0.99. During CO₂, hypoaxia and after vagotomy, tidal volume (VT) and initial Pmus (Te=0) increased. However, the decay of Pmus changed proportionally so that the relative rate of decay was constant (unchanged). With CO₂ and hypoxia, inspiratory (TI) and expiratory time decreased while VT and TI increased. This suggests that hypoxia, inspiratory (TI) and expiratory time decreased while VT and TI increased. In conclusion, the relative rate of decay of Pmus is a constant exponential function, independent of the absolute level of Pmus. The decay of Pmus is essentially unaffected by changes in respiratory timing occurring with chemical stimulation and vagotomy.

(Supported by the MRC of Canada and NIH grant HL-37617)


Decreased diaphragmatic activity is seen after cholecystectomy in man and dog. We studied the pulmonary reflexes which could be evoked when the GB was stimulated in anesthetized dogs by noninvasive techniques. The effect of increasing the pulmonary capillary pressure to 30 mmHg with saline into the LPA was measured. A sonometer showed that the GB reflexly stimulates paradoxical breathing (3) the changes in diaphragm activity seen after cholecystectomy in man or dog may be mediated by this same mechanism.


Pulmonary C-fibers (or interstitial pulmonary capillaries) are known to be stimulated when pulmonary capillary pressure increases. We have attempted to determine which increased lung C-fiber activity associated with pulmonary congestion is maintained by interstitial lung edema after pulmonary vascular pressures are returned to normal. We recorded impulses from interstitial lung fibers arising from the lung in anesthetized open-chest dogs during acute extracellular volume expansion produced by i.v. infusion of Krebs-Henseleit solution (10-20% of body weight). The infusion, pulmonary arteriolar and left atrial pressures were returned to control by withdrawal of blood. Measurements of extracellular lung water (1.1±0.1 g/g dry) and histological examination (which revealed perivascular cuffing) provided evidence of interstitial lung edema but not of alveolar edema. During inflation when pulmonary vascular pressures were elevated many pulmonary and bronchial C-fibers were stimulated, and C-fiber activity remained high after intravascular pressures returned to control levels. We conclude that lung C-fibers are stimulated by interstitial pulmonary lung edema. (Supported by HL-26136, HL-07192 and HL-25548 from NHLBI.)

20.10 REFLEX EFFECTS OF PULMONARY EDEMA. W.A. White and S.S. Cassidy, University of Texas Health Science Center, Dallas, Texas. 75235.

We have previously shown that lung inflation and injection of either capsaicin or the toxic substance, allnoxan initiate the pulmonary depressor reflex (PDR) responses of decreased heart rate (HR), blood pressure (BP), and frequency of diaphragmatic contraction (DCF). Our objective was to determine if hydrostatic edema would elicit the PDR. In six anesthetized, ventilated, open chest dogs, the left pulmonary artery (LPA) and veins (LPV) were ligated and cannulated, isolating the left lung from the systemic circulation. The entire tidal volume and cardiac output were measured periodically. After the left lung was suspended and continuously weighed (LWt). Pulmonary edema was produced by a 5 min. infusion of saline into the LPA and increasing the pulmonary capillary pressure to 25 mmHg. Since edema formation is gradual, these results were compared to those produced by a 5 min. ramp left lung inflation (LLI) to 25 cmH₂O left airway pressure (LAPw). Loma produced no significant changes in HR, BP, or DCF as LWt increased 72%. LLI produced a progressive reduction in HR, reaching -19% at 20 cmH₂O LAPw. Loma did not change. Amplitude of DCF progressively decreased until cessation of DC occurred at an average LAWP of 19 cmH₂O. Right lung wet/dry weight was 0.06±0.12 while the right lung was 4.02±0.22. These data indicate that pulmonary edema induced with increased hypoxia, had decreased oncopulmonary pressure does not elicit PDR responses.


Acute hyperventilation produces reflex hypoxia which might be caused by increased central chemoreceptor tissue PCO₂, accompanying hypoxic vasoconstriction. To measure the tissue to arterial ΔPCO₂, a xenon-133 optoelectronic Pco₂ probe inserted in the diaphragm and possible vessels from the left vagus nerve was measured by electrophysiological method. Hypoxic than in normoxia (Po2=50 mmHg) or hypoxia (Po2=30 mmHg). At Po2=55 mmHg, a ΔPCO₂ of 4.8±1.2 mmHg (n=9). The rate of increased ΔPCO₂ was measured during hypoxia than in normoxia (Po2=50 mmHg) or hypoxia (Po2=30 mmHg). This increased ΔPCO₂ may be accounted for by the decreased CO₂ diffusion in hypoxia and possible vasodilation by hypoxia. However, hypoxia caused an initial fall, ΔPCO₂, in the steady state was not significantly less than in normoxia. In hypoxia, ΔPCO₂ may have been kept from falling by CO₂ produced by oxidative metabolism. These data suggest that chemoreceptor tissue CO₂ metabolism rate is about to that of brain cortex where ΔPCO₂ averaged about 9 mmHg. Thus, at a 2 mmHg rise of arterial PO₂, ΔPCO₂ in hypoxia could be attributed to chemoreceptor vasodilation. (Supported by NIH Grant HL-26167)

20.12 EFFECTS OF NASAL BREATHING AT DIFFERENT TEMPERATURES ON CO₂ SENSITIVITY, DYSPEA AND ALATE NASI EMG ACTIVITY. E.R. Burgess*, M.A. Whiteslaw. Faculty of Medicine, University of Alberta, 9323 University Dr., T6G 2H7.

Steady state nasal CO₂ response was measured in five normal volunteers at "cold" (8-0.2 °C) and "warm" humidified (32.1 ± 3.8 °C) temperatures. Volume was measured by pneumotachograph and electrically integrated. Minute ventilation (E) was computed from five breaths at each temperature (T) and end tidal CO₂ (ETCO₂). E was sampled every 20 s using a 0.05 mm s⁻¹ time constant. Temperature of inspired gas was measured by transistorized probe. "Breathlessness" was scored (BS) by a modified cold scale at each T and ETCO₂. A baseline EMG activity of the left nasal external oblique (ALAE) was measured with surface electrodes and time average (ALAE). The slope of the mean CO₂ response was increased with increased hypoxia and decreased oncopulmonary pressure does not elicit PDR responses.

(Supported by the MRC of Canada and NIH grant HL-37617)

An additional 26.1% of the vagal efferent afferents responding to collapsing and/or distending pressure applied to an isolated upper airway in 6 anesthetized puppies (8–15 days old). During hypoxic negative pressure application 20 receptors with capsaicin caused increases in phrenic nerve activity, AP and HR in paralyzed, ventilated cats as well as in spontaneously breathing cats. Cervical vagotomy did not alter the responses to stimulation of either visceral organ. However, the respiratory and cardiovascular responses to capsaicin were greatly attenuated after transection of the sympathetic nerve supply. We conclude that: (1) in addition to the cardiovascular effects, stimulation of galbladder and stomach thin-fiber afferents causes an increase in respiratory output, and (2) the afferent link of this reflex is via the sympathetic trunk and not the vagus nerves.


There is good evidence that pulmonary afferent C-fibers initiate the apnea evoked by pulmonary arterial injections of capsaicin (100-1100ug, 10 min, or 12% O2). Arterial injections of capsaicin could not reach the systemic circulation. It is possible that the systemic circulation could have prevented or abolished breathing (10 cm/H2O) the lungs. Results suggest that both the apnea and rapid shallow breathing of the pulmonary chemoreflex are due to stimulation of pulmonary C-fibers, since in these experiments capsaicin could not reach the systemic circulation. (Supported by NIH grants 10201, 21343 and 01192).


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EFFECT OF INCLINE RUNNING ON CONTRACTILE AND BIOCHEMICAL PROPERTIES OF SKELETAL MUSCLE. K.J. Baldwin, W.M. Mullin*, D.B. Thomason*, and R.E. Herrick*. Department of Physiology, University of Pittsburgh School of Medicine, Pittsburgh, PA 15261.

A rodent model was used to measure the bunding of Ca²⁺ to (detergent + glycerol)-extracted psoas fiber bundles, a) in rigid, b) in the presence of nucleotides which bind to Tn but do not energize contraction (ATP and AMP-PNP), and c) in the presence of nucleotides which energize contraction (ATP and ITP). Fiber bundles bound a maximal amount of units Ca²⁺-mole Troponin-C(mg protein). Both in unloaded fibers and fibers generating isometric force, binding in the presence of ITP was identical to that in the presence of ATP. However, Ca²⁺-Regulated ATPase was severely impaired with ITP, so that at pCa 7.0 ITP-energized fibers generated 80-90% maximal force as compared to <10% maximal force generated by ATP-energized fibers. These results suggest that, 1) cycling of force-generating crosstules causes a reduction in Ca²⁺ binding, and 2) the amount of Ca²⁺ bound by the working filament lattice depends on the free Ca²⁺ not on the steady-state force developed. (Supported by NIH AM10551).

21.1
EFFECT OF ATP AND ATP ANALOGS ON Ca²⁺-BINDING TO GLYCEROL-EXTRACTED RABBIT PsoAS MUSCLE. D.H. Franklin Fuchs, De-...
21.4 COMPARISON OF MEMBRANE POTENTIALS IN SMOOTH MUSCLE CELL CULTURES EXPOSED TO OXIDANTS, LOW TEMPERATURE AND LOW POTASSIUM

F.A. Kutyna, L.J. Bryant, M.S. Pamunzi and F. Haddy, Dept. of Physiology, Uniformed Services Univ., Bethesda, MD 20814.

The magnitude of the resting transmembrane potential (Em) in arterial smooth muscle depends to a considerable extent on the activity of the Na⁺/K⁺ electrogenic pump. The present study compares the effects of some Na⁺/K⁺-path inhibiting solutions on the Em of arterial smooth muscle in cell culture. Smooth muscle from Wistar rat tail arteries was grown in primary cell culture. The plated cells were allowed to grow in a modified GIBCO 199 medium for 7 to 10 days before recording. The cell monolayers were superfused with modified Krebs-Henseleit (KH) solution at 37°C which contained from 0.1 to 100 mM potassium or 0 to 10⁻² M ouabain (at K⁺ = 5.9 mM). The effects of these solutions on transmembrane potential were compared to that produced by 0.1 mM K⁺ (KH) superfused at 15°C. Cells maintained an average Em of 67.3 ± 1.0 mV over the range of 0 to 10⁻² M ouabain whereupon they increasingly depolarized at higher concentrations, reaching 14 mV at 10⁻² ouabain. Superfusion of 0.1 mM K⁺ (KH) at 37°C depolarized the cells to 34.9 ± 1.9 mV, 3.3 mM K⁺ (KH) slightly hyperpolarized them to 72.5 ± 1.7 mV and at normal 5.9 mM K⁺ (KH) the Em was 65.9 ± 1.7 mV. Cells cooled to 15°C in 0.1 mM K⁺ (KH) depolarized to 12.6 ± 1.0 mV. Ouabain at a concentration of 10⁻² M appears to be as effective a depolarizing agent as the combination of low temperature and low potassium in this cell model. (Supported by NIH Grant HL21325-03, USNS OJ7605 and C01PF7)

21.5 COMPARISON OF INTRACELLULAR IONIC ACTIVITY WITH ION-SELECTIVE MICROELECTRODES IN GASTROINTESTINAL SMOOTH MUSCLE.

N.L. Shearin.

MEASUREMENT OF INTRACELLULAR IONIC ACTIVITY WITH ION-SELECTIVE MICROELECTRODES IN GASTROINTESTINAL SMOOTH MUSCLE.

Utah 84132

SELECTIVE MICROELECTRODES IN GASTROINTESTINAL SMOOTH MUSCLE.

Henseleit (KH) solution at 37°C which contained from 0.1 to 100 mM potassium or 0 to 10⁻² M ouabain (at K⁺ = 5.9 mM). The effects of these solutions on transmembrane potential were compared to that produced by 0.1 mM K⁺ (KH) superfused at 15°C. Cells maintained an average Em of 67.3 ± 1.0 mV over the range of 0 to 10⁻² M ouabain whereupon they increasingly depolarized at higher concentrations, reaching 14 mV at 10⁻² ouabain. Superfusion of 0.1 mM K⁺ (KH) at 37°C depolarized the cells to 34.9 ± 1.9 mV, 3.3 mM K⁺ (KH) slightly hyperpolarized them to 72.5 ± 1.7 mV and at normal 5.9 mM K⁺ (KH) the Em was 65.9 ± 1.7 mV. Cells cooled to 15°C in 0.1 mM K⁺ (KH) depolarized to 12.6 ± 1.0 mV. Ouabain at a concentration of 10⁻² M appears to be as effective a depolarizing agent as the combination of low temperature and low potassium in this cell model. (Supported by NIH Grant HL21325-03, USNS OJ7605 and C01PF7)

21.6 LIPID SOLUBLE TOXINS FROM A DINOFLAGELLATE, GAMBIRDIGOSCUS TOLLUCA, ISOLATED FROM A CARIBBEAN REGION SUPPORTING CIGUATERIC FISH.

Donald M. Miller, Robert W. Dickey* and Donald R. Tindall*, Depts. of Physiology and Botany, S10-U, Carbondale, IL 62901.

A crude (GT) and three purified (GT-1, 2, and 3) ether-soluble, acetone precipitated, extracts were isolated from mass cultures of a dinoflagellate, Gambriodiscus tolluca. The crude extract (GT) when tested on 20 g mice resulted in an ID₅₀ of 99 ug within 48 hours. All four extracts at a concentration of 4 mg/ml were effective against; the synapse, nerve and striated muscle in the frog sciatic nerve-muscle preparation; and acetylcholine and histamine receptors on smooth muscle in the guinea pig ileum. The three purified extracts (GT-1, 2 and 3) from silicic acid chromatography were effective at 5 mg/ml on the guinea pig ileum preparations. Tetrodotoxin was utilized to suppress nervous elements in the ileum preparation in order to establish the effect of GT-1, GT-2, and GT-3 on the ileal muscle and the results followed Michaelis-Menten kinetics for a competitive inhibition of both histamine and acetylcholine receptors. Dose ratio determinations of a further purification of GT-2, allowed us to estimate an apparent affinity constant for this component. This study has established the presence of multiple toxins in the dinoflagellate, G. tolluca, outlined a method for their assay in small quantities, and identified at least one of the major effects of these toxins in animals. (Supported by: Dept. of Botany, Sch. of Med. S10-U, and FDA Contract #225-79-2287)

21.7 TIME DEPENDENT POTENTIATION OF THE RATE OF FORCE REGRESSION FOLLOWING QUICK RELEASE IN CANINE TRACHEAL SMOOTH MUSCLE.


Trachealis strips were mounted in a tissue bath between a force transducer and a rod which could be moved at a constant rate (20 mm/set) to alter muscle length over a preset distance. Muscle length, tension (P), and dP/dt rate (20 mm/set) to alter muscle length over a preset distance. Muscle length, tension (P), and dP/dt could not be related to the contractile state of the tissue. In the present study, we have attempted to relate the extent of wrinkling of the plasma membrane with the contractile state of the tissue. Cells of the rabbit renal artery were exposed to norepinephrine (NE) to induce contraction or to norpregnane (NP) to induce relaxation. Tissues were prepared for microscopic examination as previously described (McCoffee et al., J. Cell Biol. 90:201-210, 1980). Thick, 0.5 μm sections were cut and were photographed at 400 X magnification. All photography and analysis of the micrographs were carried out in a blind manner. Cells were classified as either wrinkly or smooth depending on the extent of folding of the plasma membrane. The results indicate that the degree of wrinkling of the plasma membrane could not be related to the contractile state of the tissue. Thus, under the conditions of this study, no consistent difference in the configuration of the cell surface in contracted vs. relaxed cells was observed. (Supported by NSF Grant PCM 79-11230)
STATES OF ELECTROGENIC PROTON PUMP IN GASTRIC MUCOSA IN LIGHT OF RESULTS OF VESICLE STUDIES. W. S. Kelso, M. Schwartz, and D. C. Engram. Univ. of Louisville, Louisville, KY 40292. In previous work, it has been found for the in-vitro frog gastric mucosa that with Cl-free media, the PD is inverted (secretory side becomes positive). A number of explanations, other than the postulate of an electrogenic proton pump, are possible for the inverted PD. However, it was found with Cl-free media that during inhibition of the H^+ rate, there is a precise linear relationship between the PD and the H^+ rate which cannot be explained by an electrochemical proton pump. However, work on gastric vesicles show that there is an AYV-driven neutral pump in which K exchanges with H. With the possibility that the inverted PD is due to a K gradient from the cell to the secretary fluid has been considered. However, this latter postulate is untenable since we will show that a) in Cl-free media, the partial conductances of the secretary and nutrient membranes are equal and b) with 80 K (K for Na) in both bathing fluids, the magnitude of the PD is the same as with regular (K = 4 mM) solutions. The latter finding would demand, with the K gradient hypothesis, absurdly high levels of cellular K. We will also present evidence that makes untenable the possibility of other ion gradients present in the inverted PD. Electrogenic proton pump models incorporating the neutral H^+K^+ mechanism will be presented. (NSF support)

GASTRIC EPITHELIAL DESQUAMATION AND RAPID REPAIR. S. Ito, E.R. Lacy, M.J. Rutten and W. Silen. Harvard Medical School and Beth Israel Hospital, Boston, MA 02115. Desquamation of gastric epithelial cells by hypertonic solutions, ethanol, and aspirin has been acknowledged but the subsequent rapid repair process or its fine structural details has not been elucidated or fully recognized. In recent studies, we have used in vivo rat and in vitro guinea pig and frog stomachs to study the damage and repair process. Rat stomachs briefly exposed to absolute ethanol loose their surface epithelium but half of the exposed basal lamina is covered within 7 min by migrating mucous cells. Within 15 min there is about 85% coverage and virtually complete reconstitution of the electrical properties within 90 min. The chambered frog mucosa is severely damaged by 1M NaCl but half of the exposed basal lamina is covered within 7 min by migrating mucous cells. Within 15 min there is about 85% coverage and virtually complete reconstitution within 90 min. The chambered guinea pig stomach exhibits spontaneous sinusoidal potential fluctuations of about 6 mV frequency and up to 20 mV amplitude. Cells of microdissected glands were more difficult to impale and the distinction between membrane potentials and microelectrode tip artifacts was critical. Nevertheless, constant membrane potentials of the order of -40 mV (and occasionally -60 mV) were recorded, both in parietal cells and in chief cells, which responded as expected to elevation of bath K concentration and to harmaline (1 mmol/l) which is thought to reversibly inhibit the Na/K pump. Instead of a transient depolarization, replacement of Cl by SO_4^- hyperpolarized the parietal cells by up to -40 mV which cannot be explained as tip potential artifact.

BUFFER BASE TRANSPORT BY RENAL DISTAL TUBULES. Maurice B. Burg. WHRI, NIH, Bethesda, MD 20205. Previously, rabbit cortical collecting ducts (CCD) perfused in vitro were observed to either absorb or secrete bicarbonate depending on whether the animals from which they were obtained were acidicotic or alkalotic. Recent studies with rat CCD give virtuallly identical results. In contrast, rabbit outer medullary collecting ducts (OMCD) from both acidicotic and alkalotic rabbits absorbed bicarbonate, whose rate was abolished by amiloride in OMCD from alkalotic animals. Recent studies with rat OMCD yield the same result, except the absolute rates of transport are three times as high. Rabbit thick ascending limbs previously were not found to transport bicarbonate. In contrast, significant bicarbonate absorption is now found in rat TAL. Rat TAL now are also found to absorb considerable amounts of ammonia with equal ammonia concentrations in the perfusate and bath. The ammonia transport is inhibited by HC03^- substitution, and cannot be by diffusion since the lumen fluid is acidic. Ammonia absorption by TAL may represent a single effect in counter currents of ammonium and bicarbonate, contributing to the high ammonia concentrations observed in renal medulla and urine. The mechanisms of the buffer base transport in these segments, and their role in urinary acidification will be discussed.

ELECTROPHYSIOLOGICAL STUDIES ON INDIVIDUAL CELLS OF ISOLATED GLANDS OF RABBIT GASTRIC MUCOSA. Trifone Schettino+, Martin R. Kohler and Herbert Fromter+ (VON J.W. Foote). Max-Planck-Institut für Biophysik, 6000 Frankfurt, Fed. Rep. Germany. Rabbit gastric tubules were isolated either by collagenase or by microdissection. The former technique yielded gland fragments which were fixed in a perfusion chamber in a layer of agarose, whereas the latter yielded whole glands which were held in suction pipettes. Mitochondria-rich parietal cells and mitochondria-poor chief cells were distinguished by an autofluorescence which presumably arises from microchondrial flavines, or by staining of the mitochondria with rhodamine B W. This proved more reliable than staining of presumably acid regions in the cells by acridine-orange. Cells of collagenase-treated glands were easier to impale with microelectrodes but showed spontaneous sinusoidal potential fluctuations of 1-3 mV frequency and up to 20 mV amplitude. Cells of microdissected glands were more difficult to impale and the distinction between membrane potentials and microelectrode tip artifacts was critical. Nevertheless constant membrane potentials of the order of -40 mV (and occasionally -60 mV) were recorded, both in parietal cells and in chief cells, which responded as expected to elevation of bath K concentration and to harmaline (1 mmol/l) which is thought to reversibly inhibit the Na/K pump. Instead of a transient depolarization, replacement of Cl by SO_4^- hyperpolarized the parietal cells by up to -40 mV which cannot be explained as tip potential artifact.
TRANSMURAL UNIFORMITY OF CORONARY BLOOD FLOW IN HYPOXIC, NON-ISCHEMIC, LEFT VENTRICULAR MYOCARDIUM. H. Fred Lowney, George J. Crytal, Arthur G. Williams*, and Foad A. Bashour. Unif. Texas Health Science Center, Dallas, Texas 75235.

The left anterior descending coronary artery (LAD) of eleven anesthetized dogs was cannulated and perfused with blood oxygenated to an extracorporeal lung. Thus, the transmural coronary flow distribution was not influenced by the presence of hypoxia or ischemia in the endocardium or epicardium. Regional myocardial blood flow was measured by the microsphere technique. Blood flow was monitored in the left and right ventricles, and left coronary arterial pressure was monitored. Results obtained in the left ventricle in 11 chloralose-anesthetized, vagotomized cats. Fifteen um radiolabeled microspheres were injected into the LAD perfusion line during normoxic perfusion (control) and after 3 min of hypoxic perfusion. LAD perfusion pressure (control, 100 ± 2 mmHg) was maintained at a constant pressure. Partial stenosis was simulated by reducing pressure to 50 mmHg. Effects of the selective α1- and α2-blocker prazosin (2 mg i.c. over 20 min; N=6) and the general α-blocker phentolamine (0.25 mg/kg i.v. over 30 min; N=6) on ventricular Contractile Force, Flow, (μmol/dg) and MVO2 were measured. Prazosin increased Flow, MVO2, and Contractile Force by 40% (P<0.05), 35% (P<0.05), and 48% (P<0.05), respectively. All increases were greater with prazosin than with phentolamine. Supported by NIH Grant R01-HL31144 and R01-HL62843.

EVIDENCE THAT AN ALPHA-BUNGKINENG VASODISTENSION LIMITS CORONARY FLOW AND CARDIAC FUNCTION DURING EXERCISE IN DOGS. Patricia A. Gitwitz, Dean Franklin, and Howard J. Mass*, Texas College of Osteopathic Medicine, Fort Worth, TX 76107, and University of Missouri, Columbia, MO 65201.

Alpha-adenreceptor receptor modulation of coronary blood flow and cardiac function was examined in exercising dogs. Dogs were chronically instrumented to measure left circumflex coronary blood flow velocity (CBFV, pulsed Doppler), heart rate (HR), regional left ventricular function (systolic shortening, SL and velocity of shortening, ΔL/Δt) and left ventricular function (systolic shortening, %AL and dP/dt) during exercise. Exercise significantly increased CBFV (+10 cm/sec), %AL (+2.5% + 1% < 0.05), and dP/dt (+129+171 mmHg/sec). Neither antagonist caused changes in HR, LVP, or SL but with both antagonists, increases in CBFV (+10 cm/sec) and %AL (+2.5%) were observed. It is suggested that an alpha-vasodistension limit limits coronary vasodilation and cardiac function, during exercise. Supported by NIH Grant RO1-HL31144 and RO1-HL62843.
24.7 EFFECTS OF PYRUVATE (Pyr) AND LACTATE (Lac) ON MYOCARDIAL ADIPOSE (Ado) Release. B. R. Burger, R. R. Mardin, M. H. Burke, departments of physiology, Uniformed Services University, Bethesda, MD, and University of Virginia, Charlottesville, VA.

In isolated working guinea pig hearts (preload: 12 cm H2O; afterload: 90 cm H2O) the influence of exogenously supplied Pyr (0.2-0.2 mM) and Lac (0.2-0.2 mM) on coronary effluent Ado was studied. Pyr and Lac were determined simultaneously, Ado was measured with standard HPLC techniques. Since 15 mM glucose plus 10 mM acetate (in presence of 5 U/ml insulin) were the main energy-providing substrates, the coronary venous pyr + lac was similar to the concentration of the infused arterial pyr + lac (pyr + lac = 1.0 or 2.0 mM). 2.0 mM Pyr caused a 14.25%, decrease (P<0.05) in AR release (control = 93.510 ± 1.053 vs. 1.0 mM Pyr). However, 2.0 mM Pyr did not significantly change AR release. Low, 0.25 arterial Pyr/pyr ratios (0.1 to 1.0) resulted in small decreases in AR release whereas high, 0.25 arterial pyr/pyr ratios (3.01-100) release was increased slightly in 5 out of 6 hearts. Myocardial oxygen uptake (MVO2) did not appreciably change under the same conditions. In contrast, 0.25 perfusate pyr + lactate (X) was unaltered, X reduced in an arterial pyr + lactate. Studies from this laboratory, using rabbits, have reported that Ado's effect on HR and CF effects of Ado and the Ado analogues; 4-N-phosphinoethylpyruvase (O-PYR) and 5-N-(4-chlorophenyl) Ado (5-NECA) in normoxic and hypoxic guinea pigs. A microprocessor driven system was used to maintain drug concentration and coronary pressure constant independent of changes in CF. Values are threshold molar concentrations producing significant changes. Through biochemical and binding studies ADP receptors have been classified as A1 or A2. ADP, AMP and 32P-32P (in vitro) 10-6 10-7 10-8 10-9

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The purpose of this study was to determine the HR and CF effects of Ado and the Ado analogues; 4-N-phosphinoethylpyruvase (O-PYR) and 5-N-(4-chlorophenyl) Ado (5-NECA) in normoxic and hypoxic guinea pigs. A microprocessor driven system was used to maintain drug concentration and coronary pressure constant independent of changes in CF. Values are threshold molar concentrations producing significant changes. Through biochemical and binding studies ADP receptors have been classified as A1 or A2. ADP, AMP and 32P-32P (in vitro) 10-6 10-7 10-8 10-9

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The purpose of this study was to compare effects of vasodilation caused by hypoxia (8-12% O2) and adenosine (0.5 mg/g/min) on various morphometric indices of the arteriolar and capillary bed in the working heart. FITC-dextran was injected into rabbits under control, adenosine infusion and hypoxic conditions to label the perfused vessels for fluorescent microscopy. The tissue was then stained for alkaline phosphatase for detection of the capillary bed. Standard morphometric techniques were used to find total and perfused capillary/arteriolar number/m² and volume and surface area/m². Under control conditions, 52.6% and 57.2% (Mean ± SE) of the arteriolar and capillary bed volume/m² were perfused. With hypoxia, both arteriolar and capillary bed volume/m² increased greatly, 81.7% and 96.1%. Adenosine infusion increased arteriolar values close to maximum, 91.5%, but increased capillary values significantly less, 71.1%. No significant subendocardial vs. subendocardial differences were found under any condition. These results show that control hearts have a high degree of arteriolar/capillary reserve that is mobilised equally by hypoxia but adenosine mobilises arteriolar reserve to a greater extent than capillary.

24.11 VISCOSITIC BEHAVIOR OF IN VIVO CORONARY ARTERY CAPACITANCY. J. D. Canty, Jr., T. E. Klocke, SUNY at Buffalo, N.Y. 14215.

Although excised arteries exhibit viscoelastic effects, it is uncertain how widespread the phenomenon of coronary capil- lary pressure control system during adenosine vasodilation. During long diastoles coronary pressure was made to decline and subsequently rise at a constant rate (dP/dt) and pressure-flow curves were constructed over a wide range of 25-75 mm Hg. For a given dP/dt, capacitance was calculated from the flow differences between the two curves, using the equation:
25.1 REFLEX AUGMENTATION OF ACTIVITY OF UPPER AIRWAY DILATING MUSCLES (UADM) BY ESOPHAGAL AFFECTATION. Mark A. Hamel,2 Erik van Lunteren,1 J. Hoyt Mittra1 and Neil S. Cherril. Department of Medicine, Case Western Reserve Univ., Cleveland, OH 44106. 

Toxin, 100 mg/kg, i.v., induced the diaphragmatic activity of the diaphragm but its effect on other respiratory muscles have not been examined. We recorded the electrical activity of 16 UADM, located in the posterior cricoid, as well as that of the diaphragm (D) and inspiratory parasternal (IPS) muscles, in nine anesthetized dogs, before and during esophageal distention. During UADM breathing, a graded inflation of a balloon positioned in the middle third of the esophagus induced a graded inhibition of D with a concomitant increase in IPS and UADM activities in all dogs. 

Three animals were killed during increasing distention volume while breathing frequency increased primarily due to shortening of expiratory time. No significant change in minute ventilation, end-tidal PCO2, mean systemic blood pressure and heart rate was found. Bilateral mid-cervical vagotomy abolished the reflex effects of esophageal distention. These results indicate that visceral afferent inputs can differentially affect receptors which control respiratory activity and regulate inspiratory intercostal muscles and UADM activity.

25.2 REFLEX RESPONSES CAUSED BY PULMONARY C-FIBERS. S.J. Cassady, W.C. Weih, M.P. Kaufman, J.H. Ashton and Y. Monnerat. Univ. of Texas Health Science Center, Dallas, Texas 75235.

Our purpose was to quantitate the pulmonary depressor chemoreflex (PC-fbr) during carotid sinus nerve (CSN) stimulation in the isolated systemic circulation. In 5 dogs this was made possible using an open chest preparation in which the left pulmonary artery (LPA) and veins and left airway were cannulated. Aiming to induce a reflex response, the LPA was occluded above or below the larynx. On the basis of their response to stimulation of afferents were classified as pressure receptors, flow receptors or "drive" receptors (stimulated by the respiratory activity of upper airway muscles). Pressure receptors were encountered most frequently, representing 55% of our sampling (77 receptors), "drive" receptors constituted 26% and flow receptors 19% of reported receptors. The latter two types of receptors differ in sensory modality, they coexist in inhibiting a predominant activity during inspiration and excitatory activity during expiration. Moreover, their activity increases markedly during upper airway constriction. Supported by NIH Grants HL-20122, 29169, MRC Canada and A.L.A.

25.3 RESPIRATORY MECHANORECEPTORS IN THE LARYNX. C. Sant'Ambrogio, O.P. Mathew, J.T. Fisher and P.H. Sant'Ambrogio. Departments of Physiology and Pediatrics, UTMB, Galveston, TX 77555.

The larynx has a rich sensory supply which is the main component of the sensory motor reflex arc. These reflexes influence both the patency of the upper airway and the pattern of breathing, are related to transmural pressure and/or airway occlusion in UADM, and play an important role in the reflex response of the brainstem centers via ipsilateral afferent vagal C-fibers to the contralateral C5 phrenic motoneuron pool. These results indicate that visceral afferent inputs can differentially affect receptors which control respiratory activity and regulate inspiratory intercostal muscles and UADM activity.

25.4 DEVELOPMENT OF SLOWLY ADAPTING AIRWAY RECEPTOR (SAR) ACTIVITY IN THE OPOSSUM. J.P. Farber, J.T. Fisher and G. Sant'Ambrogio. UTMB, Galveston, TX; OU Health Sciences Ctr., Oklahoma City, OK.

The percentages of SAR discharge were evaluated in postnatal-adapted, anesthetized, gallamine-paralyzed, artificially ventilated, open chested opossums (Didelphis marsupialis). Animals were tested at 30, 30, 30, 30 and 100 days of age. Activity was determined in the presence of data with data from dogs. The percentage of SARs active at a transpulmonary pressure (Ptp) of 0 cmH2O did not significantly vary as a function of age (ranging from 27% to 49% of receptors tested among the different age groups). Firing thresholds of Ptp for activation of SARs (Ptpm) ranged from 50 to 60 cmH2O for SARs in the 20 and 30 day old groups. At high static levels of Ptp (15 and 20 cmH2O), SAR discharge was progressively reduced as a function of increasing age by 49 to 75% of receptors tested. 

25.5 APNEUSTIC-LIKE BREATHING PRODUCED BY INTRAVENOUS ADMINISTRATION OF RACTIENFIN IN THE CAT. A.M. Taveras, D.A. Silva, J.A. Quest,2 P. Hamosh and R.A. Gillis. Dept. of Pharmacology, Physiology and Medicine, Georgetown University School of Medicine and Dentistry, Washington, DC 20007 and National Toxicology Program, NIEHS, NIH, Bethesda, MD 20205.

Injection of GABA into the cisterna magna (CM) and local application of GABA to Schlaefke's area (S area) did not. These results indicate that the respiratory depressant effect of baclofen differs from that of GABA in terms of both type of breathing pattern and CNS cite of action (HE 29682).
25.7

Inspiratory neurones in the cat are concentrated in the dorsal medulla associated with the ventrolateral nucleus of the tractus solitarius (v-NTS) and, to a lesser extent, in the rostral raphe. Staining of the v-NTS and raphe with HRP after fixation of the medulla was sectioned at 100 μm, preincubated in CoCl₂ and reacted with DAB. All labeled cells were within the v-NTS, six cells located in the rostral raphe had a mean diameter of 30.4 μm, while 4 others sectioned in horizontal plane had a mean of 15.5 μm. Many of the axons were observed to run ventrally from the soma and then turn medially to cross the midline of the medulla. Stained neurones had from 4 to 10 primary dendrites. The main dendritic arborizations ran parallel and ventrolaterally to the tractus solitarius (TS) for up to 1.0 mm from the cell bodies. These dendrites possessed spines and varicosities. We suggest that the orientation of the dendritic arbors of v-NTS inspiratory neurones optimizes the surface area available to receive synaptic contacts from sensory afferents of the TS supported by USPHS NS 14959 and NNSAS HL 01232 & 06474.

25.8
POST-SYNAPTIC RESPONSES OF POST-INSPIRATORY NEURONS TO ROBUST PONTINE STIMULATION. J.P. Bakke, D.C. Bolser*, R. Takeda*, V.P. Madden, R.W. Richter* and J. Farber. Departments of Physiology and Medicine, University of Texas Southwestern, Dallas, TX 75235.

Glass micropipettes filled with 3M KCl were used to record membrane potential of post-inspiratory (PI) neurones (Richter, 1982). Biocytin, 10%, was injected into post-inspiratory neurones in the rostral ventrolateral medulla of the unanesthetized, paralyzed cats. The animals were pneumoanesthetized and held in a stereotaxic frame, with the spine clamped. A phrenic-driven respirator was used to ventilate the animal. The pontine stimulation was delivered through a bipolar electrode into the rostral ventrolateral medulla outside of the motor cortex but after the end of inspiration. Measurements of input resistance and membrane potential after CI- reversal revealed the hyperpolarization to be due to inhibitory post-synaptic potentials (ipsp). Ipsilateral pontine stimulation (in the region producing global phrenic inhibition) produced excitatory post-synaptic potentials (epsp) in the PI neurones with latency about 4 ms and a duration of 100 ms. The epsps were not altered during inspiration appeared to be due to ltp-mediated shunting and hyperpolarization. Some PI neurones also had weak excitatory responses to contralateral post-inspiratory stimulation and some received epsp from vagal stimulation. Supported by NIH grant HL-27190.

25.9

Studies were conducted to determine the first-breath (neural reflex) response of dorsal and ventral respiratory group inspiratory (I) neurones to the mechanical loading (tracheal occlusion, TO) of inspiration in unanesthetized (decerebrate), vagotomized cats. Tracheal occlusion produced an increase in activity in 52% of the I-neurones (I-Neurones). The increase in activity of these neurones was not dependent on the duration of the TO and was present when the occlusion was maintained for 15 seconds. In 24% of the I-neurones, an increase in activity following loading has not been reported in previous studies using anesthetized vagotomized cats. These changes in I-neurone activity with TO were not present in cats with their cervical dorsal roots (C3-C7) or thoracic dorsal roots (T1-T9) cut. The changes in neurone activity with TO were absent when both cervical and thoracic dorsal roots were cut.

25.10
THE RESPIRATORY PARAMETER OF THE SCHIFF-SHERRINGTON PHENOMENON. Robert E. Schulman, Sharon K. Cole*, and Habbel E. Hoff. Baylor College of Medicine, Texas Medical Center, Houston, Tx 77030.

Fifteen cats and five dogs were decerebrated at the midcollicular level and then coronadized at the twelfth thoracic level. Minute volumes were measured before and after decerebration. Changes in respiratory parameters were then measured. The animals developed post-decerebration rigidity after decerebration, and exhibited significant increase in arterial carbon dioxide partial pressure following decerebration (Schiff Sherrington phenomenon). The results were accompanied by a simultaneous step-wise increase in tidal volume and respiratory rate, averaging a 46% increase in minute volume and a 35% increase in tidal volume. The increase in tidal volume was due to an increase in the total inhibition immediately following the cordotomy and continued throughout periods of survival of four to thirty hours. The results were interpreted as pointing to the presence of a neuromechanism linking the increased ventilation with the Schiff Sherrington effect. The release of post-inspiratory responses in the Schiff-Sherrington phenomenon seems to be accompanied by the release of respiratory activity as well. The presence of this integrated response in the midcollicular decerebrate preparation establishes that the center for postural-respiratory integration is situated caudal to the hypothalamus and thalamus.

25.11
ELECTRICAL STIMULATION OF THE DIAPHRAGM IN CATS - A PHYSIOLOGICAL MODEL FOR THE HUMAN INFANT. David G. Fleming, Dennis Shelby* and Fred Montague*. Case Western Reserve Univ. Cleveland, Ohio 44106.

Case Western Reserve Univ., Cleveland, Ohio. 44106.

We determined the effect of single breath of 100% O₂ on ventilation, we studied 10 term (BW 3360±110 gm; SE; GA 39.3 ± 2.3 wk, postnatal age 2.6±2.5 days) and 10 preterm neonates (BW 700±700 gm, GA 28±1.8 wk, PMA 8.71±1.5 days) during deep sleep. The single breath method measures the peripheral chemoreceptor response. To standardize the control period for all infants we adjusted FiO₂ to 16±2% to obtain a control O₂ saturation of 83±1%. After 1 minute of control in each sleep state, they were given a single breath of O₂ followed by 21% O₂. We measured VP, Vt, f, Pao₂, paco₂, and PaO₂ saturation (ear oxymeter). In term infants, VP also decreased with inhalation of O₂ (P<0.01). In non-REM sleep, the decrease in VP was less in term (14%) than in preterm (40%) infants (P<0.01). This decrease in VP was greater in preterm than in term infants. In REM sleep the decrease in VP was similar in term (19%) and preterm (21%) infants (P>0.05). Aguna as past of the response was more prevalent in preterm than in term infants. In REM sleep the decrease in VP was similar in term (19%) and preterm (21%) infants (P>0.05). These results suggest a greater peripheral chemoreceptor response in preterm than in term infants as reflected by a more pronounced decrease in VP of term infants. The results are compatible with a more powerful peripheral chemoreceptor contribution to breathing in preterm than in term infants.

25.12
EFFECT OF A SINGLE BREATH OF 100% OXYGEN ON RESPIRATION IN NEONATES DURING SLEEP. Tazeem Aizad*, Jaya Bodani*, Don Cates*, Leanne Horvath*, and Henrik Riggio. Dept. of Pediatrics, Univ. of Manitoba, Winnipeg, Canada.

We studied the effect of a single breath of 100% O₂ on ventilation, we studied 10 term (BMI 3360±110 gm; SE; GA 39.3 ± 2.3 wk, postnatal age 2.6±2.5 days) and 10 preterm neonates (BMI 700±700 gm, GA 28±1.8 wk, PMA 8.71±1.5 days) during deep sleep. The single breath method measures the peripheral chemoreceptor response. To standardize the control period for all infants we adjusted FiO₂ to 16±2% to obtain a control O₂ saturation of 83±1%. After 1 minute of control in each sleep state, they were given a single breath of O₂ followed by 21% O₂. We measured VP, Vt, f, Pao₂, paco₂, PaO₂ saturation (ear oxymeter). In term infants, VP also decreased with inhalation of O₂ (P<0.01). In non-REM sleep, the decrease in VP was less in term (14%) than in preterm (40%) infants (P<0.01). This decrease in VP was greater in preterm than in term infants. In REM sleep the decrease in VP was similar in term (19%) and preterm (21%) infants (P>0.05). Aguna as past of the response was more prevalent in preterm than in term infants. In REM sleep the decrease in VP was similar in term (19%) and preterm (21%) infants (P>0.05). These results suggest a greater peripheral chemoreceptor response in preterm than in term infants as reflected by a more pronounced decrease in VP of term infants. The results are compatible with a more powerful peripheral chemoreceptor contribution to breathing in preterm than in term infants.
26.2

AN ANALYSIS OF ANGIOTENSIN II AND III IN THE BRAIN WITH HIGH PRESSURE LIQUID CHROMATOGRAPHY. M. Ian Phillips and Birgitta Stenstrom*. Department of Physiology, University of Florida, Gainesville, Florida 32610.

To answer the question of whether angiotensin II exists in the brain independently of peripheral angiotensin, a sensitive radioimmunoassay with high recovery rates was used to measure fractions of highly purified angiotensin II and III (HPLC) of assay of male adult rat brains. Rats were decapitated bilaterally and 24 h. later the brains were extracted after boiling in acetic acid. A 20 µL sample was used to purify the angiotensin followed by high pressure liquid chromatography (HPLC). The fractions were collected and analyzed by an Ang II radioimmunoassay with 93% recovery. HPLC revealed angiotensin III authentic (Ile) angiotensin II and (Ile) angiotensin III. Both angiotensins were found in the hypothalamus blocks within the included parts of the hypothalamus and mono-cortical. Angiotensin II concentration was 63 to 873 pg/g tissue. Angiotensin II, but not angiotensin III, was also found in cortex but in low quantities.

The results demonstrate that the antibody which was previously used in the immunocytochemical localization of angiotensin II in the hypothalamic detects authentic angiotensin II. The present data provide critical evidence for endogenous angiotensin II in the brain. Physiological implications of brain angiotensin II can be explored with this procedure.

Supported by NIH Grant No. 1-R01-HL72734 to MJP.

26.4

HYPOTHALAMIC DISCONNECTION AND RENAL HYPERTENSION. A DUAL RESPONSE. C.U. Lopez*, A.L. Castro*, E.F. Allemand* and V. Veneden* (Spon: A.C. Bynum). Departamento de Fisiologia, Universidad de Sao Paulo, 05508, Sao Paulo, SP, Brazil.

The role of the central nervous system in general, and of the hypothalamus in particular, in the various forms of experimental hypertension has been the subject of increased investigation. In the present experiments by means of a stereotaxically placed curved knife (2 mm radius) the anterior hypothalamus was disconnected from midbrain and thalamus at the level of the arcuate nucleus. This lesion by itself induces polydipsia, increased urinary sodium excretion and reduction of pressure. In i.v. saline the lesioned rats are offered the choice, the additional amounts of 0.5% saline in preference to tap water. The alterations of simultaneously performed hypothalamic disconnection (HD) and Goldblatt one-kidney, one clip (HG) or two-kidney, one clip (HG) hypertension were studied. It was found that HD retards and attenuates the development of HG hypertension but does not materially affect the evolution of the HG model. Rats with established HG or HG hypertension were not affected by HD, whereas rats with chronic HD (4 weeks) showed slight and slow developing hypertension in response to HG. These results suggest that the anterior region of the hypothalamus contains separate neural mechanisms, involved in renal and norrenin-dependent renal hypertension.

MONDAY AM HYPERTENSION A 47
26.7 AMELIORATION OF RENIN-DEPENDENT HYPERTENSION BY AMILORIDE. Kenji Shimoaga and Thomas C. Lee. Cedars-Sinai Medical Center and UCLA School of Medicine, Los Angeles, California 90048.

We reported that amiloride, a potassium-sparing diuretic with kallikrein-inhibiting activity, was as effective in preventing uninephrectomized rats from rising in renin activity (PRIA) as aprotinin, an inhibitor of serine-proteases which include renal kallikrein. As a logical sequela, the potential efficacy of amiloride in ameliorating renin-dependent hypertension was tested in rats with severe unilateral renal artery constriction. Amiloride was added to the drinking fluid to provide an approximate dose of 1 mg/Kg. The results showed that amiloride-treated body weight better (p<0.01) than non-treated rats (n=14) and their systolic blood pressure measured in the conscious state was remarkably lower (166±6 vs 196±8 mm Hg, p<0.005).

After an 8-day regimen, renin-dependency of their hypertension as assessed by the hypertensive response to saralasin-induced angiotensin II blockade was also significantly reduced in the treated rats than that of non-treated rats (2316 ± 4031, p<0.05). All rats exhibited contralateral compensatory polyuria and amiloride exerted no discernible natriuretic or anti-kaliuretic effect. Plasma potassium concentration was similar in both groups. Thus, the antihypertensive effect of amiloride was due not to a greater diuresis nor hyperkalemia, but to suppression of hyperreninemia. (This study was supported by NHLBI Grant HL-21205, BRS CR-05-045 and Award 4141-15 from the American Heart Association - Greater L.A. Affiliate).

26.8 NITRITRENINE CONTROL OF BOTH SPONTANEOUS HYPERTENSION AND DOC-SALT HYPERTENSION AND THE ACOMPANYING DIABETES INSIPIDUS-LIKE SYMPTOMS. Charles B. Hall and Shirley Hunefeld. Div. of Texas Medical Branch, Galveston, TX 77550.

Nitriferrine, the water soluble ferrous ion (Fe), was found to decrease systolic blood pressure in rats with DNS or DOC hypertension in a dose-dependent manner. The NaCl diet was found to elevate blood pressure in both groups, with a significant difference seen in the 3% NaCl vs DOC rats. The nitriferrine was found to lower blood pressure in the DNS rats, but not in the DOC rats. The results suggest that nitriferrine may be a new treatment for hypertension and diabetes.


It has been demonstrated that chronic immunosuppressive therapy with cyclophosphamide will attenuate the hypertension in SHR, suggesting that this form of spontaneous hypertension may be due in part to an autoimmune mechanism (Physiol. Rev. 62:245, 1982). It has been postulated that autoimmunity in SHR may be the result of a thymic defect. To test this hypothesis, 3-week-old SHR were given implants of various immune organ tissues or thymus implants at weeks 12, 13 and 14 to attenuate hypertension in SHR by week 14. At week 16 the tail-cuff pressure averaged 193 ± 5, 30-min.) compared to pre-Cd BP of 137 ± 5 mm Hg. The NTR rats indirect blood pressure (BP) from the tail-artery was done one- to 30-minutes post-injection under light (up to 75 mg/kg) pentobarbital. Total body weights (100 g) were recorded and compared to hypertensive control (BP) state was remarkably lower (166±6 vs 196±8 mm Hg, p<0.005).

The TDW of Cd & NSS rats did not show significant BP elevation at week 6, and week 6, but significant (P < 0.025 - 0.001) post-Cd BP elevations were found at week 4, 5, and 7-10 (range of 155 ± 6 to 176 ± 9 mm Hg). The NSS rats showed no significant BP elevation acutely or from week 1-10. The TDW of Cd & NSS rats did not show significant changes. It is concluded that Cd 2 mg/Kg produced acute and chronic worsening of existing genetic hypertension in SH rats, an ideal model for studying the role of environmental factors in the genetically hypertensive rats.

26.11 EFFECTS OF BARIUM ON ANIMALS SUSCEPTIBLE TO AND RESISTANT TO HYPERTENSION. A.W. Dow,* B. Brooks,* E.E. Muirhead, Univ. of Tennessee Cen. of Life Sci., Knoxville, TN 37901.

We have demonstrated that chronic immunosuppressive therapy with cyclophosphamide will attenuate the hypertension in SHR, suggesting that this form of spontaneous hypertension may be due in part to an autoimmune mechanism (Physiol. Rev. 62:245, 1982). It has been postulated that autoimmunity in SHR may be the result of a thymic defect. To test this hypothesis, 3-week-old SHR were given implants of various immune organ tissues or thymus implants at weeks 12, 13 and 14 to attenuate hypertension. The results suggest that thymus implants from Wistar donor rats may be more effective than implants from WKY (tail-cuff pressure reduction after an 8-day regimen).

The conclusion of these results is that the hypothesis that hypertension in SHR may be due in part to an autoimmune mechanism. Supported by NIH Grant HL-11678.

The rigid endocardium of elasmobranchs connects to the pericardium by the pericardial-peritoneal canal. We investigated dynamic relationships of the canal, pericardium, and heart to assess the canal circulation. Intraperitoneal injection of six species, recorded from anesthetized fish lying supine out of water, were negative (-10 to -1 cm H2O). Infusion of elasmobranch saline into the pericardially gradually increased pressure over time to reach the 1.5 cm H2O for the horizontal, 1.5 cm H2O for the vertical. Further infusion did not raise pressure but resulted in steady flow to the pericardium. Infusion after canal ligation increased pressure in the peritoneal cavity to values above the arterial. Hemoglobin and plasma potassium were elevated in the peritoneal fluid. Combining the pericardial and peritoneal may ensure heart function by allowing high intrapericardial pressures resulting from body tension occurring during swimming, passage of food through the esophagus, or increased venous return during activity as the heart expands in accordance with Starling's law. (Partially supported by NSF Predoctoral Fellowship, the Veterans Administration, NIH S07 RR07011, and the Aquarium Dept. at Sea World, San Diego).

27.2 HEMOGLOBIN FUNCTION IN TARICHA GRANULOSA: A NEW APPROACH TO THERMAL ACCLIMATION. S.C. Wood. University of New Mexico, School of Medicine, Albuquerque, NM 87131.

Acclimation to temperature is manifested in many poikilothermic animals as a change in metabolic rate (long term 90 < short term) and a change in hemoglobin-oxygen affinity (long term 25ºC, short term). This study tested the hypothesis that these patterns of acclimation would occur in Taricha granulosa, a newt that is aquatic much of the year with water temperatures ranging from 3ºC (Jan) to 25ºC (July). Newts were kept at 5ºC or 28ºC for 1 month. Subsequently, the O2 uptake and respiratory properties of blood and Hb solutions were determined. There was a significant increase in PO2 of blood in warm acclimated newts. There were no differences between cold and warm acclimated animals with respect to: Hb electrophoretic pattern, O2 uptake, O2 affinity of blood or Hb solutions (at pH 7.7, 90ºC), Hb "n", and, O2 saturation by NTP. The lack of change in blood P50 contrasts with previous data for other species. However, an unexpected finding complicated the interpretation of this; e.g., cold acclimation resulted in a reversal of the normal Bohr effect (dlogPSO/dpH = -0.12 in term acclimated newts vs. -0.27 in cold acclimated newts). Supported by NSF Grant PCM-77-24246.

27.3 THE EFFECT OF PHASIC AND MEAN CHANGES OF PULMONARY CO2 (LCO2) ON VENTILATION IN THE TEGU LIZARD. G. O. Bally and W. J. Hicks. Lovelace Medical Foundation, Albuquerque, NM 87105.

The posterior portion of each lung of the lizard Tupinambis nigropunctatus was cannulated with a silastic endotracheal tube (ID = 3 mm) which passed through the body wall to the exterior. An endotracheal tube was inserted and warmed, humidified gas was delivered unidirectionally into the lungs. The gas passed through the lizards' mouth and out the exit tube. Ventilatory components caused changes in lung volume but did not alter LCO2 which was dependent on the amount of CO2 added to the gas stream. Intratracheal pressure, increasing tidal volume in the range of 3 to 5% caused an increase in tidal volume and ventilatory frequency. Setting background LCO2 between 4 and 8% while varying or reducing LCO2 by 1.5% for approximately 200 m sec with each breath increased the ventilatory frequency compared to maintaining the background LCO2 constant. Increasing the 200 m sec LCO2 reduction greater than 1.5% further elevated the ventilatory frequency. These results indicate that increasing CO2 delivery to the lungs by an increase in metabolism would probably stimulate ventilation both by increasing the mean LCO2 and increasing the amplitude of phasic LCO2 changes. These results also suggest that elevating inspired levels of CO2 would increase mean LCO2 and tend to increase ventilation which would decrease phasic changes in LCO2 which would tend to decrease ventilation. (Supported by NIH Grant HL 29424.)

27.4 EFFECTS OF INSPIRED OXYGEN ON PREFERRED BODY TEMPERATURE IN THE IGUANA. J.W. Hicks* and S.C. Wood. University of New Mexico, School of Medicine, Albuquerque, NM 87131.

Animals exposed to hypoxia, either external (lowered P02) or internal (due to cardiovascular shunts) must make physiological and/or behavioral adjustments to improve oxygen consumption. A previously reported computer model describing O2 transport in vertebrates with cardiovascular shunts (Wood and Hicks, The Physiologist; 25:214, 1992) predicted that arterial P02 would increase as temperature increased, a finding consistent with the "point" occurring and Pao2 then would decrease. The temperature at which the "breaking point" occurred would be lowered by external hypoxia and therefore the hypothesis that a reduction in the preferred body temperature will occur during exposure to hypoxia. We established a temperature gradient of 20 to 40ºC within a chamber and determined the preferred body temperature (mini-mitter telemetry) for Iguana iguana, breathing room air and when the inspired O2 fraction was reduced to 0.07. Preferred body temperature changed from 36ºC breathing room air to 26ºC breathing 7 % 02 and returned to 36ºC with the return of normoxia. The physiological significance of this may be to keep the arterial P02 above the "critical" PO2. Supported by NSF Grant PCM 77-24246.

27.5 BLOOD OXYGEN TRANSPORT IN A PASSERINE BIRD POSSESSING MULTIPLE HEMOGLOBINS. Leigh A. Magnuson and Peter H. S. Division of Biology and Medicine, Brown University, Providence, RI 02912.

Adult house sparrows (Passer domesticus) exhibit hemoglobin heterogeneity; parabolic focusing gels reveal two structurally distinct isohemoglobins in a three to one molar ratio. We measured isocapnic oxygen equilibrium curves (02EC) for the whole blood of birds in a dual wavelength spectrophotometer (542-560 nm) and electrodes. Oxyhemoglobin S. = (6.5 x 10^-5)P02/[(P02 + 402) + 2.4 x 10^-5] + 11^-1.

This complex 02EC shape may reflect the presence of multiple hemoglobins. The high P50 and steep upper limb of the 02EC will facilitate blood oxygen transport in small passerine birds at altitude. The fixed acid and CO2 Bohr effects (log P50/slope) were -35.3, 0.49 and 0.01, respectively. These results demonstrated a significant pH-independent effect of CO2 on S, affinity. The fixed acid and CO2 Bohr slopes were both independent of saturation. (Supported by NSF PCM92-0370.)

27.6 WHAT IS RESPIRATORY DEAD SPACE IN BIRDS? Randall H. Hastings and Frank L. Powell. Department of Medicine 233-C, University of California, San Diego, La Jolla, CA 92033.

In a porcine ventilated ducks we measured Ficks (VbO/VD) and inspired and expired gas data. Two VbO/VD dead spaces and compared them with upper airway plus instrument volume (VDA), VOB, and VDP were estimated as VT(F-PF/PE) where F-PF was the periferal, arterial and ideal-expired PO2 above the "critical" PO2. Supported by NSF Grant PCM 77-24246.
PROSTAGLANDIN (PG) PRODUCTION IN CANINE GASTRIC CELLS IN RESPONSE TO ACID SECRETION. M.L. Skoglund, M.R. Kelleher*, A.L. Vinik*, Department of Surgery, University of Michigan, Ann Arbor, MI 48109, and The Procter & Gamble Company, Cincinnati, OH 45247.

The effect of acid secretion on prostaglandin production was investigated by measuring the amount of PGE₂ produced by isolated gastric cells. It has been postulated that endogenous prostaglandins are produced by the gastric mucosa in response to acid secretion. Once produced, these prostaglandins could then act as negative feedback inhibitors of acid secretion. Thus, we have examined the effect of four different acid secretagogues (histamine, carbachol, gastrin, and secretin) on prostaglandin biosynthesis by canine gastric cells. Two Ca²⁺ dependent acid secretagogues, carbachol and gastrin, increased PG₂ biosynthesis by gastric cells. However, two Ca²⁺ independent acid secretagogues, histamine and secretin, decreased PG₂ biosynthesis by gastric cells. We conclude that acid secretion does not stimulate PG₂ production by gastric cells. Instead, prostaglandin synthesis is controlled by some other intracellular signal such as Ca²⁺, similar to control of prostaglandin synthesis by most other cell populations.
28.3 LOCALIZATION OF GASTRIN RECEPTORS ON CANINE FUNIC FUNIC MUCOSAL CELLS. Lovelik P. Thomas, V.1, Andrew H. Soll, and Deborah A. Amrigh*, CURE, VA Wadsworth and UCLA Medical Centers, Los Angeles, CA 90073.

While there is little controversy concerning the presence of histamine H2 receptors and muscarinic receptors on parietal cells, the focus of receptors for gastrin within the fundic mucosa remains uncertain. To determine extracellular gastrin receptor presence, canine fundic mucosal cells, we have studied the localization of gastrin receptors using radioligands. Biologically active (1-13-Leu)-gastrin-17 binds specifically and reversibly to canine fundic mucosal cells. When fundic parietal cells were separated by a Beckman elutriator rotor, (1-13-Leu)-gastrin binding correlated to the large cell fractions which contained extracellular elutriation separated enriched parietal cells only to about 55%. To further enrich parietal and chief cells, sequential step density gradients were performed using a Beckman ultracentrifuge and ficoll. In the lighter and denser fractions respectively, parietal and chief cells were enriched to greater than 90%. Specific (1-13-Leu)-gastrin binding correlated positively with parietal cells (r = 0.96) and negatively to chief cells (r = -0.93). To confirm the localization of gastrin receptors to the parietal cell, autoradiography was performed using cytocentrifuge slides coated with Kodak NTB. Discrete localization of silver grains was found to plasma membranes of parietal cells, but not of chief cells. With these techniques, we detect gastrin receptors on canine parietal cells, but not on chief cells.


The purpose of this study was to quantitate, by radioimmunoassay, the molecular forms of cholecystokinin (CCK) in the rat, hamster, and dog duodenum, using a carboxyl-terminal CCK antibody (CT-ab) which detected only the entire CCK molecule (E-ab).

Species: 
- Rat (E-ab): 115 ± 8.3 ng/g
- Hamster (E-ab): 114 ± 3.9 ng/g
- Dog (E-ab): 458.5 ± 146.5 ng/g


The biological activity of 58 amino acid cholecystokinin isolated from the canine intestine and brain was compared. Cholecystokinin affinity chromatography and High Pressure Liquid Chromatography possessed identical immunoreactivities to antisera specific to the amino terminus of CCK. Both the brain and intestinal CCK's were tested for their biological potencies in in vitro isolated mouse pancreatic acini and mouse brain particulate preparation. The results are as follows:

**CONC. OF PEPTIDE REQUIRED FOR MAX. AMYLASE 50% INHIBITION OF CCK BINDING:**

<table>
<thead>
<tr>
<th>Species</th>
<th>CT-ab</th>
<th>E-ab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rat</td>
<td>115 ± 8.3 ng/g</td>
<td>458.5 ± 146.5 ng/g</td>
</tr>
<tr>
<td>Hamster</td>
<td>114 ± 3.9 ng/g</td>
<td>146.5 ± 146.5 ng/g</td>
</tr>
<tr>
<td>Dog</td>
<td>458.5 ± 146.5 ng/g</td>
<td>458.5 ± 146.5 ng/g</td>
</tr>
</tbody>
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Results: Neither CCK was only an intracellular precursor of other smaller forms, or an important circulating hormone. It appears to be the major molecular precursor of all smaller forms in brain and gut. Our results, however, indicate that the CCK's have identical potencies, compared to CCK, in eliciting amylase release from acini and in the inhibition of CCK binding to membrane receptors.

28.6 SOMATOSTATIN INHIBITION OF CAERULEIN INDUCED PANCREATIC GROWTH. J. Meritett, Centre de recherche sur les mécanismes de sécrétion, Shebrooke University, Shebrooke, Que., Canada, J1K 2R1.

These studies were undertaken to evaluate the antiproteolytic property of somatostatin on caerulein induced pancreatic growth. Sprague-Dawley rats (200-270 g) were divided in 5 groups: control (C), caerulein (C), caerulein + ant somatostatin (C+AS), caerulein + somatostatin (C+S), and caerulein + somatostatin 600 µg/kg (C+5000). Rats were given the following S.C. in gelatin: saline (c), caerulein 1 µg/kg, caerulein 300 µg/kg, or caerulein + chrophate by 20% and anti SS. U.S: I. If once daily. They were fasted overnight before sacrifice. Caused significant increases in pancreatic weight (32%), total contents of protein (5%), amylase (35%), Chit (18%), RNA (33%), DNA (11%) and thymidine incorporation into DNA (64%). The addition of somatostatin to caerulein significantly increased pancreatic weight (10%), total DNA (10%) and thymidine incorporation (32%). At the 300 vs 600 µg/kg dose reduced significantly the following increases initiated by caerulein: pancreatic weight (9%), total protein (17%) and Chit (37%), and thymidine incorporation (51%). Total RNA and DNA were respectively reduced by 7% and 5%. In conclusion, inhibition of endogenous somatostatin by a specific antibody had an additive effect on the trophic effect of caerulein. These data indicate that somatostatin can reduce pancreatic growth induced by caerulein. Supported by grants 2864 from NERCC of Canada and 733 from the ME Quebec.


Three stimulants of gastric acid secretion, histamine, gastric and bombesin, are present in the canine stomach. An acid-binding substance was identified in acidic extracts of canine non-antral gastric tissues that stimulated acid secretion in the conscious and anesthetized rat. After high pressure liquid chromatography of activity eluted into a single peak, the material was found to contain gastrin, bombesin-like immunoreactivities nor histamine. The fraction eluting earlier on the HPLC was provisionally named OA-1 and the later eluting fraction, OA-2. Both fractions stimulated acid secretion when infused intravenously into urethane anesthetized rats prepared with gastric fistulas. Both fractions were purified and sequenced presumably due to a blocked amino terminus. The presence of Glx in the composition could be consistent with a pyroglutamyl residue at the amino terminus of this peptide. Ongoing work is aimed at purification of stimulants in larger amounts. Currently a chronic gastric fistula preparation in the conscious rat is being used as the bioassay, as it appears to be more sensitive to the two activties.

28.8 GAMMA glam VS HOMOLY-LIKE PLASMA IN THE INTESTINAL FLUID OF THE STOMACH. N. W. Bunnett*, M. S. Orloff*, J. H. Walsh, Center for Utce Research and Education, VA Wadsworth Mental Center, Los Angeles, CA 90073.

Bombesin-like neuropeptides in nerve fibers of the stomach wall are putative neurotransmitters and may be inactivated locally after secretion. To examine the local pathways of bombesin we have developed a new technique: dual tube fluid collection into DNA (464%). The addition of somatostatin to caerulein significantly increased pancreatic weight (10%), total DNA (10%) and thymidine incorporation (32%). At the 300 vs 600 µg/kg dose reduced significantly the following increases initiated by caerulein: pancreatic weight (9%), total protein (17%) and Chit (37%), and thymidine incorporation (51%). Total RNA and DNA were respectively reduced by 7% and 5%. In conclusion, inhibition of endogenous somatostatin by a specific antibody had an additive effect on the trophic effect of caerulein. These data indicate that somatostatin can reduce pancreatic growth induced by caerulein. Supported by grants 2864 from NERCC of Canada and 733 from the ME Quebec.
STIMULATORY EFFECT OF THE MONOAMINE OXIDASE (MAO) INHIBITOR, N-MILAMIDE, ON AMINO ACID-INDUCED GASTRIN (G) SECRETION. T. Lichtenberger, L.A. Graziant & K. Delansane. University of Texas Medical School, Houston, TX 77025.

We have reported that amino acids present in the diet or produced intracellularly by the decarboxylation of amino acids, are potent in vivo and in vitro stimulants of G release (Am. J. Physiol. 243:G429, 1982). If amino acids are intracellular stimulants of G release, it would follow that the activity of the degradative enzyme, MAO, in the enteral mucosa should play an important role in the regulation of the local concentration of amino acids that stimulate G release. In order to investigate this possibility, the effect of secretory stimulants on G release from both in vivo and in vitro systems was studied in the presence of the MAO inhibitor, n-milamide. In the in vivo studies it was demonstrated that serum G levels 1 hr after ingestion of an amino acid rich-vitamin meal were significantly (P<0.01) increased by a milamide pretreatment (200 mg/kg, i.p.). Similarly, G release from isolated G cells in response to phytosynine (500 ng/ml) was significantly (P<0.01) increased 3.2 fold if rats were pretreated with milamide (200 mg/kg, i.p.). Similar results have been obtained with L-tryptophan, L-glycine, and L-arginine. Furthermore, n-milamide pretreatment (200 mg/kg, i.p.) results in a significant (P<0.05) decrease in mammary gland RNA and DNA contents on day 1 of lactation. We also found that L-tryptophan and L-glycine significantly increased the RNA or DNA values. Our data suggests that L-glycine, which whereas L-tryptophan had a positive effect only on the latter parameter, does not influence the secretion of G. This study was supported by NII Grants AM06560 and AM06842.

POTENTIATION OF HISTAMINE BY GASTRIN IN THE GASTRIC FISTULA DOG. Tobias D. Yellin* and Richard A. Macia,. (Spon: G. A. Feigen). Biomimetic Research Department, Stuart Pharmaceuticals, Division of ICI Americas Inc., Wilmington, DE 19897.

The maximal acid response to histamine (0.5 μmol/kg/hr) was reduced by atrazine (100 μg/kg i.v.), whereas the secretagogue action of pentagastrin (2 μg/kg/hr) was abolished. The characteristic fade observed with control histamine infusions was absent in atrazine treated dogs. Atrazine's effects could not be overcome by doubling or quadrupling the dose of histamine nor by vagal stimulation with 2-deoxy-D-glucose (200 mg/kg, i.v.). Nevertheless, the response to histamine (0.5 μmol/kg/hr), with a rate of food not different from control, was fully restored by the addition of 10' M and 10' M milamide respectively to the incubation medium.

Conclusions: Inhibition of MAO activity results in an enhancement in amino acid-induced G release. Thus, the intracellular amino acid concentration plays an important role in the regulation of G secretory activity. (Supported by NIH Grants AM06560 and AM06842).

THE STIMULATORY EFFECT OF REPRODUCTIVE AMINO ACIDS ON DIMETHYL-BENZANTHACRENE (DMBA) PRIMED MAIMARY GLAND MACROPHAGE ACTIVITY DURING LACTATION. Howard S. Pitkow, Michael Goldman & Bill Urban*. Penna. Col. of Podiatric Med., Phila., PA. 19107

Our laboratory has reported that DMBA administered to pregnant rats caused a significant decrease in mammary gland RNA and DNA contents on day 1 of lactation. We also found that some amino acids had gonadotropin-like and/or estrogen-like activity. In order to determine the effects of reproductive amino acids on MMR primed mammary gland tissue, female adult virgin Long Evans rats (12 animals/group) were intraperitoneally injected with 1 μg DMBA in 0.2 ml sesame oil on days 0 through 12 of pregnancy. On days 0 through 17 of gestation these rats were subcutaneously injected with 100 μg/kg body weight of DMBA (100 μg/kg body weight of DMBA) or saline. At 1 week after pregnancy, sera were separately injected into rats denervated for the production of normal serum. Conclusions: The elevated gastric acid response associated with DMBA is already present prenatally, and seems to be dosage related rather than dosage-related. Finally, a strong family history and elevated gastrin levels further strongly support an inherited basis of DMBA in children. (Supported by a grant from N.I.H.-NIH).

28.9
GASTRIN SECRETION AND BLOOD LEVELS OF GASTRIN PEPSINOGEN I IN CHILDREN WITH PRIMARY DUODENAL ULCER. D.L. de Angelis*, S. Stute*; G. Darchuk*; S. Dreger*; & R. Melina. Hospital and University of Parma, Italy.

We studied 5 cases of duodenal ulcer (D.U.) in male children (mean 8.8 yrs., range 6-12 yrs., mean weight 28.4 kg.). Ten healthy children, matched for weight, age and sex were used as controls. All the 16 children were studied by: 1) a protein meal for gastrin and pepsinogen I response; 2) pepsinogen 6 mg/kg i.e. for acid secretion.

RESULTS
NORMAL (--10) DUODENAL ULCER (+-5)

<table>
<thead>
<tr>
<th>A) GASTRIN pg/ml</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>basal</td>
<td>67.5</td>
<td>7.3</td>
</tr>
<tr>
<td>peak after food</td>
<td>115.0</td>
<td>22.2</td>
</tr>
<tr>
<td>PEPSINOGEN I mg/l</td>
<td>112.7</td>
<td>4.7</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>B) RAO mg/kg/hr/kg b.w.</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>basal</td>
<td>48.7</td>
</tr>
<tr>
<td>peak after food</td>
<td>8.0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>C) MACS mg/kg b.w.</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>basal</td>
<td>23.2</td>
</tr>
<tr>
<td>peak after food</td>
<td>4.5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>D) NAO mg/kg b.w.</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>basal</td>
<td>0.223</td>
</tr>
<tr>
<td>peak after food</td>
<td>0.217</td>
</tr>
</tbody>
</table>

Fetal ethanol-exposed (FEE) rats show enhanced corticosteroid exposure to ethanol (E) and morphine (M) as adults. These same challenges were given to newborns, resulting in reduced fetal effects in FEE rats. Serum corticosteroids were measured by radioimmunoassay. In contrast to the adult findings, pups showed an enhanced response to both E and M, only the latter being significant (P<0.01). Responses to saline were: 17.6±1.1 (SEM) µg/ml in normal pups, 14.7±1.9 µg/ml in pair-fed to saline and 27.3±2.2 µg/ml in E-derived pups. These results suggest that tolerance to ethanol (E) and morphine (M) may be delayed in FEE pups, which may be due to multiple stressors of birth, maternal deprivation and/or social isolation.

Developmental patterns for these effects are now being determined. (Supported by VA Medical Research Service.)

29.5
THE EFFECT OF PROSTACYCLIN ON ANGIOTENSIN II INDUCED PLACENTAL VASOCONSTRICTION. V.M. Kirk*, J.H. Mann*, and K.W. Kirk*, Univesity of Wisconsin, Madison, WI 53706.

Significant alterations in vascular responsiveness to angiotensin II (ATII) have been observed during pregnancy, and we have observed that PGI2, a potent vasodilator, does not dilate the placental vasculature of sheep. We measured the local responsiveness to ATII, 100 nM and 1 µM, in pregnant and non-pregnant sheep. Placental blood flow (BF, ml/min/gm) and the renal and uterine vasculatures showed the expected vasoconstrictor effect of ATII. The renal and uterine vasculatures showed the expected vasodilator effect of PGI2. Unexpectedly, PGI2 did not reverse the ATII vasconstriction in the placenta, but further increased R (P<0.05).

We conclude that PGI2 does not modulate the ATII induced placental vasconstriction. Further studies are necessary to determine if PG12 does not modulate ATII-induced placental constriction to ATII, which was then reversed to control levels by PGI2. Unexpectedly, PGI2 did not reverse the ATII vasconstriction in the placenta, but further increased R (P<0.05).

29.6
FEEDBACK CONTROL OF FETAL PLACENTAL BLOOD FLOW IN 11 LAMBS. Debra F. Anderson and J. Job Faber, Dept. Physiol., S.M., OHSU, Portland, OR 97201.

Placental blood flow was monitored by means of a sensor on the aorta below the renal arteries and injections of radiolabelled microspheres. An occluder was placed distal to the flow sensor. After a control period of one week, placental blood flow was reduced by 50%. The results indicate that the placenta is able to maintain an average of 54% of its control value by means of the occluder; no increase for presumed fetal growth was allowed. Fetal arterial Po2 and pH fell after restriction; changes (control vs restricted) in arterial blood pressure proximal to the occluder (50 vs 50 mm Hg) and hematocrit (34 vs 35 %) were not significant. Fetal placental resistance decreased from 0.35 to 0.38 KU/ml (KU/ml) which is approximately the normal rate of decrease in the last third of gestation in sheep. The fetuses continued to grow at a rate of 2.0 %/day (KU/ml), and again 10 min after removing ATII while continuing II (TC). Results are shown below:

<table>
<thead>
<tr>
<th>Blood Pressure (mmHg)</th>
<th>84.6 105 119 66.6 86.9 54.2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal R (PRH)</td>
<td>0.390 0.372 0.352 0.293 0.293</td>
</tr>
<tr>
<td>Uterine R (PRH)</td>
<td>0.640 0.124 0.621 0.621 0.621</td>
</tr>
<tr>
<td>Placental R (PRH-kg)</td>
<td>0.332 0.42 0.42 0.42</td>
</tr>
</tbody>
</table>

The renal and uterine vasculatures showed the expected vasoconstrictor effect of ATII. The renal and uterine vasculatures showed the expected vasodilator effect of PGI2. Unexpectedly, PGI2 did not reverse the ATII vasconstriction in the placenta, but further increased R (P<0.05).

We conclude that PGI2 does not modulate the ATII induced placental vasconstriction. Further studies are necessary to determine if PG12 does not modulate ATII-induced placental constriction to ATII, which was then reversed to control levels by PGI2.

29.7
LEFT VENTRICULAR STROKE VOLUME IN THE VENTILATED FETUS. K.L. Thornburg and M.J. Morton*, Dept. of Physiology and Medicine (Heart Research Laboratory), Oregon Health Sciences University, Portland, OR 97201.

Left ventricular stroke volume (LVSV) increases substantially at birth in the lamb despite increased arterial pressure. This increase in LVSV is not explained by elevated filling pressure. In order to determine the role of venules in augmenting LVSV, we performed pair-fed and fetal lambs with a tracheal occluder, aortic electromagnetic flow sensor, carotid, jugular, pericardial and left atrial catheters. After 9-21 days (mean ± SD) postpartum, the fetal lambs were allowed to breathe spontaneously. Blood flows were generated by rapidly withdrawing and infusing blood before and during in utero ventilation (VENT) with 100% O2 to determine maximum LVSV (LVSVmax). Two lambs were hypoxic and two lambs were hyperoxic, but showed a 25% increase in LVSVmax during VENT. In 4 lambs, O2 content doubled (17.1 ± 2.1 ml/dl) during VENT. These lambs showed a 56% increase in LVSVmax during VENT. We conclude that: 1) the fetal lamb can be resuscitated in utero; 2) VENT itself augments LVSVmax; 3) oxygenation further augments LVSVmax; 4) LVSV in the ventilated, oxygenated fetus increases substantially; and 5) the increase in LVSV is not explained by elevated filling pressure.

29.8
THE PERICARDIUM IMPROPTLY AFFECTS FETAL CARDIAC FILLING PRESSURE. Mark J. Morton* and Kent L. Thornburg. Oregon Health Sciences University, Portland, OR 97201.

Pericardial restraint of cardiac filling is well described in adult animals. However, it is not clear what factors account for this restraint in the fetus. We hypothesized that pericardial restraint is primarily referenced to amniotic fluid pressure (AM). Accordingly, we investigated the contribution of pericardial (PC) and thoracic pressure (TH) to observed mean right atrial pressure (RA). PC and RA were measured in 21 fetal lambs with a pair-fed and a fetal lamb with a tracheal occluder, a sutured pericardial and polyvinyl pleural catheter, both with multiple side holes. Continuous tracings showed no evidence of pericardial or pleural constriction. PC levels were performed 10 days (range 4-21) after surgery. Amniotic, pleural, pericardial and RA were measured during rapid hemorrhage and resuscitation or blood transfusion. We found that fetal pericardial fluid was added and measurements repeated. Transmural pressures during control were RA-PC 2.7 ± 1.5, PC-TH 1.2 ± 1.6, TH-AM 0.2 ± 0.2. After transfusion, PC-TH remained at control until RA-TH was 3.9 ± 1.4 mm Hg. At higher RA-TH pressures, PC-TH rose linearly with slopes ranging from 0.5 to 0.1. Addition of fluid to the pericardium shifted the PC-TH vs RA-TH relationship to the left with a slightly steeper slope. We conclude that the pericardium importantly restrains fetal cardiac filling at pressures above control, addition of volume to the pericardium further restrains cardiac filling, lastly that fetal cardiac growth must be permitted by increased pericardial volume. (Supported in part by NIH HL 29224.)
29.9 EFFECT OF ISCHEMIA ON FATTY ACID METABOLISM IN THE LUNG OF RABBIT FETUSES. Anita Moodk and Dipak K. Das, State University of New York at Stony Brook and Long Island Jewish-Hillside Medical Center, New Hyde Park, New York 11042.

The effects of ischemia on in vivo fatty acid metabolism in fetal lungs were studied using rabbits fetuses of 25 to 28 gestational age. Ischemia was produced by inflating the aortic balloon thereby reducing the uterine blood flow. Ischemic insult resulted significant increase in lactate/pyruvate and NAD/NADH ratios and decrease in ATP/ADP ratio in the fetal lung. Levels of CoA, acetyl CoA, carnitine and acyl carnitine decreased while those of long chain acyl CoA and long chain acyl carnitine enhanced. Tissue content of these metabolites returned to normal after 2 hr stabilization following 20 min of ischemic insult. Ischemia also caused small increase in the lypogenesis and the neutral lipid content of the fetal lungs. Our results thus suggest that oxidation in fetal lung is inhibited and becomes rate-limiting for the fatty acid oxidation during ischemia (supported in part by a grant from the Long Island Jewish-Hillside Medical Center).


We have previously reported perturbations in perinatal blood glucose (BG) levels in the offspring of rats fed ethanol (EtOH) during pregnancy. To provide insight into these effects, liver glycogen (LG) levels were measured in term fetuses and neonates of rats fed liquid diet containing moderate (2.8% w/v, ME) or high (5% w/v, HE) levels of EtOH. Controls were pair-fed (MP and HP) and ad libitum-fed (A) diet in which carbohydrates replaced ethanol isocalorically.

Maternal weight gain and term fetal weights were significantly reduced (p < 0.001) in groups HE and HP due to reduced maternal food intake. Ethanol intake was 3.3 ± 0.1 and 2.5 ± 0.1 g/day for groups HE and ME. LG was significantly reduced (p < 0.01) in carnitine-derived term fetuses from HE rats (42.7 ± 6.0 mg/g liver vs 94.3 ± 2.6 in HP controls and 92.4 ± 5.4 mg/g liver in A controls). Liver glycogen levels were 70.7 ± 7.2 mg/g liver in HE and ME fetuses and 106.9 ± 8.5 in MP control fetuses. LG was depleted more rapidly in both ethanol-fed groups. Four hours after delivery, 15% of HE and 57% of ME term LG stores remained, compared to 4% in A and 81% in MP and HP offspring. Simultaneously, HE offspring were significantly hypoglycemic relative to the other groups. It is concluded that ethanol exposure in utero can alter glycogen levels in the perinatal period. Research supported by the VA.

29.11 THE EFFECT OF CHRONIC ALCOHOL CONSUMPTION IN MATERNAL EFFICIENCY IN PRODUCTION OF FETAL TISSUE. T. Kepic*, A. Snyder*, S. Singh and M. Bennett*, Chicago Medical School and VA Medical Center, North Chicago, IL 60064.

We studied the effects of chronic ethanol (EtOH) consumption during pregnancy on maternal nutrient storage and efficiency in production of fetal tissue. Timed-pregnant Sprague-Dawley rats were assigned to three groups: One group (EF) received liquid diet containing EtOH, 5% w/v. Control diet was provided by pair feeding (group PF) or ad libitum (group AF). Weight gain was reduced in both EF and PF dams (p < 0.001). Liver (LI), lung (LU) and placenta (PL) from carnitine-derived term fetuses were used for wet weights. There was a significant decrease (p < 0.001) in body weight (BW) and LI, LU and PL wet weights in the EF pups as compared to PF and AF groups. Maternal efficiencies were expressed as mean offspring body or organ weight per kcal maternal food consumption. Efficiencies of AF dams were the same or significantly greater than those of EF dams for SW (4.68 ± 0.58 p < 0.001), LI (24.28 ± 3.78 p < 0.001), LU (11.58 ± 0.81 p < 0.02) and PL (43.49 ± 4.01 p < 0.001) in agreement with previous reports for undernourished animals. Moreover, it appears that EtOH interferes significantly in the efficiency of production of LI (12.61 ± 2.74), LU (6.74 ± 0.48) and PL (35.67 ± 6.74). Research supported by VA.

29.12 CALCIUM CONTENT AND WEIGHT OF VENTRICULAR MYOCARDIUM DURING EARLY DEVELOPMENT - INFLUENCE OF ANGIOTENSIN II, NORPHEPHRINE AND NUTRITIONAL INTAKE. Maurice S. Holder, Zelda D. Johnson and Laval N. Cothran*, College of Pharmacy, Florida A&M University, Tallahassee, FL 32307.

Physiological demands are thought to induce structural and contractile alterations in the myocardium even in the early stages of development. Such alterations may be mediated by local humoral agents and subject to nutritional intake. The involvement of Angiotensin II (Ag II), Norcinephrine (NE) and different diets in the alteration process was investigated in developing rats at 4 and 6 weeks of age. Ventricular weight (VW), body weight (BW), free calcium in myocardium (MCa) and plasma (PCa) were determined after periods of chronic Ag II, NE and Calcium gluconate (Ca++) treatment, and after regulation of type and amount of nutritional intake. Three groups of rats were studied, slow growers (SG), medium growers (MG) and fast growers (FG) depending upon the rate of post partum development. Results show that the pattern of VW/BW change seen in control rats was common in SG, MG and FG although there was a marked inter group difference in absolute size of heart and body with age. The difference was more pronounced at 4 than at 8 weeks. Diet rich in carbohydrate, protein or lipid significantly increased (p < 0.01) BW/BW, however, its decreasing pattern from 4 to 8 weeks was still present. Ag II but not NE significantly inhibited it. Diet types did not affect the level of MCA or PCA, however, both Ca++ and Ag II increased MCA at 4 and 8 weeks (p < 0.01% while PCA was relatively unchanged. The most pronounced change in VW/BW was induced with Ca++ and both this and the Ag II effect was inhibited with Verapamil. The results suggest that the observed alterations in myocardial size may be Ca++ related and that Ag II plays a positive role in the response. (Supported by DRRMBRS NHLBI 80111).
30.1 ROLE OF THROMBOXANE (TxA2) IN THROMBIN-INDUCED INCREASE IN LUNG MICROVASCULAR PERMEABILITY.

In a model of thrombin-induced alterations in lung microvascular permeability, we examined the role of TxA2 by using a specific antagonist, SQ 29,548, and by utilizing the indomethacin-resistant TxA2 synthetase inhibitor SQ 29,548. Using this approach, we determined the effect of thrombin on lung lymph flow, protein concentration, and lymphatic permeability. In addition, we studied the effect of indomethacin on the responses to thrombin.

We found that thrombin-induced increases in lung lymph flow, protein concentration, and lymphatic permeability were attenuated by SQ 29,548, but not by indomethacin. These results suggest that TxA2, but not prostaglandin (PG) E2, plays a role in the increase in lung microvascular permeability induced by thrombin.

30.2 ALVELOGRAPHIC CONTRIBUTIONS TO CAUSAL MEDIALISTINAL NODE ENLARGEMENT.

We studied the role of TxA2 in the enlargement of the causal mediastinal node (CMN) in a sheep model of pulmonary edema. The CMN was isolated by interruption of the aorta and pulmonary artery, and the CMN perfusion was studied before and after the administration of SQ 29,548.

We found that SQ 29,548 significantly reduced the CMN perfusion, suggesting that TxA2 plays a role in the enlargement of the CMN.

30.3 MEDIATORS OF TRACHEOBRONCHIAL FLUID FORMATION AND PULMONARY DESTRUCTION FOLLOWING SMOKE INHALATION.

We studied the role of leukocytes in the formation of tracheobronchial fluid (TBF) following smoke inhalation. We found that leukocyte depletion significantly reduced TBF formation, suggesting that leukocytes play a role in the formation of TBF.

30.4 EFFECTS OF ALLOXAN ON PULMONARY MICROVASCULAR PERMEABILITY AND LUNG INJURY.

We studied the role of leukocytes in the formation of TBF following smoke inhalation. We found that leukocyte depletion significantly reduced TBF formation, suggesting that leukocytes play a role in the formation of TBF.

We also studied the role of leukocytes in the formation of TBF following smoke inhalation. We found that leukocyte depletion significantly reduced TBF formation, suggesting that leukocytes play a role in the formation of TBF.

30.5 THE EFFECT OF BUNAMIDE (B) ON CACHETE OLEIC ACID (OA) INHIBITION OF LUNG INJURY.

We studied the role of bunaamide (B) on the inhibition of lung injury caused by oleic acid (OA) treatment. We found that B significantly reduced the lung injury caused by OA treatment, suggesting that B plays a role in the inhibition of lung injury.

30.6 LEUKOCYTES ARE NOT REQUIRED FOR OLEIC ACID INDUCED LUNG INJURY IN SHEEP.

We studied the role of leukocytes in the inhibition of OA-induced lung injury. We found that leukocyte depletion significantly reduced the lung injury caused by OA treatment, suggesting that leukocytes do not play a central role in the inhibition of OA-induced lung injury.

We studied the effect of methylprednisolone (MP) or ibuprofen (IBU) pretreatment on oleic acid-induced lung injury in anesthetized sheep with lung lymph fistulas. We measured pulmonary arterial (Ppa) and left atrial (PLa) pressures, cardiac output (Q), cardiac index (CI), pulmonary vascular resistance (PVR), and PA pressures, cardiac output (Q), lung lymph flow (L) and lymph/plasma protein concentration ratio (L/P). We calculated pulmonary vascular resistance (PVR) = (Ppa - PLa)/Q.

We conclude that MPS, partially protects the pulmonary arterial circulation plus its weight change. LLL injury (reflected in each category).

MPS (4) 18 5 8 0 100 0 3 0
Control (1) 19 25 3.3 10 2.2 0 0

We studied seven awake sheep with lung lymph fistulas to determine whether alpha adrenergic receptors in the pulmonary circulation play a role in normal lung fluid balance. We measured pulmonary arterial (Ppa) and left atrial (PLa) pressures, cardiac output (Q), lung lymph flow (L) and lymph/plasma protein concentration ratio (L/P). We calculated pulmonary vascular resistance (PVR) = (Ppa - PLa)/Q.

We conclude that beta receptors are not involved in normal lung fluid balance in sheep. (Supported by NHLBI 5 P01 HL-19155 and MRC Canada)

30.8 BETA RECEPTORS AND LUNG FLUID BALANCE IN AKEHWE P. L. Culver, W.H. Rao, P. Dodde and N.C. Staub. Cardiovascular Research Institute and Department of Physiology, University of California, San Francisco, CA 94143.

Previously, we reported an interstitial fluid pressure (IFP) measurement by intravascular ultrasound of the lung. We now report IFP at two inflation levels. We blood perfused 2 isolated lower lobes of dog lungs which we continuously weighed. When lobe weight doubled we equalized vascular pressures to 10 cmH2O to avoid vascular compromise. We conclude that IFP measured in dog lungs is similar to that found in man.

At the lower inflation IFP was 4.6 cmH2O less than alveolar pressure. When alveolar pressure was increased, IFP increased slightly (P<0.01). We conclude that in edematous lungs, first alveolar pressure was poorly transmitted to the peri-alveolar interstitium; second, inflation increased Pd, probably by compressing interstitial fluid. (Supported by the California Lung Association.)

30.10 INTRAVASCULAR FLUID PRESSURE MEASURED BY MICHROSCOPY OF ISOLATED, EDEMATOUS DOG LUNGS AT DIFFERENT LEVELS OF INFILATION. J. Bhattacharya, M.A. Gropper and A. Eaton. Cardiovascular Research Institute and Department of Physiology, University of California, San Francisco, CA, U.S.A. 94143.

Previously, we reported an interstitial fluid pressure (IFP) measurement by intravascular ultrasound of the lung. We now report IFP at two inflation levels. We blood perfused 2 isolated lower lobes of dog lungs which we continuously weighed. When lobe weight doubled we equalized vascular pressures to 10 cmH2O to avoid vascular compromise. We conclude that IFP measured in dog lungs is similar to that found in man.

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30.13

EFFECT OF BLOOD pH ON LUNG HYPOXIC MICROVASCULAR PRESSURE

In cats, I. Rohovzov, A. Wolfson, M.A. Grenier, and M.C. Staub. Cardiovascular Research Institute and Dept. of Physiology, University of California Los Angeles, CA 90024.

We investigated the effects of hypoxic vasoconstriction in cats (Fed Proc 42:556, 1983). We measured the blood flow at the level of the superior pulmonary vein (SPV) and the left atrium (LA) and the pulmonary artery (PA) in 14 cats, comparing the pressure at each level.

In hypoxic vasoconstriction in cats (Fed Proc 42:556, 1983), the blood flow at the level of the superior pulmonary vein (SPV) and the left atrium (LA) was significantly lower compared to the pulmonary artery (PA). This suggests that hypoxic vasoconstriction occurs in the pulmonary vasculature.

30.15

CYCLOSPORIN A (CYA) AND DEXAMETHASONE (DX) PROTECT

RATS AGAINST THE CAPOULMONARY EFFECTS OF MONOCYTO-C


Mastocytosis is a mild disease in humans, but it can be a more severe condition in rats. The study investigated the effects of cyclosporin A (CYA) and dexamethasone (DX) on the pulmonary circulation in MCTP-treated rats.

In MCTP-treated rats, CYA and DX were administered daily. The results showed that CYA and DX were effective in protecting against the pulmonary effects of MCTP.

30.16


Bronchial artery vasoconstriction has been postulated as a mechanism in the induction of bronchial hyper-reactivity. The study investigated the effects of cold air hyperventilation on bronchial blood flow in human subjects.

During cold air hyperventilation, there was a significant decrease in bronchial blood flow, indicating that bronchial vasoconstriction occurs in response to cold air.

30.17

PULMONARY VASCULAR RESISTANCE (R) IS NOT STRONGLY DEPENDENT ON LUNG VOLUME (Vl).

K.C. Beck and S.J. Lai-Yook, Mayo Clinic, Rochester, MN.

R in isolated lungs is dependent on VI, the variation of R over the range of VI becomes less at higher vascular pressures (Beck et al., Fed Proc. 44:162). To determine the implications of these findings for distributions of R in intact lungs in which VI increases and vascular pressures decrease, with breathing, the relationship between blood flow and pulmonary vascular resistance was determined using data from isolated perfused rabbit lungs in zones 2 and 3.

In hypoxic vasoconstriction in cats (Fed Proc 42:556, 1983), the blood flow at the level of the superior pulmonary vein (SPV) and the left atrium (LA) was significantly lower compared to the pulmonary artery (PA). This suggests that hypoxic vasoconstriction occurs in the pulmonary vasculature.

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31.1

PREDICTION OF BODY COMPOSITION BASED ON WHOLE BODY ELECTRICAL IMPEDANCE. Lyle H. Hamilton, Steven M. Horvath, Michael G. Maksud, Ernest D. Michael, Gerald B. Spurr, Ronald L. Jackson. Wood Va Med. Ctr. and Med. Coll. of Wisconsin, Milwaukee, WI; Univ. of Calif., Santa Barbara, CA 93106; Oregon State Univ., Corvallis, OR 97331.

Measurements of whole body impedance (Z) or the ratio of Z at two frequencies have been proposed as an index of body composition. Anthropometry, body density (BD) by underwater weighing, skin-fold thickness (SF) at 3 sites (in most subjects) and Z at 10 KHz (EL) and at 100 KHz (EM) were measured in 43 males (39) and 93 females (F4) ranging in age from 18 to 71 years.

Most were college students in good to excellent physical condition. Correlations between body fat calculated by density and body surface area were generally based on the method of Jackson and Pollock (r = 0.721 for M and 0.760 for F). Correlations between body density and ZL/HL and the ratio ZL/HL (ZL) were, respectively: r = 0.21, r = 0.157 and r = 0.417 for M and r = 0.203, r = 0.200 and r = 0.354 for F. Multiple regression analyses were necessary to provide prediction equations useful for body density. Equations were:

M: BD = 0.231119 + 0.00115432ZL - (1.772 × 10^-3)Wt - (1.774 × 10^-3)ZH

F: BD = 0.22019 + 0.00088202ZL - (3.524 × 10^-3)Wt - (7.029 × 10^-3)ZH

With coefficients for F, but not for M, multiple correlation coefficients were 0.207 (r2 = 0.041) and 0.279 for F.

31.2

NASAL SALT GLAND SECRETION INHIBITED BY ANGIOTENSIN II. H. T. Hameel and J. E. Maggert. Physiological Research Laboratory, Scripps Institution of Oceanography, La Jolla, CA 92037.

Adult Pekin ducks received an intravenous control infusion of 1000 meeq NaCl/Kg H2O at 0.4 ml/min for 90 min. The amount of salt and water secreted by the nasal salt glands was 100+5% of the amount infused. When the infusion included Angiotensin II (Asp-Arg-Val-Tyr-Ile-His-Pro-Phe), Sigma A4390, at the rate of 8×10^-9 gm min^-1 Kg^-1, 70% of the salt solution was secreted during the infusion and 20% subsequently. When angiotensin II accompanied the infusion at the rate of 8×10^-9 gm min^-1 Kg^-1, only 1% of the salt solution was secreted during infusion and more than 90% was secreted during the subsequent 60 min. Since the rate of secretion by the nasal salt gland cannot be fully explained by variations in plasma osmolality, NaCl concentration, extracellular and intracellular volumes, we postulate that variations in the circulating level of Angiotensin II are affecting the secretory rate, NSF Grant PCM 78-23460.

31.3


A two-week intranasal saline infusion (1250 ml/kg body weight) resulted in a significant increase in circulating concentrations of endogenous AVT, a vasopressin-like hormone, in normal and apoplexy-prone turkeys. The increase was significant in the saline-adapted ducks and was accompanied by a significant increase in the cholinergic activity of the nasal glands, indicating that AVT may play a role in the regulation of nasal gland function.
31.5 HIGH METABOLIC ACTIVITY IN THE SEPTAL TRIANGULAR NUCLEUS IN RAT MODELS OF THIRST. M. Kadokawa*, P.J. Ross*, A. Sokoloff, Laboratory of Cerebral Metabolism, NIMH, Bethesda, MD 20892.

The septal triangular nucleus (STN) and subfornical organ (SFO) have been regarded as essential components of the circuit of structures subserving fluid balance. Anatomical studies have demonstrated: 1) afferent fibers from STN to SFO; and 2) merging of the ventrocaudal extent of STN with the ventral stalk of SFO, findings that suggest a functional relationship between these two structures. We previously reported high rates of glucose metabolism in the SFO of homologous rat brain tissue maintained in a collodion bag at 37°C. Using 14C-deoxyglucose method and computerized image-processing, we have demonstrated high metabolic activity in the STN of thirsty animals. Rates of glucose utilization are significantly higher in the STN of dehydrated animals compared to the respective control. These findings indicate that the STN is a locus of high metabolic activity during conditions of thirst.


Pichinde virus produces fatal infections without marked histopathological changes. Height loss of 25% of initial body weight occurs between days 13-19. Plasma AVP levels were 25-50% of normal. Increased AVP levels have been reported in cirrhosis of liver and in dehydrated rats. Although the mechanism of AVP release is unknown, we hypothesized that the increase in AVP is secondary to renal hemodynamic changes. To test this hypothesis, we examined the renal function and electrolyte balance of guinea pigs infected with Pichinde virus. Guinea pigs were divided into two groups: group 1 was infected with Pichinde virus and group 2 was infected with control virus. The infected animals were compared to age-matched control animals. The results showed that the plasma AVP levels were significantly higher in the infected group compared to the control group. The plasma AVP levels were also correlated with the changes in body weight and electrolyte balance. The results suggest that the increase in AVP levels is secondary to renal hemodynamic changes in Pichinde virus infection.


Plasma protein concentration (PPC) was increased in unanesthetized dogs over a 17 day period by daily intravenous infusion of 30 ml autologous plasma to determine the long-term effects of hyperproteinemia on renal function and arterial pressure. The renal function tests of the plasma PPC group of dogs revealed a 10% increase in GFR compared to controls. The PPC group also showed a 10% increase in urinary protein excretion.


Extract from the right atrium contains a substance which acts as a competitive inhibitor of angiotensin II. The rabbit aortic ring was bathed at 37°C in 10 ml of oxygenated Krebs buffer. Dose-response curves to ATII (2.5 to 100 ng/ml) were measured in the presence of various concentrations of AE. Extract from the left atrium has no effect on the contractile response of rabbit aortic rings to ATII.

31.9 PLASMA AND CEREBROSPINAL FLUID VASOPRESSIN DURING DEHYDRATION IN THE STEER. F.R. Bell* and P.A. Doris*.

Hematocrit increased from 39.9 ± 0.64% to 44.1 ± 1.24% of control. Vasopressin (AVP) was secreted into blood. (Supported by The Wellcome Trust and Medical Research Council, GB.)

31.10 RENAL FUNCTION IN WATER-SATURATED AND WATER-DEPRIVED RATS. M. Kadekaro*, P.M. Gross, & L. Sokoloff. UCLA Medical School, Los Angeles, CA 90024.

The subjects were given water p.o. until endogenous AVP was suppressed. A bolus of 2 U. of Pitressin was injected i.v. 10 min. for next 40 min., and every 20 min. for another 60 min. Increased AVP levels have been reported in this disease. Whether the AVP levels are due to secretion or release remains to be determined in the future.

Hemodynamic responses and ADH were measured during body position changes designed to induce central blood volume shifts in 10 cardiac transplant subjects to assess the contribution of cardiac volume receptors in the control of ADH release. Each subject underwent 15 min of sitting control period (C) followed by 30 min of 5° head-up tilt (T) and a 30 min of resumed sitting (S). Venous blood samples and cardiac dimensions (echocardiography) were taken at 0 and 15 min of C, 5, 15, and 30 min of T, and 15, 30, and 45 min of S. Blood samples were analyzed for hematocrit and ADH. Plasma volume (PV) was measured by T-1826. Heart rate (HR) and mean arterial pressure (MAP) were recorded at 15 min (PV) in T but returned to C levels following S. Heart volume was increased (PV) with T and reduced (PV) with S. These responses were similar in control subjects. Preliminary data demonstrated that ADH was reduced with T and increased with S in cardiac transplant subjects as well as controls. These data may suggest that cardiac volume receptors are not significant in the control of ADH release in man.

32.1 RESTORATION OF NORMAL DYNAMIC INSULIN SECRETION IN AGING RATS. Francis H. Premachandra and Joseph M. Molina* and Loren G. Lipson. U.S.C. School of Medicine, Los Angeles, California 90033.

Glucose-stimulated insulin secretion is decreased from islets of older rats. We present postulate for this have been decreased activity of adenylate cyclase and decreased glucose oxidation. In attempts to define this age-related defect, we showed that insulin secretion to D-glycerohyde is not diminished in aging. To further explore this in the effects of D-glycerohyde versus D-glucose in aging and to ascertain if normal insulin release could be restored in islets of older rats, dynamic insulin secretion from isolated islets from 2.5 and 13 month old rats was studied by perfusion to 2.8 mM and 16.7 mM D-glucose or 2.8 mM D-glucose with 5, 10, or 14 mM D-glycerohyde. The resulting perifusates were assayed for insulin by RIA. Total insulin release was reduced by 36% from islets of older rats in the presence of 16.7 mM D-glucose, but total release was similar from both islets of older and young rats in the presence of 16.7 mM D-glycerohyde. The release process from older rats was increased by 101 ± 4 bpm in C to 94 ± 4 bpm in T and returned to 101 ± 4 bpm with S. MAP was not significantly altered during body position changes. PV was increased by 6.2±(PV) in T but returned to C levels following S. Heart volume was increased (PV) with T and reduced (PV) with S. These responses were similar in control subjects. Preliminary data demonstrated that ADH was reduced with T and increased with S in cardiac transplant subjects as well as controls. These data may suggest that cardiac volume receptors are not significant in the control of ADH release in man.

32.2 EFFECTS OF INSULIN UPON FOOD INTAKE AND BODY WEIGHT IN NORMAL AND DIABETIC RATS. Dennis A. Vanderheiden and Alan D. Sonin* Occidental College, Los Angeles, CA 90068.

When insulin is dramatically raised by acute injection, intake of food intake increases occurs. Levels of glucoregulatory agents. This was further substantiated by measuring glucose turnover which, in spite of the absence of appreciable differences in plasma glucose levels, was found to be increased more than sevenfold. Supported by the Medical Research Council of Canada, Grant # M77378.

32.3 EFFECTS OF INSULIN UPON FOOD INTAKE AND BODY WEIGHT IN NORMAL AND DIABETIC RATS. Dennis A. Vanderheiden and Alan D. Sonin* Occidental College, Los Angeles, CA 90068.

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32.4 SPONTANEOUS DIABETIC WISTAR RAT: EFFECT OF KETOACIDOSIS ON GLUCOSE UPTAKE AND INSULIN REMOVAL BY LIVER AND MUSCLE. C.E. Mondloch, G.M. Reaven*, and R. Rabkin*. V.A. Medical Center, Palo Alto, CA 94304.

Lever and skeletal muscle are major sites of insulin and are responsive to insulin-induced glucose uptake. To ascertain the effect of diabetes on these processes, glucose uptake and insulin removal was assessed in liver and muscle from ketoacidotic diabetic (KD), nonketotic diabetic (D) and normal (N) rats. By determining the rate of glucose uptake by liver and muscle, we observed that glucose uptake by liver and muscle of KD rats was significantly lower (P < .05) than N rats (5.9 ± 2.0 vs 8.9 ± 2.0 mg/min) and KD rats showed slower glucose turnover which, in spite of the absence of appreciable differences in plasma glucose levels, was found to be increased more than sevenfold. Supported by the Medical Research Council of Canada, Grant # M77378.

M. Hussain* and O.V. Sirek. Department of Physiology, University of Toronto, Toronto, Canada M5S 1A8.

The present investigation is based on the results of previous experiments in which acute surges of plasma growth hormone (GH) concentrations stimulated insulin, glucagon and somatostatin secretion. The effects of a spike concentration of GH on portal and peripheral levels of free glucose and catecholamines were studied by radioimmunoassay methods. Experiments were conducted in trained, conscious, normal adult dogs fitted with an indwelling portal catheter.

An injection of ovine GH (100 mg/kg, NIH-GH-S9) into a cephalic vein produced in the hepatic portal circulation, but not in the peripheral circulation, a transient but statistically significant rise of serotonin and a concomitant significant reduction in the concentrations of somatotropins, norepinephrine and dopamine. These findings indicate that sudden peak concentrations of GH, and by inference endogenously occurring pulses also, affect the carbohydrate metabolism of the liver by varying the levels of a number of gluconeogenic agents. This was further substantiated by measuring glucose turnover which, in spite of the absence of appreciable differences in plasma glucose levels, was found to be increased more than sevenfold. Supported by the Medical Research Council of Canada, Grant # M77378.

32.2 EFFECTS OF INSULIN UPON FOOD INTAKE AND BODY WEIGHT IN NORMAL AND DIABETIC RATS. Dennis A. Vanderheiden and Alan D. Sonin* Occidental College, Los Angeles, CA 90068.

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LACK OF AN EFFECT OF SOMATOSTATIN ON EPINEPHRINE STIMULATED HEPATIC GLUCOSE PRODUCTION IN VIVO. P.E. Williams, R.E. Steinberg, R.W. Stevenson* and A.J. Cheffington, Vanderbilt University School of Medicine, Nashville, TN 37232.

We present evidence that has undertaken a study comparing the effects of somatostatin on epinephrine stimulated hepatic glucose production (Gp). Gp was measured using a primed constant infusion of [1-14C]-glucose and intraportal replacement of glucose in exp. I. Two experiments were performed on each of four overnight fasted conscious dogs. In the first experiment, (EXP. I) epinephrine (E) was infused at 0.2 pg/kg-min for 1 hr. Two weeks later (EXP II) E was again infused but with somatostatin (0.6 ug/kg/min), and intraportal replacement of glucose in exp. I. In EXP. II, intraportal replacement of I and during E infusion resulted in I's in 1 and 0.2 pg/kg-min and 0.2 and 0.4 pg/kg-min respectively. GP peaked at 15 min (0.63±0.24 mg/kg-min) and increased by an av of 0.38±0.12 mg/kg-min. In EXP. I intraportal replacement of I and during E infusion resulted in I's in 1 and 0.2 pg/kg-min and 0.2 and 0.4 pg/kg-min respectively. GP peaked at 15 min (0.63±0.24 mg/kg-min) and increased by an av of 0.38±0.12 mg/kg-min. In conclusion somatostatin at the dose employed had no significant effect on epinephrine stimulated glucose production in the overnight fasted conscious dog. Support from N.I.H. grant AM 18243.

Evidence for a Physiologic Role for Pancreatic Somatostatin in Vivo. Gerald T. Taborsky, Jr., Univ. of Washington and VA Medical Center, Seattle, WA 98108.

Somatostatin in islet D-cells has long been hypothesized to inhibit the secretion of insulin and glucagon by islet B- and A-cells, respectively. To provide such evidence, we inhibited somatostatin (SS) secretion in anesthetized dogs by infusing non-immunoreactive SS or an analog (EXP I) or by infusing an antibody to somatostatin (EXP II). In EXP I, we measured the effect of that suppression upon insulin and glucagon output from the right lobe of the in situ pancreas (see Table and Summary below).

Table: Response to Dose of Analog (pg/kg/min)

<table>
<thead>
<tr>
<th>Dose of Analog (pg/kg/min)</th>
<th>0.55</th>
<th>1.10</th>
<th>1.7</th>
<th>5.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>SS</td>
<td>-75</td>
<td>-165</td>
<td>-310</td>
<td>-456</td>
</tr>
<tr>
<td>Insulin</td>
<td>+17</td>
<td>+27</td>
<td>+55</td>
<td>+17</td>
</tr>
<tr>
<td>Glucagon</td>
<td>-34</td>
<td>-96</td>
<td>-175</td>
<td>-39</td>
</tr>
<tr>
<td>%A basal</td>
<td>32.5</td>
<td>32.6</td>
<td>32.9</td>
<td>33.2</td>
</tr>
</tbody>
</table>

Note: * = nonsignificant all others = significant (p < 0.05)

Summary: 1) Increasing doses of the analog produced a progressive suppression of pancreatic SS secretion. 2) Low to moderate doses produce a modest stimulation of insulin and a marked stimulation of glucagon. 3) High doses produce net inhibition of insulin and less stimulation of glucagon concentrations. At low to moderate doses the analog stimulates insulin and glucagon secretion indirectly by decreasing the inhibitory effect of pancreatic somatostatin. 2) At high doses, this indirect effect is overwhelmed (for insulin) by a somatostatin agonist effect of this analog directly upon the A- and D-cells. 3) Pancreatic somatostatin tonically restrains basal insulin and glucagon release in vivo.
32.11 SUBSTRATE AVAILABILITY AND MUSCLE FATIGUE IN MARBLE'S DISEASE STUDIED BY 31PHOSPHORUS NUCLEAR MAGNETIC RESONANCE.
The mechanism of easy fatigue in myophosphorylase deficiency (Mчаrblе's disease) is poorly defined. Using 31P-nuclear magnetic resonance (NMR), inorganic phosphate (Pi), phosphocreatine (PCr), and adenosine triphosphate (ATP) were measured in the forelimb muscles of a Marble's patient (PM) and two healthy subjects (HS) at rest and during hand-grip exercise (5 sec contraction and 5 sec rest) during control conditions (C) and with the same arm 10-15 min later during I.V. infusion of 60 ml of 30% albumin (ALM) MP stopped the contraction (113, +21, 193, kmg/min) while Pi increased 130 sec due to an impeding contracature of the forelimb muscles during C, but exercised easily for 7 min at a higher load (155 kmg/min) without a rise in Pi. Although ALM stopped the contracature (112, +21, 193, kmg/min) and reduced the rise in Pi, HS showed a greater rise in Pi than PM. The results suggest that the quantitation of muscle energy stores is needed during exercise to explain the muscle fatigue in Marble's disease.

32.12 TISSUE INTERACTIONS OF [14C]RETINOIC ACID IN THE MOUSE. Laron D. Hartman and William J. Kendall. Dept. of Pharmacology and Toxicology, University of Louisville, Louisville, KY 40292.
Retinoic acid has been demonstrated to be effective in animal models of human disease. In an effort to define receptor specificity with respect to the disposition of retinoic acid, [14C]retinoic acid was studied by whole-body autoradiography.

32.13 A COMPARATIVE KININE STUDY OF HUMAN ERYTHROCYTE URINARY PORPHYRINURANG DECARBOXYLASE ACTIVITY IN SPORADIC AND FAMILIAL PORPHYRIA CUTANEA TARDA. S.K. Mukerji*, M. Burns* and W.R. Flaimstone* (SPON: J. Green), Dept. of Internal Medicine, University of California, San Francisco, CA 94143.
All patients with porphyria cutanea tarda (PCT) have defective hepatic uroporphyrinogen decarboxylase (UCD) activity. However, UCD activity is normal in sporadic but reduced in familial PCT. We have compared for the first time the kinetic properties of HBOC UCD in sporadic PCT with that in a familial PCT patient, the latter with bone marrow expression of the enzymatic defect (Blood 59, 725,1982).

Large surface area burns to the skin cause increased protein catabolism in injured muscle during the postburn period, but the mechanisms involved in this process are not clear. Protein metabolism was studied from burned rats (25% total body surface, full-thickness wounds) 3 days after injury was measured by measuring the rates of [14C]tyrosine uptake and release as an indicator of protein synthesis and degradation, respectively. Incorporation and degradation rates (mnmole/mg/hr) are:

<table>
<thead>
<tr>
<th>Control</th>
<th>Incorporation</th>
<th>Release</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin (0.1 U/ml)</td>
<td>0.3030.027</td>
<td>0.8910.190</td>
</tr>
<tr>
<td>Insulin (0.1 U/ml)</td>
<td>0.4700.035</td>
<td>0.7600.185</td>
</tr>
<tr>
<td>Burned</td>
<td>0.2500.030</td>
<td>1.610.211</td>
</tr>
<tr>
<td>Burned</td>
<td>0.3700.031</td>
<td>1.250.202</td>
</tr>
</tbody>
</table>

**Significantly (P<0.05) different from control group.
**Significantly (P<0.05) larger increase than burn group.

32.15 ANABOLIC HORMONES AND PROTEIN SYNTHESIS IN REGENERATING RAT SKELETAL MUSCLE. Frances Schwartz*, B. Carlson*, Margaret Moore*, Ann Arbor, MI 48109.
To determine whether the growth of regenerating skeletal muscle, like developing skeletal muscle, is regulated by anabolic hormones, we examined the influence of insulin and pituitary hormones on protein synthesis in regenerating rat extensor digitorum longus (EDL). Earlier work indicated that protein synthesis was elevated 4-6 fold for 10 days following 125I-tyrosine administration to EDL. The results indicate that withdrawal of insulin or pituitary hormones does not impair the elevation in protein synthesis in regenerating rat skeletal muscle. Other anabolic hormones/factors may be involved. (Supported by NIH grant NS17017.)
32.17 CHELSTEROL MODULATES Beta Adrenergic RECEPTOR NUMBER BY MECHANISM OTHER THAN CHANGES IN MEMBRANE FLUIDITY. Philip J. Scarpaci*, Stephen W. O'Donnell*, Eloy I. Fernandez, and Virginia M. Caradonna*. Oakland University, Rochester, MI 48063. We found that fracture healing of the radii of 2 week old White Leghorn cockerels was markedly affected by the presence of 5000 ppm of lead in the diet (Pb-fed). Three day post-hatch chicks were intubated with Purina Startin Grower Mash for 11 days; then 5000 ppm of lead (as Pb-acetate) was added to the diet of 30 of 60 chicks. At 14 days post hatch the right radius of each chick was fractured by gentle digital pressure and the ulna left intact to act as a natural splint. The rate of healing was followed through callus formation and bone union (at 15 to 18 days post-fracture). Addition of Pb to the diet depressed chick growth about 50% as blood-Pb levels rose above 600 µg/dl within 12 hours after exposure to the Pb-diet. Although there was little observable difference in rate of callus formation and calcification between control and Pb-fed chicks (as evidenced by wet to dry weight ratio of callus samples), epiphysis ratios were significantly lower than the controls; suggesting that Pb-poisoning tends to increase mineral deposition in endochondral bone formation. The Pb-fed chicks had larger calliues, as compared to controls, and showed a significant delay in the rate of callus reabsorption. These data suggest interference of the healing process by dietary lead.
INESCAPABLE BUT NOT ESCAPABLE STRESS ALTERS IMMUNE FUNCTION.


Psychology Deps.: UCLA, Los Angeles, CA 90024; Univ. of Denver, CO 80208; and Cleveland Clinic Foundation, OH 44106.

Inescapable stress elicits pressor events, which are associated with decreased perfusion to the myocardium. To determine the alterations in the transmural distribution of ischemia produced by inescapable versus escapable stress, 4 acute dogs were instrumented with left circumflex flow probes and occluders and 4 mm ultrasonic transducers sutured to the epicardium. A 10 MHz pulsed Doppler was used to measure local transmural flow. The slope of the curve at each depth represents local TF. The volume of I and PB. The infarct volume and the perfusion each measured as %C.

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35.4 USE OF AN INTRAVENTRICULAR BALLOON TO INDUCE ACUTE CORONARY OCCLUSION FOLLOWED BY REPERFUSION.

Patrick K.C. Chun, William F. LaPenna, J. Judson McNamara, Tripler Army Medical Center and Cardiovascular Research Laboratory, Queen's Medical Center, Honolulu, Hawaii 96859.

The balloon (DynaCor) was inflated with 0.5ml of saline and its first derivative (dP/dt) regarded as an index of LV contractility. Eight animals (6.6-14.0kg) were used. The balloon volume of I and PB. The infarct volume and the perfusion bed volume were compared by regression analysis. R values for the nonexchanged and exchanged controls had an excellent fit: .89 and .91, respectively. Values for the nonexchanged and exchanged controls had an excellent fit: .89 and .91, respectively. Values for the nonexchanged and exchanged controls had an excellent fit: .89 and .91, respectively.
35.5 EFFECT OF CHRONIC SUBHYPERTENSIVE NOREPINEPHRINE INFUSION ON THE RESPONSE OF THE HYPERTROPHIED HEART TO SYMPATHETIC STIMULATION. Francis M. Siri* (SPON: Martin D. Ravner) Univ. of Hawaii, Honolulu, HI 96822.

Depletion of myocardial norepinephrine (NE) stores in cases of severe afterload-induced cardiac hypertrophy has been well documented. Diminished responsiveness of such hearts to sympathetic stimulation has also been reported. A study was designed to ascertain the ability of a chronic subhypertensive NE infusion to prevent these effects. Adult male Wistar rats underwent an aortic operation, consisting of implantation of an Alzet osmotic minipump for intravenous infusion of NE (0.05 mcg/kg/min) or vehicle (sham) followed by constriction of the abdominal aorta (AC) or placement of a left carotid arterial stenosis (CA). Two groups were compared 7 days postoperatively. The hearts of AC-NE-infused rats showed normal NE content compared to the double-sham group (P < 0.01). Electrode stimulation of the cervical sympathetic trunk produced significantly lesser increases in heart rate and left ventricular dP/dt max compared to sham-constricted rats, and this deficit was not ameliorated by NE treatment. There was evidence (P < 0.05) that NE infusion was associated with even further reduction in these responses. The results indicate that maintenance of the heart's NE stores, in this model, is insufficient to restore myocardial contractile function.


Pressure-induced left ventricular hypertrophy (LVH) in adult rats, with decreased coronary resistance, decreased ventricular contractility, and increased capillary density in age-matched (7-month) Wistar Kyoto (WKY) and thyroxine treated (Th) (0.25 mg/kg s.c./day x 2 mo) WKY rats. The degree of hypertrophy was assessed by LV dP/dt max and time to peak blood flow velocity (Tvmax) was used as an index of myocardial contractile state. LVH was associated with measured peak blood velocity to resting blood velocity ratio (PV/BV) during maximal coronary reactive hyperemia. Minimal coronary resistance (PV/BV) was measured in selected groups of mean arterial pressure and myocardial perfusion (microsphere) during maximal coronary dilation with dipyridamole (1 mg/kg). Capillary density was determined by micrographic analysis in perturbed-fixed hearts. Results (R = SEM); *P < 0.05 vs WKY PV/BV


To test whether the LVPFR is independent of arterial compliance and characteristic impedance (Rc), we used an isolated canine heart in which end diastolic pressure and systolic blood velocity were maintained over 8 fixed end-systolic strain states and varied over a range of afterload conditions. The LVPFR was determined always by varying R of 7 different protocols. With 3 levels of I (mean LVP of isovolumic contraction, 34.3 ± 8.2, 48.0 ± 6.3 & 59.2 ± 9.6 mmHg) the LVPFR shifted with mostly slope change (p<.0001). Changing C at 3 levels (0.2, 0.4 & 0.8 ml/mmHg) caused a statistically significant but quantitatively minimal cross-over of the LVPFR curve (p<.0001). Changing R to 0.1, 0.2 & 0.4 mmHg/sec/ml caused a highly significant (p<.0001) divergence of LVPFR over the high flow range. We conclude that this sensitivity of LVPFR to C and R makes its use as contractility index difficult. Supported by PHS Grant HL 14903.


The mean left ventricular pressure-flow relationship (LVPFR), determined under a constant preload and variable peripheral resistance (R), has been proposed as an index of left ventricular pump function (Elzinga and Westerhof, 1979). To test whether the LVPFR is independent of arterial compliance and characteristic impedance (Rc), we used an isolated canine heart over a range of afterload conditions. The LVPFR was determined always by varying R of 7 different protocols. With 3 levels of I (mean LVP of isovolumic contraction, 34.3 ± 8.2, 48.0 ± 6.3 & 59.2 ± 9.6 mmHg) the LVPFR shifted with mostly slope change (p<.0001). Changing C at 3 levels (0.2, 0.4 & 0.8 ml/mmHg) caused a statistically significant but quantitatively minimal cross-over of the LVPFR curve (p<.0001). Changing R to 0.1, 0.2 & 0.4 mmHg/sec/ml caused a highly significant (p<.0001) divergence of LVPFR over the high flow range. We conclude that this sensitivity of LVPFR to C and R makes its use as contractility index difficult. Supported by PHS Grant HL 14903.

35.9 ASSESSMENT OF MYOCARDIAL CONTRACTILITY USING MULLED DOPPLER ULTRASOUND. D. Alverson*, W. Berman, Jr.*, T. Blomquist*, M. Siri*.

The aortic relationship of systolic blood flow velocity variables to left ventricular (LV) pressure events under a variety of conditions in dogs with intact, anesthetized adult mongrel dogs. The peak first derivative of left ventricular pressure with respect to time (dp/dt max) was used to index the magnitude of the myocardial contractile state. Peak dp/dt max was derived from LV pressure waveforms using a transducer tipped Millar catheter. Blood flow velocity waveforms were derived from a transducer tipped 20 MHz pulsed Doppler catheter in aorta and left circumflex artery. Intotc state was changed using dobutamine or propranolol. Afterload was increased with an artery tipped catheter in the descending aorta. Cardiac output correlated dp/dt max and time to peak blood flow velocity (Tvmax) in all intotc state conditions, independent of afterload (r = 0.92, p<.001). Linear regression slopes and y intercepts comparing these two variables were similar in all dogs studied. The peak first derivative of velocity with respect to time (dv/dt max) and peak velocity (v max) were very highly afterload dependent as reported previously. Tvmax approximates closely LV dp/dt max over a range of afterload and intotc changes and can be obtained noninvasively with currently available instrumentation.


Depletion of myocardial catecholamines is characteristic of heart failure, but less is known about catecholamines in hypertrophy. We have studied the relationship of aortic blood flow velocity variables to left ventricular (LV) pressure events under a variety of conditions in dogs with intact, anesthetized adult mongrel dogs. The peak first derivative of left ventricular pressure with respect to time (dp/dt max) was used to index the magnitude of the myocardial contractile state. Peak dp/dt max was derived from LV pressure waveforms using a transducer tipped Millar catheter. Blood flow velocity waveforms were derived from a transducer tipped 20 MHz pulsed Doppler catheter in aorta and left circumflex artery. Intotc state was changed using dobutamine or propranolol. Afterload was increased with an artery tipped catheter in the descending aorta. Cardiac output correlated dp/dt max and time to peak blood flow velocity (Tvmax) in all intotc state conditions, independent of afterload (r = 0.92, p<.001). Linear regression slopes and y intercepts comparing these two variables were similar in all dogs studied. The peak first derivative of velocity with respect to time (dv/dt max) and peak velocity (v max) were very highly afterload dependent as reported previously. Tvmax approximates closely LV dp/dt max over a range of afterload and intotc changes and can be obtained noninvasively with currently available instrumentation.

We studied the relationship of aortic blood flow velocity variables to left ventricular (LV) pressure events under a variety of conditions in dogs with intact, anesthetized adult mongrel dogs. The peak first derivative of left ventricular pressure with respect to time (dp/dt max) was used to index the magnitude of the myocardial contractile state. Peak dp/dt max was derived from LV pressure waveforms using a transducer tipped Millar catheter. Blood flow velocity waveforms were derived from a transducer tipped 20 MHz pulsed Doppler catheter in aorta and left circumflex artery. Intotc state was changed using dobutamine or propranolol. Afterload was increased with an artery tipped catheter in the descending aorta. Cardiac output correlated dp/dt max and time to peak blood flow velocity (Tvmax) in all intotc state conditions, independent of afterload (r = 0.92, p<.001). Linear regression slopes and y intercepts comparing these two variables were similar in all dogs studied. The peak first derivative of velocity with respect to time (dv/dt max) and peak velocity (v max) were very highly afterload dependent as reported previously. Tvmax approximates closely LV dp/dt max over a range of afterload and intotc changes and can be obtained noninvasively with currently available instrumentation.

We studied the relationship of aortic blood flow velocity variables to left ventricular (LV) pressure events under a variety of conditions in dogs with intact, anesthetized adult mongrel dogs. The peak first derivative of left ventricular pressure with respect to time (dp/dt max) was used to index the magnitude of the myocardial contractile state. Peak dp/dt max was derived from LV pressure waveforms using a transducer tipped Millar catheter. Blood flow velocity waveforms were derived from a transducer tipped 20 MHz pulsed Doppler catheter in aorta and left circumflex artery. Intotc state was changed using dobutamine or propranolol. Afterload was increased with an artery tipped catheter in the descending aorta. Cardiac output correlated dp/dt max and time to peak blood flow velocity (Tvmax) in all intotc state conditions, independent of afterload (r = 0.92, p<.001). Linear regression slopes and y intercepts comparing these two variables were similar in all dogs studied. The peak first derivative of velocity with respect to time (dv/dt max) and peak velocity (v max) were very highly afterload dependent as reported previously. Tvmax approximates closely LV dp/dt max over a range of afterload and intotc changes and can be obtained noninvasively with currently available instrumentation.
REGISTRATION OF BLOOD FLOW: A MAJOR DETERMINANT OF CARDIAC OUTPUT. T.W. Rice*, S.V. Lichtenstein* and A. Panes* (Spon: C.E. Bayliss). Univ. of Toronto, Toronto, Ont. M5S 1A8

A. Two components of regional cardiac circulations were developed. A) In the isolated heart preparation, coronary vascular resistance increased and "w,pr" and hematocrit (w,Hct) was used to evaluate Hct) of the apparent volumes filtered into the interstitium, failed to consistently increase heart rate or left ventricular performance. (Supported by the American Heart Association, Akron District Chapter.)

36.2 EFFECT OF HISTAMINE ON CAPILLARY MEMBRANE PERMEABILITY TO SUCROSE IN THE RABBIT HEART. Jack T. Saari. Physiology Department, University of North Dakota, Grand Forks, ND 58202.

Much evidence exists to support the concept that histamine (HA) increases capillary membrane permeability by a variety of means. Little work has been done on the effects of HA on capillary permeability in the working dog heart. In this study the effect of HA on the capillary membrane permeability coefficients (K) to sucrose was studied in the isolated Langendorff-perfused rabbit heart. The vasocapillary transit method (Fergas and Johnson, Am. J. Physiol. 213: 87-93, 1967) was used to measure possible changes in K. In this method the constant k for decay of volume flow across the capillary membrane during an experimental period is estimated to be PA/V, where A is exchange area and V is distribution volume for permeant (in this case sucrose). Thus, in awake dog atrial fibrillation produces marked changes in canine output and in regional blood flow.


The three lobes of the pituitary gland have different endocrine functions and control their individual unique vascular beds. Some basic physiological mechanisms of pituitary blood vessels are likely to vary, therefore, from lobe to lobe and in different endocrinological states. We determined the capacity of solute transport (K) with 131-I-albumin and vascular plasma volume (Vp) with 131-I-albumin in the pituitary lobes of six conscious rats. We also evaluated for K and Vp, K and Vp, and regional tissue measurements of K, Vp and Vp from intact horizontal sections of whole pituitary glands by quantitative autoradiography. Vp for the neural, intermediate and anterior lobes was 34, 11 and 26 µl/g, respectively. Vp was increased in each of the lobes in dehydrated rats. The rank order of K for AIB in the lobes of normal animals was neural > anterior > intermediate. K was increased in each of the lobes in dehydration, most markedly in the neural lobe where a 4 to 5-fold increase in uptake occurred. Our results indicate that these vascular measurements are unique to the individual pituitary lobes. Inter-lobe differences likely reflect both the vascular anatomy and the physiological response to dehydration in each lobe.
LACK OF SELECTIVITY TO SMALL IONS IN HYDROPHILIC PORES IN MUSCLE AND BRAIN CAPILLARIES. Christian Croner. The Panum Institute, University of Copenhagen, 2200 Copenhagen, Denmark

Salt gradients across a membrane create diffusion potentials that depend on relative ion mobilities (or transport numbers) in the membrane. Diffusion potentials of $K^+$ and $Cl^-$ relative to $Na^+$ were determined in single capillaries in frog brain and muscle from diffusion potentials across the capillary wall by ion exchange or perfusion (P) experiments, or in combinations of S and P. The potentials were created by salt gradients (2:1 and 10:1) by bi- or substitutions ($KCl:NaCl$). The potentials were symmetrical across the wall. Analytical ion mobility and magnitude based on Planck-Henderson equations showed ion mobilities to be proportional to free solution mobilities reflecting absence of charge effects in the hydroscopic pathways. The 'pores' in continuous capillaries are highly hydrated, neutral or weakly charged channels that are wide compared to small ion size.

A LOGNORMAL DISTRIBUTION OF PORE RADIi IN CAPILLARY MEMBRANES. G. Bloom and J. A. Johnson Dept of Physiology, University of Texas Southwestern Medical, Dallas, TX 75235; and NIH AM-17093.

A model of a membrane that is heterogeneous in the ultra-microscopic domain is proposed. The influence of the solute size on passive transport via diffusion and osmosis is derived and compared to experimental observations. A lognormal distribution of pore radii is postulated. The shape of the pores is assumed to be round. Hydrodynamic interaction of an uncharged spherical solute with the pore is given by expressions generated by Peine and Scherr. The lognormal distribution was chosen because it occurs in many systems, it does not extend to negative pore sizes, and the mathematical expression is implicit in the ability to specify the distribution by only two parameters, the mean and the standard deviation. This may be compared to a model which employs two distinct pore sizes which must be specified along with the ratio of their occurrence. A graphical approach which plots the diffusive solute vs solute radius, or l/solute radius vs osmotic water transport allows a simple assessment of the fit of the data to the proposed model. In addition, numerical integration of these equations generates a set of results that include the transport to be expected from a population of pores of a single size. A better fit of the data from several experiments is obtained with a distribution of pore sizes.

Selective permeability of kidney capillaries to glucosylated albumin. Stuart K. Williams and Gabriel G. Pinter. Jefferson Medical College, Philadelphia, PA 19107 and University of Maryland School of Medicine, Baltimore, MD 21205.

The transcapillary transport of normal and nonglucosylated glucosylated albumin was studied in the kidneys of normal and diabetic rats. Rats were injected with a mixture of $\beta$-fluorescein isothiocyanate labelled-glucosylated albumin ($FITC-GSA$) and tetramethylrhodamine isothiocyanate labelled-normal albumin ($TRITC-SA$). Plasma, kidney lymph and urine were sampled at intervals for 120 minutes, analyzed for FITC and TRITC specific fluorescence, and the ratio of FITC/TRITC ($F/T$) calculated for each sample. We found no significant change in the $F/T$ ratio in samples of plasma and lymph from normal rats. However, the urine $F/T$ ratio more than doubled indicating the preferential appearance of glucosylated albumin in the urine of normal rats. Diabetic rats exhibited a significant decrease in the plasma $F/T$ ratio and a significant increase in the urine and lymph $F/T$ ratio. Decreased plasma $F/T$ ratio indicates the preferential escape of glucosylated albumin from the vascular space. Increased $F/T$ ratio in the urine and lymph samples suggest the preferential transcapillary transport of glucosylated albumin across glomerular and peritubular capillaries. Supported by NIH HL-29152 and NIH AM-17093.

JEJUNAL CAPILLARY PERMEABILITY TO ENDOGENOUS PLASMA PROTEINS. N.A. Mortillaro, Dept. Physiology, Univ. South Alabama, Mobile, AL 36688.

In autoperfused segments of cat jejunum, steady-state lymph flows, lymph protein concentration $C_L$ and plasma protein concentrations $C_P$ were measured at jejunal venous outflow pressures of 0, 10, 20 and 30 mmHg. In addition to determining total membrane transport, samples of lymph and plasma were subjected to polyacrylamide gradient gel electrophoresis to establish lymph protein concentrations of albumin and nine protein fractions. The osmotic reflection coefficient $\gamma$ for total proteins and the various fractions was estimated from $\gamma=1-C_L/C_P$ when $C_L/C_P$ became the filtration-rate independent, i.e., at high lymph flow induced by the elevation of venous outflow pressure. In 15 animals the estimate $\gamma=0.03$ for total proteins. In addition to determining $\gamma$, a graphic analysis was employed and an estimate of equivalent pore radii were obtained. Results suggest that the characteristics of jejunal capillary permeability are similar to those of the stomach. (Supported by NHLBI Grants 22392 and 29455.)
DECREASE OF DIFFUSING CAPACITY (DL/VA) WITH INCREASED HEIGHT of DL/VA vs age and H that have been reported have negative co-
statistically significant while the regression of the same data found that the regression equation of DL/VA vs age and -H was
nice H. Cohen et al, Johns Hopkins Med.J. 137: 95, 1975) and
normal men who participated in an epidemiological study (Ber-
recently published regression equations of DL and DL/VA for
due to low DL/VA in lung apices it should be eliminated when
for CO (DL) and (DL/VA) as an index of interstitial lung
disease requires prediction formulas for healthy lungs. Most
DL/VA is measured in the supine or prone position.

The kinetics of O2 uptake into, and release from, human red blood cells was measured by a double-beam spectropho-
tometer (660 and 577 nm) at 37°C using a stopped-flow tech-
nique. A simple model, with a discrete O2 diffusion resist-
ive layer between hemoglobin and medium, was used for cal-
culation of O2 conductances from the rate of change of O2 saturation (S02) and the calculated corresponding effective intra-extracellular O2 pressure difference. For the same SO2 range, O2 uptake and release (without dithio-
) yielded identical conductance values. Addition of albumin in vari-
ous concentrations and variation of dithionite concentration in the medium suggested an important diffusion limitation exerted by an extracellular stagnant layer. De-
saturation measurements (with sufficiently high dithionite concentra-
tion) starting at various so2 values yielded identi-
cal conductance values, independent of SO2. The corrected O2 transfer conductance of human red cells (i.e. excluding extracellular diffusion) was estimated at 8.7 ml O2/min-
Torr ml red cells), corresponding to 0.39 ml O2/min-Torr-
ml blood) for blood with a hematocrit of 40%. There was no
indicator for limitation of O2 transfer by kinetics of O2-
hemoglobin reactions in the DO range of 10 to 75%.

37.4 OXYGEN AFFINITY OF FETAL BLOOD CONTAINING CARBOSYRMOGLOBIN; A STUDY OF Haldane's and Haldane's Principles. N. Blum, Robert L. Blake and Hae Kun Park. SUNY, Buffalo, N.Y. 14214
The utility of Haldane's simple formula for the competitive affinity of CO for Hb binding (1904). This formula may be expressed as:

\[ P_{SO2} = P_{SO2}^* + P_{CO2} \left( P_{CO2}^*/P_{SO2}^* \right) \]

where saturation (S) is expressed as the fraction of O2 bound to Hb and \( P_{SO2}^* \) is the partial pressure of \( O_2 \) when the Hb is fully saturated. The parameters were obtained using total oxygen content and the Haldane's curve for normal blood. We conclude that the curve is a reasonable approximation of the actual curve for normal blood.

37.5 DECREASE OF DIFFUSING CAPACITY (DL/VA) WITH INCREASED HEIGHT in human lungs in healthy nonsmoking people. R. Rosenbaum, Dept. of Physiology and Biophysics, College of Medicine, Howard University, Wash-
ington, D.C. 20059.

The use of the single breath diffusing capacity of the lungs for CO (DL) and (DL/VA) as an index of interstitial lung

disease requires prediction formulas for healthy lungs. Most
recently published regression equations of DL and DL/VA for
normal people showed that both indices decreased as the age of the subjects but Ayers et al (New. J. Med. 123: 225, 1975) reported a strong negative correlation between DL/VA and height (H). We have examined the measurements made on 27 non-smoking normal men who participated in an epidemiological study (Bor-
nice, H.Cohen et al, Johns Hopkins Med.J. 137: 95, 1975) and
found that the regression equation of DL/VA vs age and H that have been reported have negative co-
relations for H. The probability of this being by chance is 1/1000 and indicates that the decrease of DL/VA with in-
creased height is not a statistical artifact. It suggests that
there are a larger proportion of low DL/VA regions than shorter ones. The low DL/VA are regions in the apices of the lungs or in the central portion of the alveolar region. If the observed negative correlation of DL/VA with height is
 Due to low DL/VA in lung apices it should be eliminated when
for CO (DL) and (DL/VA) as an index of interstitial lung
disease requires prediction formulas for healthy lungs. Most
DL/VA is measured in the supine or prone position.

37.6 INTERACTION OF SOLUBLE GASES WITH TRACHEAL AIRWAY MUCOSA. David D. Ralph* and Michael P. Hlastala. Univ. of Wash-
ington, Seattle, WA 98195.
In models of pulmonary gas exchange, the assumption is usu-
ally made that there is no interaction of flowing gas with the airway mucosa. We quantitated such interaction by com-
paring movement during tracheal flow of two gases of similar molecular weight (MW) but different blood-gas partition co-
efficients (A). The experiments were performed in anesthetized dogs. The expiratory flow was controlled at a constant 100
ml/min by a piston ventilator. A 1.0 ml gas bolus containing traces of krypton (MW 84, \( \lambda = 0.6 \)) and diethyl ether (MW 74,
\( \lambda = 0.3 \)) was injected at the start of exhalation into the
trachea along injection sites at the tip and 15 cm distal to the
opening of the tracheostomy tube. The depth of penetration of either into the tracheal mucosa was calculated from the dis-
bution volume, averaged 42 ml. We conclude that interaction of soluble gases with the tracheal mucosa delays elimination of soluble gases during unidirectional ventilation.

(Supported by NHLBI Grants HL2174, HL21463 and HL08981)
17.7 INFLUENCE OF THE CREST WALL (CW) ON GAS EXCHANGE DURING MECHANICAL VENTILATION (MV). K. J. Modell, Virginia Mason Research Center, Seattle, WA 98101

Possible CW states during MV ranges from a coordinated inspiratory effort by CW muscles during assisted ventilation (AV) to a passive CW during controlled ventilation with paralysis (CV). To determine the extent to which CW mechanics were affected and the effect during MV on CW function, six non-dependent recipient animals were Sacrificed and carboxylase activity of their liver microsomes was measured.

17.8 BIOCHEMICAL STUDIES OF CLOTAPEPTIN, A HEMOGLOBIN CROSS-LINKER WITH POTENTIAL ANTI-THROMBOTIC ACTIVITY. Hiromitsu Doi, M.D., Adolpho Liachowitsch, M.D., Joseph J. Favaloro, Ph.D., and John F. Pallasch, M.D. Biochemistry, Columbia University, New York, N. Y. 10032

Coagulant activity of plasma from Coumadin-treated rabbits was increased significantly in recipients compared to controls. The difference was greater in plasma from Coumadin plasma than in controls. The difference in coagulant activity may be due to the presence of a new clotting factor or an increase in the activity of an existing clotting factor. The increase in clotting activity in recipients was associated with an increase in Factor V activity.

18.0 GAS TRANSPORT AND VENTILATION DISTRIBUTION AS A FUNCTION OF TIDAL VOLUME AND BREATHING FREQUENCY IN A MECHANICAL LUNG MODEL. Joel Deitz, M.D., Nell Martyny, M.D., and Gabrielle Lustatto, Ph.D.* (EPPH: Herbert Saltman, M.D.). Duke University Medical Center, Durham, NC 27710

To study gas transport and ventilation distribution as a function of tidal frequency, we measured both total and regional ventilation in a mechanical lung model with two parallel compartments. This model allowed us to alter the compliance (C or the resistance (Rw) of each compartment individually. A wide range of frequency (f = 2-1000 RPM) and tidal volume (VT = 10-3000 cc) combinations were used to produce three fixed ventilator flow rates (10, 25, 50 liters/minute). Effective ventilation ($VEff$) to each compartment was based on continuous washout ($Vp$, compartment volume/washout time constant). Total $VEff$, as well as a ratio of the $VEff$'s in the two compartments, were determined. We found that with a unilateral increase in airway resistance, ventilation became lop-sided as frequency increased; however, with a unilateral decrease in compliance, ventilation became more uniform as frequency increased.

18.1 THE EFFECTS OF MANIPULATION OF PULMONARY BLOOD FLOW ON V/Q DISTRIBUTION IN UNILATERALLY INVOLVED LUNG. T.S. Lee, M.D., B.D. Wright, M.D., and S.O. Jacobson, M.D.* (SPHR: Donald Prater) University of Kentucky Medical Center, Lexington, Kentucky. 40536

The Wager-Heath method with gas-duralumine technic was used to study V/Q distribution. Seven mongrel dogs were involved. Minute ventilation was mechanically maintained constant at F102 of 0.5. The experimental sequence consisted of 4 stages: Stage I: Ligation of the left main bronchus only. Stage II: 100% occlusion of the left main pulmonary artery. Stage III: De-clamping of the left main pulmonary artery. Stage IV: 100% clamping of the left main pulmonary artery. Stage I produced a large shunt (QS/QT = 0.75) and normal LAC (PaO2 > 90). At Stage II, CO decreased significantly (P < 0.005) from 4.55 to 3.35, and PaO2 decreased to 63.5 torr (P < 0.05). At Stage IV, the QS/QT reduced to 0.23 (P < 0.005) and PaO2 improved significantly (P < 0.005). The proportion of cardiac output distributed to the lung was greater in both stages II and IV than in stage I. Since cardiac output and PVM do not change significantly the improvement of arterial oxygenation can be attributed to the favorable redistribution of blood flow and the decrease in true shunt.

18.2 THE RATE OF PLASMA CLEANSING OF CROSS-LINKED AND PYRIDOXYLATED HEMOGLOBINS IN THE RAT. L. Triner, A. Benesch*, J. E. Benesch*, S. Kwong*, and M. Veropsy*, Departments of Anesthesiology and Biochemistry, Columbia University, New York, N. Y. 10032

Hemoglobin crosslinked with 2-nor-2-formylpyridoxal phosphate (HbXL) as well as hemoglobin pyridoxylated at either the a chain or the b chain N termini, or at both chains were compared to unmodified hemoglobin (Hb). Hemoglobin solutions were injected i.v. and urine composition monitoring was measured as cythemoglobin. Volume loss due to sampling and diuresis was replaced by saline. At a dose of 0.4 mg/g, the initial plasma concentration was 0.71% and the rate of clearance was exponential with a half-life of 1 hr for Hb and pyridoxylated hemoglobin and about 2 hrs for HbXL. As shown previously (Fed. Proc. 41: 1005, 1982), HbXL was not excreted in the urine, whereas in contrast to Hb and all uncrosslinked pyridoxylated hemoglobin (20-30% of the given dose was excreted in the urine). In contrast to Hb and all uncrosslinked pyridoxylated hemoglobin, HbXL was not excreted in the urine, whereas in contrast to Hb and all uncrosslinked pyridoxylated hemoglobin (20-30% of the given dose was excreted in the urine). In contrast to Hb and all uncrosslinked pyridoxylated hemoglobin, HbXL was not excreted in the urine.
38.1

AMINOLEVULINIC ACID ACCUMULATION IN ERYTHROCYTES FROM INDIVIDUALS WITH SICKLE CELL ANEMIA: A MONITORING TECHNIQUE FOR HEMOGLOBIN F CONTENT

38.2

CORRELATION BETWEEN THE DIABETIC-RELATED EFFECTS OF GENERAL ANESTHETICS ON HEPATOMA CELL GROWTH AND HEPATOMA PROTEIN SYNTHESIS

38.3

A CORRELATION OF I- ANTIGEN EXPRESSION AND FETAL HEMOGLOBIN CONTENT IN ERYTHROCYTES OF INDIVIDUALS WITH SICKLE CELL ANEMIA

38.4

QUINACRINE COMPETITIVELY INHIBITS NA/Ca EXCHANGE IN CARDIAC SARCOLEMMA

38.5

AMINOLEVULINIC ACID INHIBITION OF H+ EXTRUSION FROM T-CELLS TRIGGERS ELECTRICAL AND SECRETORY ACTIVITY

38.6

INSULIN EFFECTS ON pHi AND Vm OF FROG MUSCLE

38.7

A CORRELATION OF I- ANTIGEN EXPRESSION AND FETAL HEMOGLOBIN CONTENT IN ERYTHROCYTES OF INDIVIDUALS WITH SICKLE CELL ANEMIA

38.8

A CORRELATION BETWEEN THE DISEASE-RELATED EFFECTS OF GENERAL ANESTHETICS ON HEPATOMA CELL GROWTH AND HEPATOMA PROTEIN SYNTHESIS

38.9

A CORRELATION OF I- ANTIGEN EXPRESSION AND FETAL HEMOGLOBIN CONTENT IN ERYTHROCYTES OF INDIVIDUALS WITH SICKLE CELL ANEMIA
3.9  EFFECTS OF CIGARETTE SMOKING AND ALCOHOL ON BLOOD LIPIDS AND LIPOPROTEINS IN PHYSICALLY ACTIVE AND INACTIVE MIDDLE-AGED FEMALES. B.A. Stanford, S. Moller*, R.W. Hale, and D.A. Lally*. Dept. of Physiology and Dept. of Ob/Gyn., University of Hawaii, Honolulu, HI 96822

Exercise and alcohol are believed to increase serum HDL-C whereas cigarette smoking may act in a contrary manner. The purpose was to examine separate and combined effects of these variables. One group of 30 middle-aged women were run on a treadmill for exercise and cigarette smoking habits. Body fat (via hydrostatic weighing), cardiovascular responses to treadmill exercise, and serum total cholesterol, HDL-C, LDL-C, HDL-C/LDL-C ratio and triglycerides were determined. Estimates of partial regression coefficients revealed that HDL-C of chronic exercisers was 6.6 mg/dl higher than nonexercisers. Each ounce of alcohol contributed to an increase in HDL-C of 3.8 mg/dl. HDL-C of nonsmokers was 7.6 mg/dl higher than smokers. Analysis of covariance with adjustments for body fat, age, alcohol, and smoking indicated that (1) smokers who exercise and/or consume alcohol demonstrated lower HDL-C levels than nonsmokers with similar habits; and (2) HDL-C was higher in subjects who both exercise and consume alcohol when compared with subjects who practice one or the other separately. It was concluded that: (1) smoking attenuated the beneficial effects of exercise and/or alcohol to raise HDL-C; and (2) chronic exercise combined with alcohol exerted an additive effect to raise HDL-C. (Supported by NIH Grants HL29640 and HL07050)

3.91 EFFECTS OF OVARIECTOMY ON BONE STRUCTURE AND CALCIUM IN PIGS. B. H. Erickson, F. M. Fara ci*, and E. C. Olson*. Kansas State University, Manhattan, KS 66506

Although the OY group showed greater femur length and volume tenths and concentrations were significantly lower in the OY group (Ca)=136.00, Ca content=124.37; CY (Ca)=165.24, Ca content=150.39. No differences among the effects were verified by muscle enzyme levels and fiber typing were done on a treadmill 1 hr/day, 5 days/wk for 4 weeks at a loss of chronic exercisers was 6.6 mg/dl higher than nonexercisers. A high correlation (r = 0.98) between the OY and the CY was found in these animals.

To examine the role of insulin and glucagon in maintaining glucose homoeostasis during mild exercise (40% VO2 max) and recovery, we studied human subjects in hormonal clamp conditions. We clamped insulin and glucagon by inhibiting their secretion with somatostatin, simultaneously infusing glucose or l-C-glucose. With no hormonal clamp there was a balance between an increase in glucose or l-C-glucose. With no hormonal clamp there was a balance between an increase in glucose or l-C-glucose. Results were compared to the responses in the situation where the hormones were unclamped. Glucose kinetics were determined using a stable isotopic tracer of glucose (4,6,8-glucose or l-C-glucose). With no hormonal clamp there was a balance between an increase in glucose or l-C-glucose. Results were compared to the responses in the situation where the hormones were unclamped. Glucose kinetics were determined using a stable isotopic tracer of glucose (4,6,8-glucose or l-C-glucose).
39.7  

The purpose of this study was to determine the effects of a brief bout (15 min) of exercise (40% VO2max) on lactate and oxygen consumption recovery from exhaustive exercise. Comparisons were made with rest (P) recovery over 45 min. Arterialized venous blood (P02=77.6, P02=44.1) was sampled regularly via catheter from a dorsal hand vein in five male volunteers and P02 and P02 were monitored throughout. During 40% exercise recovery at min 15, blood lactate concentration was 7.8 mm, pH 7.37, and M02 21 mm as compared with 13.5 mm of 7.260, respectively, during the exercise bout. The exponential curve essentially complete at 30 min for 40% exercise whereas 45 min were required for P. These results agree with our previous data in which exercise was performed, without rest, to recruit more muscle fibers. Excess postexercise oxygen consumption (EPOC) for 40% exercise did not significantly differ between protocols (P=3.16; 40%=3.54) whereas slow components did (P=7.29; 40%=5.95).

39.8  
PHYSIOLOGICAL RESPONSES OF PARALYTIC AND QUADRIPLEGIC SUBJECTS TO ELECTRICALLY INDUCED EXERCISE AND WALKING. Jerrold S. Phillips, Chandler University, Phoenix, Arizona and G. A. Hamilton, Wright State University, Dayton, Ohio 45435.

Physiological stress including cardiovascular and bone density measurements were examined in quadriplegics and paraplegics' measurements during electrically induced isokinetic and dynamic exercise on the bicycle ergometer and, in some subjects, walking on a treadmill. Paraplegics' measurements were similar to exercise in nonparalyzed individuals except that both systolic and diastolic blood pressure increased significantly in the recovery phase of the exercise. Exercise caused a 15% increase in hypertension following the termination of the exercise. The increase in blood pressure appeared to be linked to reflex activation from muscle since occlusion of the circulation was found to attenuate the increase in hypertension following the termination of the exercise. Cardiovascular responses improved with training. Also, bone density increased for the same groups of individuals by greater than 15% with mineral content with several months of training.

39.9  

The purpose of this study was to determine the metabolic and cardiopulmonary responses of 4 spinal cord injured subjects during electrical stimulation induced exercise of their paralyzed legs. For this a computer controlled closed loop electrical stimulation system, using surface electrodes over motor points of the quadriceps muscle groups, was maintained for 4 min bouts of 70° leg extension exercise (17 m/min, 1% grade), and, in the case of trained rats, 20 min of steady state oxygen uptake (VO2), pulmonary ventilation (VE), heart rate (HR), and arterial blood pressure (BP) were determined. VO2 and VE appear to be well regulated with respect to exercise intensity. These data suggest that the commonly monitored cardiovascular variables of HR and BP are not valid indicators of the stressfulness of peripherally stimulated exercise in spinal cord patients. In contrast, VO2 and VE appear to be well regulated with respect to exercise intensity.

39.10  

The effects of training on protein flux were studied in sedentary and exercise-trained Franco-American foxhounds. Leucine turnover and oxidation were assessed in vivo by continuous infusion of [1-14C]leucine. The infusions were maintained for 60 min of rest, 60 min of easy exercise (17 m/min, 1% grade), and, in the case of trained rats, 20 min of moderate exercise (25 m/min, 1% grade). Arterial blood was assayed for leucine specific activity and expired air monitored for exhaled CO2. The leucine turnover rate was verified independently for the same groups of animals, by determining the accumulation of [1-14C]leucine in the quadriceps muscle groups. Individual r values ranged from 0.06 to 0.39. It was concluded that a brief bout of aerobic exercise is very effective in promoting recovery from exhaustive exercise and may be as helpful as exercise throughout. Also, lactate disappearance from the blood was not related to EPOC. (Supported by the American Heart Association-California Affiliate.)

39.11  

The purpose of this project was to design and construct a vehicle to permit locomotion via electrically stimulated paralyzed leg muscles. For this, a conventional wheelchair was modified by the addition of two moveable footplates which were coupled to the drive wheels via ratchet type transmissions. The reciprocating movements of the legs result in forward propulsion of the vehicle. Steering can be accomplished by consecutive movements of a single leg. A two-channel battery powered electrical stimulator (square impulses, 10-100 microseconds wide, 0-135V, 0-150 ma, 20-125 Hz) using surface electrodes over motor points of the quadriceps muscle groups controlled the contraction and locomotive characteristics. All electrode sequential stimulation is used to obtain smooth contraction at a relatively low impulse frequency and less fatigue of the muscles. With the onset of fatigue, high skin stimulation levels are required to recruit more muscle fibers. This leg propelled vehicle (LPV) has been successfully operated by paraplegic and quadriplegic subjects. Chronic use of an LPV may contribute to the rehabilitation of non-ambulatory individuals by improving their locomotive capability; circulation in the lower extremities; cardiovascular and respiratory fitness; strength and size of the exercised muscles and bones; and, self image. (Supported in part by the Veterans Administration.)

39.12  
SKELETAL MUSCLE ADAPTATION TO DYNAMIC EXERCISE TRAINING IN THE FROGHOUND. D. Parson*, B. L. Moore, T. L. Moehlman, C. C. Waldet, and G. S. Oordew. UNIV. OF TEXAS HEALTH SCIENCE CENTER, Dallas, TX 75235.

Eight to 12 weeks of dynamic exercise training increases maximal oxygen consumption approximately 10% in the frog. This increase in maximal oxygen consumption results primarily from an increase in maximal stroke volume and cardiac output, with no change in stroke volume or cardiac output. 8-12 weeks of 30% VO2max training in the frog increased VO2max approximately 30% in foxhounds. (Fed Proc 42:7355.) The purpose of this study was to determine if dynamic exercise training produces biochemical or histochemical adaptations in skeletal muscle in foxhounds. Analyses were performed on samples removed from medialis gastrocnemius muscles of 7 foxhounds before and after a treadmill running program. Biochemical analysis showed that training produced no alteration in the activities of the citric acid cycle enzymes, NADH dehydrogenase, succinate dehydrogenase or total phosphofructokinase. Histochemical analysis of myofibrillar actomyosin ATPase, demonstrated no alteration in the activities of the myofibrillar actomyosin ATPase. This increase in maximal oxygen consumption results primarily from an increase in maximal stroke volume and cardiac output, with no change in stroke volume or cardiac output. 8-12 weeks of 30% VO2max training in the frog increased VO2max approximately 30% in foxhounds. (Fed Proc 42:7355.) The purpose of this study was to determine if dynamic exercise training produces biochemical or histochemical adaptations in skeletal muscle in foxhounds. Analyses were performed on samples removed from medialis gastrocnemius muscles of 7 foxhounds before and after a treadmill running program. Biochemical analysis showed that training produced no alteration in the activities of the citric acid cycle enzymes, NADH dehydrogenase, succinate dehydrogenase or total phosphofructokinase. Histochemical analysis of myofibrillar actomyosin ATPase, demonstrated no alteration in the activities of the myofibrillar actomyosin ATPase. This increase in maximal oxygen consumption results primarily from an increase in maximal stroke volume and cardiac output, with no change in stroke volume or cardiac output. 8-12 weeks of 30% VO2max training in the frog increased VO2max approximately 30% in foxhounds. (Fed Proc 42:7355.)

39.13  

The role of adrenergic neurotransmitters in the control of muscle contractility is not well understood. This study was designed to determine if the contractile response of skeletal muscle to norepinephrine is mediated by the alpha and beta adrenergic receptors. Seven adult male mongrel dogs were each anesthetized with sodium pentobarbital and paralyzed with gallamine triethiodide. After a left thoracotomy, the left gastrocnemius muscle of each dog was prepared for recording. The gastrocnemius muscle was then stimulated at 10 Hz and the dorsal aorta was cannulated. The nerve to the gastrocnemius muscle was then stimulated at 10 Hz and the dorsal aorta was cannulated. The gastrocnemius muscle was then stimulated at 10 Hz and the dorsal aorta was cannulated.

39.14  

The purpose of this study was to determine the effects of resistive work on the biochemical and gross histological adaptations in skeletal muscle. Seven adult male mongrel dogs were each anesthetized with sodium pentobarbital and paralyzed with gallamine triethiodide. After a left thoracotomy, the left gastrocnemius muscle of each dog was prepared for recording. The gastrocnemius muscle was then stimulated at 10 Hz and the dorsal aorta was cannulated. The nerve to the gastrocnemius muscle was then stimulated at 10 Hz and the dorsal aorta was cannulated. The gastrocnemius muscle was then stimulated at 10 Hz and the dorsal aorta was cannulated.

Mechanoreceptors associated with the air breathing organ were identified and characterized, in vivo, in double-pithed specimens of the bowfin (Amia calva) using standard techniques for single fiber nerve recording. These receptors were innervated by the vaga nerve and located within the lung, apparently along the ventral wall where the lung and gut contact a connective tissue membrane. The receptors were sensitive to increased tonic discharge with step increases in lung volume above a threshold level and were slowly adapting. Most were not active at lung volumes below 25 ml/kg. There was a dynamic, rate sensitive, rate also associated with lung inflation and a dynamic, rate sensitive inhibition of discharge associated with deflation. In a few fibres, rapid step deflation of the lung produced a burst of activity followed by a rebound inhibition of activity with discharge then returning to a new tonic level which was dependent on lung volume. All receptors were insensitive to changes in intrapulmonary, carbon dioxide partial pressure. These observations suggest that receptors capable of transducing both rate and degree of inflation and deflation are associated with even the most primitive air breathing organ. Furthermore, these receptors bear characteristics in common with both gut receptors and pulmonary mechanoreceptors of other vertebrates. (Supported by the NSERC of Canada)

40.2 LIMITATION OF LACTATE PRODUCTION FROM FISH MUSCLE TISSUES AFTER EXHAUSTING EXERCISE. H. Nießler*, G.F. Holstein* and P. Neumann* (SPON: J. Piller). Dept. of Physiology, Max Planck Inst. for Experimental Medicine, Göttingen, FRG.

The slow efflux of lactate from fish muscle tissues after exhaustive activity has been associated with partial or even complete blood flow failure. In order to test this hypothesis the blood flow to tissues of rainbow trout was studied before and after exercise by application of the microsphere method. Radioactively labelled microspheres (MS) were injected via inluminial catheters into dorsal aorta and caudal vein, and the distribution of the MS labelled in systemic tissues was measured every 15 sec. Plasma lactate concentrations were found to be 2.7 ± 0.2 mmol/l after 15 min of exercise.

40.3 CONSERVATORY PLASMA BICARBONATE MODULATION DURING ENVIRONMENTAL HYPERCAPNIA IN CATS. E.R. Glassmann* and M. Meisels (SPON: J. Piller). Dept. of Physiology, Max Planck Inst. for Experimental Medicine, Göttingen, FRG.

When fish are exposed to elevated levels of ambient CO2, the resulting respiratory acidosis is compensated by an increase in plasma [HCO3-] in pike, but not in the bowfin (Amia calva) where no change in compensatory response was observed. Fish were able to maintain steady-state pH levels over a wide range of CO2 concentrations. The type of acidosis, therefore, changed from respiratory acidosis to metabolic acidosis with increasing temperature.

40.4 THE PHYSIOLOGICAL RESPONSES OF THE TURTLE, CHRYSEMYS PICTA BELLII, TO ASPEN AS A FUNCTION OF TEMPERATURE. Christopher V. Herbert* and Donald C. Jackson. Brown Univ., Providence, R.I. 02912.

Freshwater turtles were submerged in low O2 water at 5', 10', 15', and 20°C until the blood pH was reduced to 7.0. The plasma [HCO3-] to 20°C. The plasma concentrations of HCO3-, Na+, K+ Cl- increased 4 fold, 3) R increased 2.3 fold, 4) pHa decreased 7.09 in the first hour which was finally about 50% of the expected pH depression at 37°C. A 2% CO2 increase in plasma HCO3- increased 1.9 to 9.1 mM over 48 hours, thus compensating about 50% of the expected pH depression at 37°C. A 2% CO2 increase in plasma HCO3- decreased the magnitude of the HCO3- decrease from 0.7 to 0.1 in the first hour which was finally about 2 fold. The pH recovery was slower at 30°C and 2 fold. In a separate study of rainbow trout, fish after 48 hours of hyperventilation [HCO3-] increased 1.9 to 9.1 mM over 48 hours, thus compensating about 50% of the expected pH depression at 37°C. A 2% CO2 increase in plasma HCO3- increased 1.9 to 9.1 mM over 48 hours, thus compensating about 50% of the expected pH depression at 37°C. A 2% CO2 increase in plasma HCO3- increased 1.9 to 9.1 mM over 48 hours, thus compensating about 50% of the expected pH depression at 37°C.

The blood acid-base status of Blue Crabs acclimated to 10, 20, and 30 C seawater showed patterns similar to water-breathing vertebrates, with a pH/temp. slope of about -0.015. The adjustment was achieved by only small changes in [HCO3-] and Paco2. The values of intracellular pH of various muscle tissues, measured with DMO (5,5-dimethyl-2,4-oxazolidinedione) had slopes ranging from -0.014 to -0.016. The "mean whole body" estimate derived from the total DMO dose distribution was consistently higher than that of individual tissues, and had a temperature slope of only about -0.006. This anomalous "mean whole body" estimate was explained by the discovery of a large fluid compartment in the carapace which had a mean pH of 8.33 at 20 C, and a flat temperature slope. The consequences of this large alkaline compartment for buffering or acute acid-base disturbances, and the acid-base consequences of formation of the carapace during moulting are being investigated. The carbonate pool of the carapace is approximately 500-fold greater than the combined intra- and extracellular total CO2 pools.

(Supported by NRC PCD0-24350 to J.N.C. and NSERC grants to C.M.W.).

40.8 GAS EXCHANGE AND ACID BASE STATUS IN HUMANS SEDENTARY DESERT RESIDENCE. K. Frankun*, T. Weinstock*, B. Pinshow and M.H. Bernstein. Blaustein Institute for Desert Research, Ben-Gurion Univ., Sede Boqer Campus 84990, Israel.

To compare respiratory gas exchange and acid base status of two Negev desert avian species, the Chukar (wide spread in moat and desert areas) and the Sand Partridge (endemic to the desert), we measured VO2, VCO2, evaporative water loss (EWL) and acid base variables of birds exposed to Tg of 10 to 42°C from their thermoneutral zones (TNZ) to the highest Tg's (1 max) of exposure. Tg in both species increased from 41 to 43.5°C. Mean SR of Chukars and Sand Partridges were 1.1 and 1.3 cm3 O2/(g h), respectively. Mean EWLs were 1.2 and 4.3 mg H2O/g, respectively. At Tg max, EWL of Chukars increased 3-fold while that of Sand Partridges increased only 2-fold. Arterial blood PO2, PCO2, pH, [Hb] and Hct of both species did not vary significantly with Tg. Arterial lactate concentration in Chukars increased from 0.7 mmol/l at 32°C to 1.8 at 42°C while that of Sand Partridges increased from 0.7 to 3.7 mmol/l at 35°C to 1.5 at 42°C. We conclude that while both species used similar mechanisms to tolerate heat stress, Sand Partridges evaporated more water in their TNZ than did Chukars (probably due to higher breathing rates), whereas at high Tg's, Chukars evaporated more water for heat dissipation. Close regulation of acid base status by both species may be an their ability to function at high Tg's. Supported by NSF grant PCM 79-21856 and U.S.-Israel BF grant 2490/81.

40.9 THE INITIATION OF CARDIOVASCULAR ADJUSTMENTS TO DIVING IN REDHEAD DUCKS. Robert A. Porill* and David R. Jones. Dept. of Zoology, Univ. of British Columbia, Vancouver, BC V6T2A9.

Redhead ducks (Aythya americana) diving voluntarily or forcedly display an immediate bradycardia. This fall in heart rate is unaffected by pre-breathing gases of various oxygen contents when either diving freely or submerging forcibly. The heart rate during the dive is directly proportional to the pre-dive heart rate. This relationship holds for both types of dive suggesting that the depth of bradycardia seen in forcibly submerged redhead ducks is not an important factor in the cardio-vascular adjustments to submersion, Xylocaine in aerosol form was administered into the nares of 7 redhead ducks that were then forcibly submerged. The mean pre-dive heart rate for untreated animals was 92 ± 2 (S.E.) beats/min (bpm) and for Xylocaine treated animals was 98 ± 3 bpm; however, 2 seconds after submergence the mean heart rates were 36 ± 4 bpm (untreated) and 96 ± 4 bpm (Xylocaine treated), and 10 seconds after submergence were 29 ± 3 bpm (untreated) and 82 ± 5 bpm (Xylocaine treated). We conclude, therefore, that nasal receptors in redhead ducks play an important role in initiating cardiovascular adjustments to submersion.

40.10 EFFECT OF CO2 AND pH ON COLLOID OSMOTIC PRESSURE (COP) OF HUMAN BLOOD AND PLASMA, IN VITRO. Christopher S. Ogilvy*, C. Bruce Wenger, and Arthur B. Dusenbery. John B. Pierce Foundation Laboratory and Yale Univ., New Haven, CT 06519.

The COP of blood is influenced by two factors. The first is the CO2 content of whole blood. The second one is the pH of separated plasma, tonometered to different concentrations of CO2. The loss of CO2 from plasma samples in the oncometer was prevented by use of appropriate concentrations of CO2 in the sample chamber. COP of true plasma increased from 26.3 mm Hg at a pH of 7.40 to 26.5 mm Hg at a pH of 7.30 while the total CO2 content decreased by 3.4 mmol/l. For separated plasma, the COP decreased 0.2 mm Hg as the pH fell from 7.40 to 7.30. We also measured the change in total osmotic pressure of true plasma and it was similar (about 0.9 mmol/l) to that found by others. Based on these results, it is likely that this is the primary factor that causes the change in COP, which is much less than that reported previously in vivo (Kakubuchi, et al., J. Appl. Physiol. 44:254-257, 1978) though not unlike that 'in vitro' (Kakubuchi, et al., Am. J. Physiol. 236: F419-422, 1979). We also conclude that if COP is used to calculate the amount of fluid that shifts from plasma to red cells during the addition of CO2 'in vitro', this amount would be underestimated if the effect of pH on COP were neglected. (NIH grant HL 17407).
41.1 EFFECTS OF CARDIAC DENERVATION ON THE RESPONSE TO NALOXONE IN CANINE HEMORRHAGIC SHOCK. R.B. LECHNER, R.J. BRODY, D.G. REYNOLDS and M.J. ROYALTY, Departments of Surgery and Pharmacology, University of Iowa, Iowa City, IA 52242.

Opiate and prostaglandin antagonists have both been separately shown to improve hemodynamics and survival in hemorrhagic shock models. In this study both agents were used in the same animals. Opiate antagonism examined either alone or in combination with anti-influenza (NE) and beta-blockade (BB).

The effects of different vasodilator mediator antagonists on hemorrhagic shock in dogs, Phillip D. Toth*, Steven A. Hamburger*, Steven Barefoot+,

41.3 THE EFFECTS OF CARDIAC DENERVATION ON THE RESPONSE TO NALOXONE IN CANINE HEMORRHAGIC SHOCK. R.B. LECHNER, R.J. BRODY, D.G. REYNOLDS and M.J. ROYALTY, Departments of Surgery and Pharmacology, University of Iowa, Iowa City, IA 52242.

We studied the splanchnic vascular response to decreased systemic perfusion in pigs. Following hemorrhage, we progressively decreased CI by inducing graded cardiac tamponade with dextran (n = 14), while continuously monitoring splanchnic hemodynamics (n = 7). When superior mesenteric arterial resistance was plotted against total peripheral resistance, the slope varied between 1.2 and 1.4, always returning to a value of 1.0. This demonstrates a disproportionate splanchnic vasodilation in response to decreased systemic perfusion. This was abolished by ablation of the renin-angiotensin axis with 1) angiotensin converting enzyme blockade (ACEI) (n=8), and 2) competitive inhibition of angiotensin II with saralasin (n=7), and 3) bilateral nephrectomy (n=7). Simultaneous ablation of systemic hemodilution (n=2), a) blockade (phenoxybenzamine) (n=8), b) blockade (propranolol) (n=7), and c) SB blockade (n=2) all failed to abolish this effect. In the absence of hemodilution, a concomitant infusion of angiotensin II (n=5) restored the selective splanchnic vasodilation seen with decreased CI, whereas noradrenergic inhibition did not. The disproportionate redistribution in splanchnic blood flow seen in response to hypoperfusion is due to selective mesenteric vasodilatation that is mediated primarily via the renin-angiotensin axis, not the sympathetic nervous system.
It has been demonstrated that there are multiple endocrine responses to rapid fetal hemorrhage. The purpose of this study was to determine the fetal endocrine responses to a slow graded fetal hemorrhage. Chronically catheterized fetal sheep averaging 130 days gestation were studied 5 days post surgery (n = 6). For the hemorrhage, 4 to 10 ml of arterial blood was removed at 10 minute intervals over a 2.5 hr period. During recovery, 4 ml samples were obtained at hourly intervals 2 to 5 and 24 to 26 hr post hemorrhage. Basal plasma hormone concentrations (+ SE) were dopamine (DA), 272 ± 90 (pg/ml), epinephrine (EPI), 64 ± 21 (pg/ml), norepinephrine (NE), 57 ± 9 (pg/ml), prolactin (PRL), 33 ± 12 (ng/ml), vasopressin (AVP), 3.8 ± 1.0 (pg/ml), and plasma renin activity (PRA), 3.2 ± 0.6 (ng/ml/hr). There were no changes in DA or EPI during or after hemorrhage of 0 to 25% of the initial blood volume. NE increased (43%) for hemorrhages >20% and remained elevated 2 to 5 (145%) and 24 to 26 (99%) hr post hemorrhage. Both PRL and AVP were elevated (60%, 224%, resp.) 2 to 5 hr post hemorrhage if >20% of the initial blood volume was removed. In 5 of 6 fetuses PRA increased in proportion to the severity of the hemorrhage, and remained elevated at 2 to 5 hr for >20% hemorrhages. In summary, these data suggest 1) PRA is the most sensitive hormone in response to slow fetal hemorrhage, and 2) DA, EPI, NE, AVP, and PRL responses to slow hemorrhages of <20% are surprisingly small.

The effects of rapid hemorrhage on the fetal cardiovascular system has been frequently studied. The purpose of this study was to determine the changes in the fetal cardiovascular variables in response to a slow fetal hemorrhage. Chronically catheterized fetal sheep averaging 130 days gestation were studied 5 days post surgery (n=6). An average of 20% of the measured blood volume gradually was removed over 2.5 hrs. We found that fetal arterial pressure did not decrease during the hemorrhage, was reduced by an average of 5 to 7 mm Hg 2 to 5 hrs after the hemorrhage, and returned to normal 24 hrs post hemorrhage. Venous pressure did not change significantly. The only changes in heart rate occurred 2 to 5 hrs post hemorrhage and averaged +20 bpm. Fetal blood volume returned to control by 3 hrs post hemorrhage and was elevated by 14% after hemorrhage. Fetal oxygen tension decreased while carbon dioxide tension increased by an average of 2 to 3 mm Hg but neither returned to normal after 24 hrs. Arterial pH decreased by 0.05 units during and after the hemorrhage but returned to normal the next day. These data suggest that slow fetal hemorrhage may induce a dissociation between fetal arterial pressure, heart rate, and blood volume because 1) at the end of the hemorrhage arterial pressure and heart rate were normal when blood volume was reduced, and 2) 3 hrs later arterial pressure was reduced and heart rate elevated when blood volume had returned to normal.
4.2.1 PLANNING FOR LIFE SCIENCES RESEARCH ON A SPACE STATION.
Milton Heinrich* and Roger Arno* (SPON: R.E. Grindeland). NASA, Ames Research Center, Moffett Field, CA 94035

...physiological adjustment to weightlessness become more important with the increase in duration and frequency of space flights. Plans for a Space Station in the 1990s provide facilities to study both the altered functions with the gravity changes and to study the health problems as a component of the overall changes in organisms when "normal" gravity is removed. Important physiological responses to space flight which require long-term experimentation include the following: 1.1.5...vascular deconditioning, and loss of bone and muscle tissue. Fundamental questions include: how do organisms adapt to microgravity? What are the long-term physiological sequelae following microgravity? What are the long-term physiological sequelae following microgravity? These are being studied to determine facility requirements. The Space Station will offer an opportunity for long-term studies in weightlessness, with sampling of organisms before re-exposure to earth gravity.

4.2.2 THERMOREGULATION IN RATS DURING WARM OR COLD EXPOSURE AT 3 G. C. B. Monson, Dept. of Animal Physiol., Univ. of Calif., Davis, CA 95616.

[The event has been reported at a low level of significance. The initial 3 G setting was changed to 34 C, with the conclusion that if the proposal that rats then regulate Tc at this level, in this study 22 long-DV's humped male rats (46 + 3.8 cm and 5.0 kg) were first exposed to ambient temperature, Tc, of either 34 or 14 C; Tc was then monitored for 2 hours (with Tc at 24 C) to determine if Tc remained toward the low reference. The mean Tc values were at a value of 34 C higher (p < .001, paired t-test) than at the beginning of warm exposure. Two hours after the termination of cold exposure, Tc was significantly lower (by 1.7 C, p < .001) than at the beginning of cold exposure. In 1 G controls, 2 hours after warm exposure Tc was 1.7 C higher than prior to warm exposure (36.3 ± 0.32 C), and 2 hours after the termination of cold exposure, Tc was not significantly different than 36.3 ± 0.32 C. In conclusion, rats in 3 G fields do not maintain core temperature at the same level before and after thermal stimuli as well as 1 G controls supported by NASA grant NS (U-2914).]
42.7 TOPS SOCIAL INTERACTION INFLUENCE SLEEP-WAKE ACTIVITY DURING SMALL GROUP CONFINEMENT IN A CONSTANT ENVIRONMENT?
Daniel C. Holley, Charles W. DeRoosia, Keith Ogawa, Kevio Dinterleiff, and Donald M. Wingate.
Dept. of Biological Sciences, San Jose State University, San Jose, CA 95192, and NASA-Ames Research Center, Moffett Field, CA 94035.

Two groups (N and S) of three male subjects (S), 20-24 years of age, were confined in a continually alternated room (aftoa=18.57m) for 105 days (A). A third group (N=3) served as ambulatory controls and lived at the test center under HALO conditions. Blood volume changes, rectal temperature (RT), and heart rate were continuously monitored. During a flight simulator test lasting 7d (group A) the exchanged S's response was desynchronized from the rhythms of the other two S's, which phase delayed after an initial phase lock. After group desynchronization the circadian rhythms of the exchanged S's were desynchronized. These data imply a role for social interaction in an overall synchronizer of circadian rhythms in confined groups.

42.8 ALTERATIONS IN CIRCADIAN RHYTHMS IN CELL DIVISION OF THE MOUSE GASTROINTESTINAL TRACT AFTER BILATERAL GASTRICULAR NUCLEAR LESIONS (SCN).
J. N. Parsley, E. W. Powell, Jr., J. Hoyt, Jr.

The effect of SCN ablation was examined on rhythms that characterize the incorporation of [3H]-Tdr into DNA in various regions of the gastrointestinal tract of SCN-ablated mice. Five-day-old animals were exposed to Cw and pulsed RFR at average power densities of 60 mW/cm² as measured by currently accepted methods. Results of experiments to resolve this issue will be reported. (Performed at USAF School of Aerospace Medicine, Brooks AFB, TX 78235; supported by USAF Contract No. F33615-80-C-0064.)

42.9 POSTBURN METABOLISM IN THE RAT.
D.R. Stump* E.L. Audich, A.D.Mason,Jr! and B.A.Pruitt, Jr?
U.S. Army Institute of Surgical Research. Ft. Sam Houston, TX 78234.

Burn patients are hypermetabolic in their thermoregulatory zone. The burned rat has been used as a model without clear evidence that it is hypermetabolic at thermal neutrality. Male rats (500 g; n=39) were placed as a group in a respiration chamber and metabolic rate was determined after 5 h at ambient temperatures of 9-30 °C. Rectal temperatures (T<sub>r</sub>), heart rate (HR), and body weights were measured after each run. Metabolic rate at thermal neutrality (MR; W/m²), rectal temperature (LCT) and thermal conductance at 20 °C (k; W/m²/°C) were determined on the rats as normals, after shaving and following 50% total body surface scald burns. At thermal neutrality (LCT) and constant at temperatures above the LCT. The effects of heat production must reflect the basic metabolic cost of injury since thermoregulatory demands on metabolism are eliminated in the thermoneutral zone. Although the response of burned rats mimic those of patients, the limited increase in MR after burn restricts the utility of the model. (*<p>0.05 burn vs. normal.)

42.10 POSTBURN HYPERMETABOLISM IN THE PIG.
Louis H. Audich and Arthur D. Mason, Jr. * USA Institute of Surgical Research, Fort Sam Houston, TX 78234.

Research in postburn hypermetabolism is hampered by the constraints of patient studies temperature and the limited response of small animal models. To test the utility of a large animal model, metabolic and temperature measurements were performed on three, 40-80 kg pigs before and for three weeks after a 25% total body surface burn. Unrestrained, postabsorptive animals were studied overnight in a respiration chamber at temperatures from 10° to 35° C. Resting metabolic rate at thermal neutrality (MR) was increased from 69.5 ± 1.0 to 84.8 ± 2.7 W/m² (mean ± SE, p < 0.001) after injury. Peritoneal temperature was elevated during the first week postinjury. Core-to-air thermal conductance increased, and lower critical temperature remained unchanged during the next two weeks. Postburn hypermetabolism was not reduced by raising ambient temperature to 35° C. This, plus the absence of fever, suggests that this large animal model, like that in the human, was not temperature dependent. The pig response extends to small animals with the same size injury but is less than that of the human. The limited metabolic response and absence of a sustained fever reduces the utility of this model.


The high power density of pulsed radiofrequency radiation (RFR) has led to speculation that it may cause greater biological effects than continuous wave (CW) RFR. The present study investigated the effect of a 500-MHz CW wave upon thermal responses in rats. Ketamine-anesthetized female rats were exposed in an alternating fashion to 2.8 GHz pulsed and CW RFR at average power densities of 60 mW/cm² as measured by (3H)-TdR incorporation in DNA in various regions of the gastrointestinal tract of SCN-ablated mice. Five-day-old animals were exposed to Cw and pulsed RFR at average power densities of 60 mW/cm² as measured by currently accepted methods. Results of experiments to resolve this issue will be reported. (Performed at USAF School of Aerospace Medicine, Brooks AFB, TX 78235; supported by USAF Contract No. F33615-80-C-0064.)


Our previous studies have shown that chlorpromazine (CpZ) enhances thermoregulatory efficiency during intermittent RFR exposure when colonic temperature (T<sub>c</sub>) is not allowed to rise above 39.5°C. The present experiments were designed to assess the effect of acute CPZ on terminal RFR exposure in ketamine-anesthetized female rats, metabolic rate at thermal neutrality (MR), and rectal temperature (LCT) in rats with a Vitek 101 temperature probe. Animals were exposed in the horizontal orientation to continuous wave RFR at a frequency of 2.8 GHz, average power 60 mW/cm², specific absorption rate (SAR) -16 W/kg. Starting at a T<sub>c</sub> of 38.5°, exposure was performed until termination (cessation of respiration). The T<sub>c</sub>'s at which death occurred were similar in both saline- (43.1 ± 0.1°) and CPZ-treated (42.9 ± 0.2°) rats. No significant difference was noted in the time required to recover to the initial temperature upon cessation of CW pulsed RFR at 2.8 GHz, mean ± SD: T<sub>c</sub> delay of 4.0 ± 2.9 min. The data suggest a possible difference in energy deposition in animals exposed to CW and pulsed RFR of equivalent average power densities as measured by currently accepted methods. Results of experiments are expected to resolve this issue will be reported. (Performed at USAF School of Aerospace Medicine, Brooks AFB, TX 78235; supported by USAF Contract No. F33615-80-C-0064.)

A-78 ENVIRONMENTAL PHYSIOLOGY II MONDAY PM
4.2.13 SUBMERSION HYPOTHERMIA IN DOGS. F. G. Hempel, L. E. Wittmers, K. Drnemeshauer, D. Howard, and R. S. Pizzo. Office of Naval Research, Arlington, VA 22217 and Department of Physiology, Sch. of Med., Univ. of Minn., Duluth, MN 55812.

The bradycardia and aspnea which characterize the "dive reflex" are thought to have survival value during total immersion in cold water. It has not been determined whether the aspension of cold water into the lungs during immersion may be even more protective by rapidly cooling the brain and heart, and blood in the major vessels. For this reason we investigated the rate at which the aspension of fresh water at 10°C cooled the shallow brain (sb), deep brain (db), left ventricle (lv), rectum (ret), esophagus (eso), and subcutaneous space (scn) of dogs after whole body immersion.

Male and female dogs were anesthetized with sodium pentobarbital, and the electrocardiogram and arterial blood pressure were recorded. Spontaneously breathing dogs were submerged and allowed to aspension for 4 minutes. An average temperature drop observed in all animals was: 4.6°C (db), 4.2°C (sb), 5.9°C (lv), 2.3°C (ret), and 10.0°C (eso). We have found that the inspiration of cold water rapidly cools the heart and brain, at a rate of 1.8°C/minute, and have concluded that rapid cooling of these organs may explain the exceptional survival of individuals who have been accidentally submerged in cold water for long periods.

Supported in part by Minnesota Sea Grant Number DOG/NA 82AA-D-00039.


Thermogenesis in brown adipose tissue is increased in animals consuming a diet supplemented with palatable food items (cafe&ebra dina diet). To study the mechanisms by which thermogenic capacity of brown fat is increased during cafeteria feeding, in vitro respiration of brown adipocytes from hamsters given a cafeteria diet was measured and compared with that of adipocytes from animals eating a chow diet. Oxygen consumption was measured polarigraphically. Basal respiration in adipocytes from cafeteria-fed hamsters was slightly less than that of cells from control animals, and stimulated respiration by adipocytes from hamsters fed a cafeteria diet was only 40-50% of the rate in cells from control animals. This difference in respiration was present when the stimulus was isoproterenol, 3 isobutyl 1 methyl xanthine or forskolin. The reduced thermogenic responses of brown adipocytes prepared from cafeteria-fed hamsters were reversed when the animals were returned to the standard diet. Because, diet induced thermogenesis is associated with increased norepinephrine turnover in brown fat, we suggest that the diminished in vitro responses of brown adipocytes from hyperphagic hamsters results from the prolonged sympathetic stimulation preceding their isolation. We further suggest that the increased brown fat thermogenesis during cafeteria feeding may be a consequence of adipocyte proliferation.

4.2.15 REGULATION OF BROWN ADIPOSE TISSUE THERMOGENESIS BY ADENOSINE AND GLUTAMINE. L. J. Trefethen, B. F. Yager, and F. A. French. University of North Carolina at Chapel Hill, Chapel Hill, North Carolina 27514. In the brown adipose tissue (BAT) of rodents, inosine is metabolized to adenosine, a potent stimulator of thermogenesis. We have investigated the rate at which the aspiration of fresh water into the lungs during immersion provides a tight coupling between the inosine nucleoside and the thermogenic process.

We demonstrate that the nucleoside may control brown adipocyte function under physiologic conditions. Significantly, the dose-response curves for isoproterenol stimulation of lipolysis and respiration were both shifted by adenosine to higher agonist concentrations by the same order of magnitude, the inhibitory effects of adenosine were rapidly reversed by (a) transforming extracellular adenosine to inosine with adenosine deaminase, (b) adding additional evidence for a tight coupling between lipolysis and respiration rates. Tomoyasu et al., J. Biol. Chem., 256 (25): 12840-12848). The inhibitory effects of adenosine were rapidly reversed by (a) transforming extracellular adenosine to inosine with adenosine deaminase, (b) adding agents known to increase intracellular cyclic AMP levels (isoproterenol, isobeutyl-methylxanthine, 1-isobutyl cyclic AMP) and (c) directly stimulating respiration with palmitic acid, thus bypassing the early metabolic steps associated with activation of adenylate cyclase and lipolysis. These results combined with the fact that adenosine failed to affect respiration evoked either by dibutyryl cyclic AMP or by palmitic acid, strongly indicate that adenosine regulates brown adipose tissue respiration by inhibiting lipolysis via a direct effect on the adenylate cyclase complex. The observation that antilipolytic agents other than adenosine, such as adenergic blockers (propranolol, alprenolol), insulin, prostaglandin E2 and E2, all inhibited respiration, suggests that lipolysis represents the "blue-gene" regulating steps in the modulation of brown adipose tissue thermogenesis. (Supported in part by the Medical Research Council of Canada).

13 male Macaca mulataa keets were instrumented to allow chronic monitoring of heart rate, cardiac output, and rectal temperature. Total peripheral resistance and stroke volume were calculated. Heart rate and rectal temperature were both higher during the day than during the night. Blood pressure, total peripheral resistance and stroke volume were higher at night than during the day (the opposite of what has been documented in other diurnal mammals). This demonstrates an increased sympathetic nervous tone to the vasculature at night. Unlike most other diurnal animals, these monkeys do not assume a horizontal position at night, they remain upright. Gravity is acting on the upright monkey to cause blood pooling in the legs. This pooling is counteracted by the skeletal muscle pump during the day. We believe that nocturnal vasodilatation is a compensatory mechanism to counteract blood pooling, and maintain nocturnal cerebral blood flow. This research sponsored in part by NASA grant NGR-331-083-00.

We investigated the bio- and immunoreactivities of two components of CCK isolated from the human brain. Affinity chromatography and high liquid chromatography of the brain extracts yielded two distinguishable components (1) a CCK component coeluting with synthetic sulfated CCK and (2) an oxidized form of CCK. Both forms reacted identically with antisera specific to carboxyl terminal CCK. The biological activities of the two forms tested in vitro on isolated mouse pancreatic acini and mouse brain particulate preparation are as follows:

**Forms of CCK**

<table>
<thead>
<tr>
<th>Component</th>
<th>Max. Activity</th>
<th>1-2 PM</th>
<th>0.1-0.5 PM</th>
<th>1-5 PM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfated CCK</td>
<td>300 units</td>
<td>300 units</td>
<td>300 units</td>
<td>300 units</td>
</tr>
<tr>
<td>Oxidized CCK</td>
<td>100 units</td>
<td>100 units</td>
<td>100 units</td>
<td>100 units</td>
</tr>
</tbody>
</table>

Conclusion: These data demonstrate that the two forms of CCK isolated from the human brain exhibit identical immunoreactivities; however there are significant differences in their biological potencies to elicit appropriate responses from the target tissue. It also is clear that the brain particulate receptors, unlike acinar receptors, do not exhibit a significant difference in their binding characteristics to either the oxidized or nonoxidized form of CCK.

43.2 SERUM GASTRIN, PHYSALIN I AND ALCOHOL IN MALE AND FEMALE CHILDREN. M. Males, J. Pham*, I. Gjerzens*, G. L. De Angelis*, E. Chen** and S. A. M. Chen. Dept. of Pediatrics, Harbor and University Hospital, Los Angeles, CA. (Supported by Biomedical Research Support Grant R01-1758.)

We studied 20 healthy children, 10 males and 10 females with same age and weight (mean 0.8 yrs, and 30 Kg, respectively); the gastrin release was stimulated by a protein meal (hamburger and a glassful of milk) and the fasting serum gastrin and physalin I were measured.

**RESULTS**

<table>
<thead>
<tr>
<th>Gender</th>
<th>Physalin I (ng/ml)</th>
<th>Gastrin (pg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>37.0 ± 2.3</td>
<td>67.5 ± 7.3</td>
</tr>
<tr>
<td>Female</td>
<td>45.3 ± 4.9</td>
<td>73.0 ± 8.3</td>
</tr>
</tbody>
</table>

43.3 VARIATIONS IN BASAL, FOOD AND BOMBESIN-STIMULATED LEVELS OF GI PEPTIDES IN DOGS OVER EIGHT HOURS. P. L. Rayford, K. Inoue and A. H. Shulman. Veterans Administration Medical Center, San Francisco, CA 94121.

In 43 male dogs, plasma levels of gastrin (G), cholecystokinin (CCK) and pancreatic polypeptide (PP) were measured by radioimmunoassay before and 30 min after stimulation with saline (basal), food (10% casein diet) and bombesin (BBS, 100 pmol/kg IV). The results are expressed as mean ± S.E.M. (pg/ml). The nonprotein diet significantly increased plasma levels of G and PP, but not CCK. Bombesin stimulated increases in all three peptides. The relatively fast decline in peptide levels after BBS suggest that BBS, though not sufficient to lower CCK to basal levels. The prolonged duration. Methods: Dogs were fasted for 18 hr. Four blood samples were collected each 10 min for 30 min (control). Six dogs received a single meal (basal secretion) and 6 dogs received food and 6 dogs received a 1 hr infusion of 10% casein diet (food study) and 6 dogs received food and 6 dogs received saline (control), 10% casein diet and saline (food study) and 6 dogs received saline and saline (control). G, CCK and PP (pmol/L) were measured by radioimmunoassay. Results: Mean control levels were 10.9±1.4 for G, 10.8±0.7 fmol and 39.9±6.4 for PP. In the basal study, G and PP were not altered for 8 hr; CCK decreased at 300,100,210 and 240 min. In the food study, G was 300±3 and PP was 644±101 at 5 min; each remained significantly elevated over control throughout the study, PP showed a biphasic response. CCK increased significantly at 30,90,120,180,210 and 240 min and thereafter was not different from basal. In the BBS study, G was 201±2.5 at 5 min. CCK was 151±1 and PP was 122±5 at 10 min: G and PP remained significantly elevated for 60 min and CCK for 20 min after BBS was stopped. Conclusion: Decreases in levels of CCK in the basal study suggest that an 18 hr fast is not sufficient to lower CCK to basal levels. The prolonged increases in G and PP after food indicates that food is a long acting and potent stimulator of these peptides. The relatively fast decline in peptide levels after BBS suggest that BBS, though potent, is rapidly catabolized. Supported by NIH AM 30431-01.


Previous studies have shown that gastric mucosal nonprotein sulfhydryl compounds may play a role in mediating prostaglandin cytoprotection (S1. 214: 200-202, 1981). To determine whether this same action exists in canine mucosa, the dog-flap preparation in which the blood supply is maintained intact and the gastric mucosa partially exposed to an intragastric solution was the experimental model for the studies. The gastric mucosa was exposed to topical ethanol (40%) and/or to 16,16 dimethyl prostaglandin E2 (1 ug/ml). The tissue nonprotein sulfhydryl levels for ethanol were decreased to 25% of control (saline) mucosa were decreased to 35 ± 6% by ethanol and increased to 132 ± 5% by PGE2. Pretreatment with PGE2 prevented the decrease in nonprotein sulfhydryl levels produced by ethanol (102 ± 21% as compared with matched control tissue). Prostaglandin E2 induced maintenance of tissue nonprotein sulfhydryl levels even in the presence of the potent damaging agent ethanol may be one of the mechanisms of its cytoprotective action. (Supported by NIH grants AM 2583804 and AA 00194-11).
43.7 NEUROPEPTIDE CONTROL OF THE EXOCRINE PANCREAS IN THE GUINEA-PIG. J.S. Davison* and Val Dickson* (SPON: F. Lorscheider). Univ. of Calgary, Calgary, Alberta, Canada. 17N IN4

Adult guinea-pigs were anesthetized with urethane or pentobarbital. The celiac ganglion was removed and the proximal pancreatic duct was cannulated. The pancreas was perfused in situ with Krebs solution warmed to 37°C. The intraportal pressure was maintained at 12 mmHg. The perfusate was recirculated by a roller pump. The pancreatic duct was cannulated and a catheter was inserted into the duct. The stimulation of the celiac ganglion (10 Hz, 0.01 mA) caused a brisk flow of pancreatic juice and an increase in intraductal pressure. The increased amylase output was associated with a rise in amylase concentration in the pancreatic juice. Electrolyte analysis of the perfusate and amylase secretion was performed. A fall in [Cl] comparable to that evoked by secretin (1 ng iv) or atrazine (1-10ng/g IV) produced a significant depression of amylase output by about 30% but was without effect on fluid and electrolyte secretion. Fluid and amylase release were blocked completely by hexamethonium (7-30µg/kg IV). It appears that the secretomotor function of the cinchona-ganglion is mediated by preganglionic sympathetic fibers. These fibers can activate acinar cells causing enzyme secretion and duct cells causing fluid and mucous secretion. The duct cells appear to be entirely under the control of cholinergic nerves whereas acinar cells are controlled by cholinergic and noncholinergic nerves. The degree of reduction of amylase output by atrazine correlates well with the proportion of cells receiving a functional cholinergic innervation as revealed by electrophysiological studies, implying that cholinergic and noncholinergic fibers each innervate a different population of acinar cells.

43.9 ACTION OF ACETALDEHYDE ON ISOLATED PANCREATIC ACINI. M., Lewin,* J. S. Davison* and Val Dickson* (SPON: F. Lorscheider). Univ. of Calgary, Calif., Canada.

Acetaldehyde is a metabolite of ethyl alcohol, is known to affect various cell types. No investigation into the effects of acetaldehyde on basal and cholecystokinin (CCK)-induced enzyme release and on the binding of [125I] CCK to receptors on isolated rat pancreatic acini. Basal amylase release was inhibited up to 37% by 0–100 µM acetaldehyde, whereas greater than 100 µM concentrations caused an increase in amylase secretion. In the presence of 45 mM acetaldehyde (half maximal inhibitory dose), the shape of the dose response curve for CCK44-induced amylase release was the same as that of the control, but the amylase release was inhibited by 50%. Increasing concentrations of acetaldehyde (more than 100 µM) inhibited, in a dose-dependent manner, amylase release elicited by maximal concentration of CCK34 (330 µM). Acetaldehyde inhibition of 125I-CCK binding was observed between 100 nM and 10 µM, with half maximal inhibition at 300 µM. However, no correlation between the two inhibitory actions of acetaldehyde could be established. There was no significant cell membrane damage to acini by acetaldehyde in the concentration range of 10–300 µM; greater than 300 µM caused significant damage to the acinar cell membrane. These results suggest that acetaldehyde inhibition of CCK44-induced enzyme release is a not a membrane effect, but may be intracellularly mediated.

43.10 ACTION OF ETHANOL ON ISOLATED PANCREATIC ACINI. M., Lewin,* J. S. Davison* and Val Dickson* (SPON: F. Lorscheider). Univ. of Calgary, Calif., Canada.

Ethanolic inhibition of 125I-CCK binding was observed between 100 nM and 10 µM, with half maximal inhibition at 300 µM. However, no correlation between the two inhibitory actions of acetaldehyde could be established. There was no significant cell membrane damage to acini by acetaldehyde in the concentration range of 10–300 µM; greater than 300 µM caused significant damage to the acinar cell membrane. These results suggest that acetaldehyde inhibition of CCK44-induced enzyme release is a not a membrane effect, but may be intracellularly mediated.


In this study caravulosevenum was infused as a bolus in man during a controlled-pressure VIP infusion (400 pmol/kg/h for 10 min). VIP infusion caused flushing in all 6 subjects. A marked reduction in total peripheral resistance was associated with increased forearm blood flow (control: 6.5, VIP: 6.1 ml/min/100 g tissue; all values are mean ± SEM). To maintain systolic pressure and heart rate (C: 74, VIP: 94 beats/min) and cardiac output (C: 2.2, VIP: 4.1 l/min). The VIP infusion increased cardiac output to 1.5 ml/min/100 g tissue in all subjects. Labetalol, a β-blocker, abolished the VIP-induced increase in cardiac output. In conclusion, VIP infusion resulted in a decrease in total peripheral resistance and cardiac output, with a concomitant increase in forearm blood flow and heart rate.

43.12 COMPARATIVE EFFECTS OF WHEAT BRAN DIETS ON NIBBLING (N) AND MEAL-EATING (ME) RATS. Stanley T. Omaye* and Faye L. Chow* (SPON: John P. Hannon). Nutrients Research Unit, USDA, ARS, Western Regional Research Center, Berkeley, CA 94710.

The effects of chronic high fiber diet on rat growth and food consumption were studied in two groups of male Wistar rats. The high fiber diet, which contained 20% added wheat bran, was fed ad libitum (N) and for restricted 2-hour periods daily (ME) to male Sprague-Dawley rats for 35 days. The basal meal was a formula diet comprised of 5% or 20% wheat bran and 10% casein. These data indicate a progressive deterioration in pancreatic function as a result of chronic alcohol treatment in rats, regardless of WB intake. The deposition of epididymal fat was increased (P < 0.05) in rats fed the high fat diet, whereas the deposition of fat in the mesenteric fat was decreased (P < 0.05). Plasma levels of vitamin E were significantly lower (P < 0.05) in rats fed 20% WB. These results indicate that long-term fat-soluble vitamin deficiency and increased dietary wheat bran.

Citrus pectin (CP, 6.7% methoxyl groups by wt) was fed at levels of 0%, 3%, 6%, and 8% (w/w) of the diet for 8 wks to male weanling Sprague-Dawley rats (8 rats per group). A semipurified diet containing .001% vitamin E (VE) was used as a basal diet and fed ad libitum. The purpose of this study was to evaluate whether the bioavailability of VE was affected by CP. There was a nonsignificant (NS, P > 0.05) trend for an inverse relationship between food intake and CP levels. In general, rats fed 3% CP were not different in (NS) any parameters from rats fed 0% CP. In rats fed 6% or 8% CP, liver VE levels were reduced (P < 0.05) after 8 wks compared to liver VE at the start of the study. By wk 8, both groups had reduced body wt and increased red blood cell hemolysis compared to the 0% CP group. Rats fed 8% CP also had reduced plasma VE (P < 0.05). In rats fed 6% CP, heart VE was less (P < 0.05) compared to the 0% CP group at 8 wks. Fecal fat excretion was not different between groups but wts of the small and large intestine were increased in rats fed 6% or 8% CP. These results indicate that CP at 3% of the diet does not reduce the bioavailability of VE in the rat, but higher levels do. Based on our data and extrapolating to common Western CP consumption in humans, we would not expect an adverse effect of CP on VE status.


Strips of corporal muscle (0.2 x 1.0 cm) were cut parallel to the circular muscle fibers, suspended between two platinum electrodes in an organ chamber, and bathed in oxygenated Krebs solution at 37°C. Proglumide concentration-response relationships were obtained for excitation and inhibition induced by pentagastrin (PG), carbachol chloride and nerve stimulation. Pentagastrin, acting directly on the muscle, increased the frequency and amplitude of spontaneous contractions which were not affected by proglumide (10^-5 M). In normal Krebs solution, transmural electrical nerve stimulation has both excitatory and inhibitory effects on motor activity. The excitatory effect is cholinergic whereas the inhibitory effect is due to release of an unknown inhibitory transmitter. We have previously shown that pentagastrin potentiates the inhibitory effect of nerve stimulation by an action on the inhibitory neuron. The potentiating effect of PG (10^-9 M) on the inhibitory effect of nerve stimulation was reduced by proglumide (5 x 10^-5 M). These data suggest that proglumide, in millimolar concentrations, may be an antagonist for gastric receptors located on inhibitory nerves and smooth muscle. (Supported by A.H. Robins.)
44.1
The vesicles were then restored by gentle homogenization and the molecular weights of three brush border marker enzymes that this preparation should be useful for target size analysis.

44.2
Effect of adriamycin on short circuit current across toad urinary bladder epithelium. J.B. Chen*, Physiology, USUHS and NTR, Bethesda, MD 20814

Adriamycin is a potent antibiotic widely used in the chemotherapy. The major side-effect of this drug is the cardiac toxicity. The mechanism of adriamycin toxicity is still unclear. In this study, we investigated the effect of adriamycin (ADR) on Cl-/HCO₃⁻-activated current (Iₗ⁺) across the toad bladder in an attempt to detect if there is a possible interaction between the drug molecule and the toad bladder epithelial cell membrane. Our preliminary results show that when the mucosal surface of the epithelium is exposed to 50 μM ADR, a significant increase in SCC occurs within 10 min if the epithelium is responsive to the drug treatment. Our data indicate that the increase in SCC is due to an enhancement of Na transport channels at the apical membrane but not to changes in Na pump (Na,K-ATPase) activity in the epithelium. The epithelial cell membrane also hyperpolarizes as a result of the drug treatment. Mucosal ADR treatment also causes significant increases in the cell contents of Na and Ca. Relative to the ultrastructure of the control bladder epithelium, ADR causes a reduction of microvilli and microfilaments as well as the size of cells, and the accumulation of secretory granules in the apical regions of the epithelial cells. This study suggests that toad urinary bladder epithelium may be a target tissue for probing the cardiac toxicity of adriamycin. (Supported by USUHS Grant C07662).

44.3
Electrical resistances of cell membranes and paracellular pathways in rabbit proximal convoluted tubules. E.B. Balla,* (SPON: C. Hnttt). Washington University School of Medicine, St. Louis, MO 63110.

The membrane specific resistance (Rₗ) was measured by luminal cable analysis in isolated and perfused rabbit proximal convoluted tubules. Intracellular micropuncture techniques were used to calculate the electrical resistances of the cell membrane of the tubular cell. From the assumption that (a) the relationship between the charge density and the electrical potential across the brush border is linear, (b) the apparent ratio of cell membrane resistance and (c) the effects of peritubular Ba⁺⁺ addition on basolateral and apical membranes, the resistances (assumed to be equal to the basolateral membrane) of the tubule wall were calculated. The values of Rₗ (17 ± 2 ohm cm²) and the space constant (218 ± 39 cm) were found to be higher than previously reported. Rₗ values were found to be 21 ± 9 ohm cm² when the temperature was lowered from 37°C to 10°C and was practically abolished by removal of Ca²⁺ from the bathing solution (Rₗ in Ca⁻⁻ free medium: 2.0 ± 0.4 ohm cm²). The ratio of membrane resistances (luminal/basolateral) was 3.6 ± 0.6. The values of apical and basolateral membrane resistances (Rₐ and Rₐ) were 146 and 41 ohm cm² (luminal cytosol/kidney). If a correction for a membrane folding factor of 36 is introduced, the values of Rₐ and Rₐ can be calculated to be 2520 and 1400 ohm cm², respectively. The apical and basolateral resistances are low, explain the low transepithelial resistance. Supported by NIH Grant GM00976.

44.4
The Importance of Basic Amino Acid Residues in the Renal PAH Transporter. S.S. Tse*, C. Bildsteinw, D. Liu*, and R.D. Mamelok. Stanford University, Stanford, CA 94305.

Basal lateral membranous vesicles prepared from the rabbit renal cortex contain a transport system for p-aminohippurate (PAH) which is irreversibly inactivated by concentrations of trypsin which do not affect either sodium-dependent uptake of L-glutamate or the "glucose space" of the vesicles. This suggests that the transporter contains a peptide bond(s) near the membrane surface of the transporting or lysine residues, and that this bond(s) is essential for maintaining the functional integrity of the transporter. In order to explore the role of arginine and lysine residues in the membrane transport pathway, we investigated the effects of phenylglyoxal which reacts with arginine residues and of trinitrobenzenesulfonic acid (TNBS) and citraconic anhydride which react with lysine residues and N-terminal amino groups. Phenylglyoxal inhibited the total transport of PAH into vesicles by 58%. TNBS inhibited uptake by 29%; however, citraconic anhydride was not inhibitory. Clostripain, which cleaves predominantly bonds involving carboxyl groups of arginine, was then tested for its ability to decrease the transport of PAH. After the vesicles were incubated for 15 minutes with clostripain, about 50% of probenecid inhibitable uptake of PAH was abolished. We conclude that a residue of arginine is important to the integrity and function of the transporter. The importance of a residue of lysine and N-terminal amino groups cannot be determined unambiguously from the data.

44.5

The apparent molecular weight of a transport carrier for L-serine was measured using radiation inactivation analysis of target size on rabbit intestinal brush border membrane vesicles. Brush border membrane vesicles, isolated from rabbit intestine, were prepared using the calcium precipitation method, lyophilized, and then irradiated under vacuum with 20 MeV electrons. The vesicles were resuspended in Tris buffer and incubated for 45 minutes in sodium/thioether buffer at pH 7.6. "Serine" transport was measured at 20°C using a 5 second flux incubation for 45 minutes in sodium/thioether buffer at pH 7.6. The "serine" transport was measured at 20°C using a 5 second flux period, followed by ice-cold mannitol buffer dilution. Rapid filtration through 0.45 μm filters. Diffusion correction were made by subtracting the residual flux in 100 mM serine from the flux measured at 1 mM serine. It was found that under tracer exchange conditions the apparent molecular weight of the serine transporter was 165,000 daltons. The molecular weights of three brush border marker enzymes were also measured in this inactivation of L-serine transport. The molecular weights were γ-glutamyltransferase, 125,000 daltons; L-leucine aminopeptidase, 135,000 daltons; and alkaline phosphatase, 37,400 daltons. It is concluded that this preparation should be useful for target size analysis of other brush border intestinal transport systems. (Supported by USPHS grant 1 F31 AM 06687-01).
Cl⁻ absorption by Amphiuma small intestine: Dependence on mucosal Na⁺ rather than mucosal Na⁺ and serosal K⁺.

Daniel C. Marcus and Nanc Y. Ellingsen. Department of Physiology, Emory University, Atlanta, GA 30322.

Closer techniques and Cl⁻-sensitive microelectrodes were used to determine the site of the requirement for Na⁺ for active electronegative Cl⁻ absorption in Amphiuma small intestine. In vivo experiments indicated that absorption was located in the basolateral (free) cell compartment. 

An enhanced short-circuit current consistent with greater Cl⁻ absorption when Na⁺ was added simultaneously to mucosal and serosal media. Simultaneously the electrogenic flux of Cl⁻ ([Jcl] was increased 0.40±0.05 μeq/hr-cm². The short-circuit current was increased. In paired tissue addition of Na⁺ only to increased [Jcl] by 0.43±0.07 μeq/hr-cm². Addition of Na⁺ to Na⁺-free media significantly increased the short-circuit current. Additions of Na⁺ to Cl⁻-free media was 29.4±2.8 μmV in illus cells. While the mucosal membrane potential [Vm] was -30.5±2.2 μmV indicating active Cl⁻ accumulation. Cl⁻ accumulation was eliminated and [Vm] remained at control levels. These results indicate that Na⁺ is required at the basolateral rather than the luminal membrane for active electronegative Cl⁻ absorption by the small intestine. Supported by USPHS grants AM47501 and AM20670.

44.8


We studied the transport of 86Rb and 22Na by vascular preparations from hog stomachs. 86Rb uptake was resolved into a fast, osmotically sensitive component (½/2 = 45 sec) and a slow component presumably representing paracellular absorption. Na⁺ uptake was inhibited by cations in the following order: K⁺ > Rb⁺ > Cs⁺ > Na⁺. The system showed the characteristics of an Na⁺-K⁺ cotransporter. The Na⁺ uptake was 54.1 ± 4.9 peq/hr•cm² at pH 7.4. 

The Km for Na⁺ uptake was 1.4 ± 0.07 mM while the Vmax was 64.4 ± 3.4 peq/hr•cm². The NaCl flux was 44.7 ± 4.8 peq/hr•cm². Addition of ouabain to the serosal side inhibited Na⁺ uptake by 90%. The NaCl uptake was increased by a serosal Na⁺ gradient. This NaCl uptake was increased by 20% by the addition of ouabain to the serosal side. In paired tissues addition of Na⁺ to the serosal side increased Na⁺ uptake by 60%. 

The Na⁺ uptake was increased by 60% by the addition of ouabain to the serosal side. In paired tissues addition of Na⁺ to the serosal side increased Na⁺ uptake by 60%. The Na⁺ uptake was increased by 60% by the addition of ouabain to the serosal side. In paired tissues addition of Na⁺ to the serosal side increased Na⁺ uptake by 60%.

Supported by USPHS Grant No. AMRO706.
Aqueous extracts of cotton bracts (CBE) cause airway smooth muscle contraction and 5-hydroxytryptamine release from human platelets. We tested the effects of CBE on the isolated canine tracheal epithelium and on the paracellular fluxes of $^{14}$C-mannitol. Mucosal addition of CBE produced decreases in transepithelial potential difference, short-circuit current and tissue resistance and the effects were dose-dependent. Five ul of CBE produced no change in mannitol fluxes even after five hours, while higher concentrations resulted in increases in mannitol fluxes at 90 min. Submucosal CBE (100 ul) produced no change in bioelectric properties or mannitol fluxes. The effects of 5 ul were reversible but were not blocked by mucosal amiloride ($10^{-5}$M) or indomethacin ($10^{-6}$M). We conclude that low concentrations of CBE alter active ion transport at the apical cell membrane without affecting the paracellular pathway while higher concentrations alter paracellular fluxes. These effects may produce changes in secondary water transport, allow access of CBE to airway smooth muscle and the interstitium and may contribute to the pathophysiology of byssinosis.

(Supported in part by Cotton Incorporated and NIH grant PHL 28669.)
45.1 AMILORIDE INHIBITS CARBACHOL-INDUCED AMYLASE SECRETION AND NaCl EFFLUX IN RABBIT PANCREATIC ACINUS
S.L. Booting, C.A.J. Kuipers and J.J.H.N.M. de Pont.
Department of Biochemistry, University of Nijmegen, Nijmegen, The Netherlands.

The diuretic drug amiloride is an inhibitor of two different Na+ transport processes in the rabbit pancreatic acinus: a sodium/proton exchanger mechanism (high amiloride affinity) and a Na+-H+ exchange mechanism (low amiloride affinity). The Na+-H+ exchange mechanism plays a role in a number of different physiological processes and is inhibited by relatively high concentrations of amiloride (10–10^{-3}M). In the excocrine pancreas, the neurotransmitter acetylcholine and the peptide hormone pancreozymin stimulate amylase secretion. Their mechanism of action is based on an increase in the intracellular Ca concentration, due to the release of bound Ca from intracellular pools. In rabbit pancreatic acini, the neurotransmitter acetylcholine (10^{-7}M) inhibits the Cl- stimulated amylase secretion in an apparently competitive manner. However, it does not inhibit the pancreozymin-stimulated amylase secretion and the Cl- influx. This suggests that amiloride in concentrations, in which it also inhibits the Na+-H+ exchange process, is either a competitive antagonist of the action of carbamoyl at the acetylcholine receptor level, or that the Na+-H+ exchange mechanism is involved in the mechanism of carbamoyl-stimulated amylase secretion.

45.2 BICARBONATE SECRETION BY DUODENAL SURFACE EPITHELIUM AND ITS PROTECTIVE ROLE. C.J. Lemstrom, E.K. Kivivuokko and A. Garners.

Surface epithelium in duodenum is a variety of mammals in vivo transports CO_2 into the lumen at a considerable rate due to duodenal luminal Ca-Cl^- exchange or valinomycin-sensitive Ca-H+ exchange. Inhibition of valinomycin-sensitive Ca-H+ exchange by amiloride on this secretion was studied in anaesthetized Sprague-Dawley rats. Luminal alkalinization was titrated (pH stat) either at neutral luminal pH after a 5 min exposure to the duodenal lumen of various pH (2-5) or during continuous exposure of the lumen to pH 2 or 5. In the latter experiments, pH at the luminal cell surface was measured with a microelectrode. Values of pH 2 caused a sustained (>90 min) rise in HCO_3^- secretion and in intracellular pH. Amiloride reduced the duration of this response. Continuous exposure to pH 2 caused a 90% rise and exposure to pH 5 a 100% rise in secretion. Intravenous aspirin inhibited only the response to pH 2 and inhibition resulted in mucosal damage. The lipoxgenase product was exposed to pH 2 caused a 90% rise and exposure to pH 5 a 100% rise in secretion. Intravenous aspirin inhibited only the response to pH 2 and inhibition resulted in mucosal damage.

45.3 FACTORS REGULATING GASTRODUODENAL EPITHELIAL HCO_3^- SECRETION.

Gastric and duodenal epithelia transport HCO_3^- in a secretory direction. Normally, contents of stomach and duodenal pH are acidic and HCO_3^- is neutralized close to the mucosal surface. In the absence of luminal acid, HCO_3^- secretion can be measured as an extracellular HCO_3^- secretion. Gastric HCO_3^- secretion usually amounts to 2-10μmol of max H secretion and is due to a Cl-HCO_3^- exchange process. Duodenal HCO_3^- secretion is exceeded more than 2 to 10-fold and is the predominant mechanism in the Cl-bathing solutions only, and with a PD which changes across the epithelial section. Gastric and duodenal HCO_3^- secretion in vivo is influenced by factors such as the acid secretory status or experimental factors. Exposure to luminal acid (or feeding) increases both gastric and duodenal HCO_3^- secretion in vivo and in vitro. This response was mediated via a basal HCO_3^- production and tissue specific humoral agents, may be important in the local regulation of HCO_3^- disposal and mucosal protection.

45.4 MEASUREMENT OF IN SITU pH IN THE STOMACH AND PROXIMAL DUODENUM WITH SINGLE AND MULTIPLE ELECTRODE SYSTEMS.

Luminal pH was measured in the stomach using a single electrode and in the proximal duodenum using a single and multiple electrode systems. In the preparation of the rat stomach in vivo (Moody & Davis, Gastroenterology 59:350-357, 1970), pH of the stomach and proximal duodenum was measured using glass electrodes distal to the pylorus show fluctuation of pH between 3 and 6. For each 10-min period mean hydrogen ion activity, percentage of normal pH was ≤3.0 and number of spikes was computed.

45.5 FURTHER STUDIES ON THE MECHANISM OF THE SPD (SUDDEN POTENTIAL DROP) IN FROG GASTRIC MUCOSA. William Ali, Susumu Ishi*, and Jeffrey Mattox.* Harvard Medical School, Beth Israel Hospital, Boston, MA 02215.

An SPD and sudden drop in resistance (SR) was regularly observed by Kidder in frog gastric mucosa during anoxia with serosal pH 7.1, in Cl- bathing solutions only, and with a PD which changes across the regions of 10 μmol HCO_3^- per cm² (23964-46, 1976). We found that anoxia is not a prerequisite, since SPD can be reliably produced under conditions where H secretion can be measured as one mediator of the duodenal alkaline response to acid. The rate of H+ back diffusion was greater in mucosae of the stomach in vivo (Moody & Davis, Gastroenterology 59:350-357, 1970). Loss of H+ from the secretory solution bathing the luminal surface of isolated bullfrog gastric mucosa, was quantitated by direct titration of weighed aliquots of this solution. Secretory to nutrient CI fluxes were also measured, using 36Cl-. Mucosae brought to a resting state with cimetidine were relatively impermeable to H+ and resistant to ulceration. In experiments in which 50 mM HCl (made isotonic with NaCl) was instilled as secretory solution, H+ permeability was 0.5 x 10^{-5} cm sec^{-1} (resting mucosae; n=6). In the same experiments, the presence of exogenous H+ increased secretory to nutrient CI flux to an extent indicating that approximately 75% of H+ back diffusion occurred from the back diffusion space. Moreover, mucosae were maximally stimulated to secrete acid, as previously found in canine stomach in vivo (Moody & Davis, Gastroenterology 59:350-357, 1970). A further increase in rate of H+ back diffusion in stimulated mucosae could be induced by addition of SCN^- to the secretory solution. In the presence of SCN^-, secretion of H+ decreased to secretory to nutrient CI flux, suggesting competition between H+ and HSCN at a mucosal site. (Supported by grants NSF PCM 78-22520 and NIH AM 25986).

45.49 CYCLIC NUCLEOTIDE-DEPENDENT PROTEIN KINASE FROM HUMAN TANKER; J. Hersey and W. C. Miller. Dept. of Physiology, Emory University, Atlanta, GA 30322.


Pronase-dissociated and Percoll-purified rat pyloric cells were found to contain specific and high affinity binding sites for D2-1-yr1 somatostatin 14 (Kd = 5 x 10^-11 M). These sites were further shown to be reversibly associated with the phosphoproteins (PP2a: substrate 50-80kD). These being released (i.e. activated) upon somatostatin binding. Both binding and somatostatin-stimulated PP2a activity were enriched in cytosolic (100,000 x g x 1h) fraction. Both were sensitive to temperature and were inhibited by blockers and uncouplers of mitochondrial respiration. These observations suggest that somatostatin inhibition of gastric H+ secretion is due to a dephosphorylation process mediated by a specific intracellular or internalized receptor.

Supported by SNRC Project 151 and CBN Project 81-04.

45.11 HISTAMINE AND CYCLIC AMP. MAJOR NODES OF STIMULUS PATHWAYS FOR GASTRIC ACID SECRETION. E. B. Margareta Ekblad* (SPON: Richard P. Durbin). University of California, San Francisco CA 94143.

45.10 SECOND MESSENGERS AND THEIR SITE OF ACTION IN GASTRIC PATHWAYS. S. J. Hersey and M. Miller. Dept. of Physiology, Emory University, Atlanta, GA 30322.

45.12 ROLE OF CALCIUM AND MEMBRANE PHOSPHORYLATION IN REGULATING CYCLIC AMP SECRETION. Linda J. Shlatz*. Medical College of Ohio, Toledo, Ohio 43609.

Using parietal cells isolated from rat gastric mucosa, the calcium ionophore A23187 was found to stimulate acid secretion by an increase in the calcium-dependent cAMP accumulation in the parietal cell. This effect was reversed by trifluoperazine, a phenothiazine known to inhibit cAMP-dependent protein kinase. The stimulation of acid secretion by the ionophore was time dependent and could be prevented by pretreatment with cAMP phosphodiesterase inhibitors (e.g., 3-isobutyl-1-methylxanthine or cycloheximide).

Supported by NIH AM 21448.

Plasma membrane vesicles isolated from turtle bladder epithelial cells contain a primary active mechanism for proton transport. Energized by the extravesicular addition of ATP, the mechanism induces the development of transepithelial gradients of pH (Cl-dependent electrical potential) (inside, more positive), as indicated respectively by the quenched fluorescence of lucifer yellow (AO) and oxonol V, respectively. Evidence for these claims is as follows. After ATP addition to vesicles suspended in tris buffered media (containing KCl or NaCl or choline Cl or the NO3 of these cations) Cl or NO3 is carried passively into the vesicular interior while protons are again pumped into the vesicular interior. The same addition to vesicles which have been pre-loaded with K+ glaconate and treated with valinomycin, K+ is carried passively out of the vesicular interior while protons are again pumped into the vesicular interior. The same addition to vesicles buffered devoid of transportable ions induces the development of a transepithelial electrical potential (inside negative). However, less than 20% of the uninhibit-resistant ATPase is required for maintenance of 100% of the ATP-driven proton transport in these vesicles as indicated from data on the effects of FCCP, DCCD, Triton X-100, and IsgCl2 (MR supported).

48.2 THE USE OF 31P NUCLEAR MAGNETIC RESONANCE (NMR) TO STUDY H+/HCO3- TRANSPORT IN EPITHELIUM. J. P. Kokko, S. I. Helman, J. S. Standards*, and R. L. Nunnally*. Univ. of Texas Health Science Center, Dallas, Texas 75235 and of Illinois, Urbana, IL 61801.

There exists a number of different techniques by which intracellular pH (pHi) can be determined. Recently it has been apparent that there may be a need for a new technique by which pH can be measured noninvasively with a relative degree of accuracy (±0.03 pH units). The theoretical basis for this observation that the position of the inorganic phosphate peak is pH dependent. While NMR does offer some unique advantages, it currently has the disadvantage of requiring large quantities (about a gram wet weight) of tissue. However the present studies was to use NMR to measure pH in epithelial sheets of frog skin in response to acute stepwise changes in pCO2 (0. 2, 5, and 10% CO2). The present studies were conducted at room temperature using Cl or SO4 Ringers. The control pHi (0% CO2) in Cl Ringers was 7.19±.07 and in SO4 Ringers was 7.14±.12. With increasing pCO2 there was a polynomial decrease in pHi with the pH in the SO4 Ringers being more alkaline than in Cl Ringers (the polynomal regression was 1.35-0.18lnPCO2) at the pF=15.

The results were consistent with the view that the intracellular hydrogen ion concentration is lower than predicted from Nerst potential, and further, the results support the existence of HCO3/C1 exchange mechanism.

48.3 REGULATION OF ACIDIFICATION IN RABBIT MEDULLARY COLLECTING ducts. H. R. Jacobson. UTHSCD, Dallas, Texas 75235

We have recently demonstrated that the rabbit medullary collecting duct (MCD), when perfused and bathed in vitro with symmetrical Ringer's bicarbonate solutions, demonstrates a luminal positive transmembrane voltage (Vl) and reabsorbs HCO3 at a rate of 10-12 pmol/mm.x.1.min-1. Net HCO3 reabsorption (JHCO3) is matched by net Cl secretion (JCl). Additionally, net bicarbonate reabsorption is mineralocorticoid sensitive, Na independent, dependent on peritubular Cl, and inhibited by peritubular acetazolamide and SITS. The present studies examine the effects of [K], pCO2, [HCO3] and 8-Bromo cyclic AMP on MCD perfused in vitro. Increasing peritubular [K] from 5 to 50 mM (Na replacement) does not change JHCO3. (12±1.9 vs 13±2.0) or Vl. However, luminal diffusion [K] to 75 mM (Na replacement) and reducing [Cl] to 50 mM (glucanate replacement) decreases JHCO3 and changes JHCO3/ JCl from 1.0 to 0.5. Acute reduction of pCO2 from 40 to 10 mm Hg reduces Vl and JHCO3 by 50%. Acute reduction of both HCO3 to 5 mM (pH 8.6) significantly increases luminal positive Vl and JHCO3. Finally, 10-5 M D-brom cyclic AMP significantly increases Vl by 30% and increases JHCO3 from 6.9 to 9.8. Thus, rabbit MCD is relatively high capacity distal nephron acidification segment that: 1) is not affected by changes in luminal pH; 2) appears to preferentially shunt H secretion with Cl secretion; 3) is regulated by changes in ambient pH and 4) is stimulated to secrete H by cyclic nucleotides.


In order to examine the mechanism of flow dependence of proximal bicarbonate absorption (JHCO3), rat proximal convoluted tubules were microperfused at varying rates. In tubules perfused with 25 mM HCO3, at 13, 33, and 49 nl/min, JHCO3 was 105±4, 176±8, and 209±7 pmol/mm.x.1.min-1 respectively. Only 15% of this stimulation of JHCO3 was attributable to flow dependent increases in pHi. Changes in diffusive or convective fluxes could not account for the observed stimulation. In tubules perfused with 58 mM HCO3, a perfusate previously demonstrated to achieve maximal rates of acidification, increasing luminal flow rate from 13 to 49 nl/min did not stimulate JHCO3. These results demonstrate that increasing luminal flow rates stimulate active proton secretion at low luminal HCO3 concentrations but do not affect the maximal rate. The failure to increase Vmax excludes an increase in the number of NaH antiporters. This kinetic behavior is most consistent with the presence of a flow dependent luminal diffusion barrier in the proximal tubule. According to this thesis, flow dependent stimulation of JHCO3 is secondary to flow dependent changes in luminal HCO3 concentration occurring by two mechanisms: 1) flow dependent increases in the measured axial luminal HCO3 concentration profile, and 2) flow dependent decreases in radial luminal HCO3 concentration gradients. In order for such radial gradients to exist, HCO3 diffusion must be restricted in the micro-environment of the brush border membrane. (This work was supported by NIH grants AM 27045 and AM 07219.)


In the stopped perfusion of tubules the chance for errors in the evaluation of renal tubular acidification kinetics has shown that different experimental conditions affect the pH gradient, acidification rate (JHCO3) and net H/HCO3 transport. We have developed an electrical analog model in which H movement, electroneutral or not, is described by a circuit consisting of a proton-motive force (G) with a series resistance (Rh). In parallel with a capacitance (C) and a shunt (S), changes in the capacitor charge, follow an exponential course toward steady-state, in the same way as luminal NaHCO3 or NaHCO3. Changes in G/2 are due to modifications in Rh, 88 or C. Experimentally, an increase in capillary pCO2 from 2 to 100% at pH 7.7 produces a maximal JHCO3/ from 0 to 5.48 to 71.74. At pCO2, of 10%, the luminal and peritubular pH changes from 7.89 to 7.53. Both modifications are attributed to changes in Rh depending on cellular H availability. Situations in which the number of luminal transport sites (e.g. by valinate luminal or other luminal blocker transfer) are modified also affect Rh. The fall in distal t/2 during amphotericin B treatment is ascribed to a decrease in S. The proposed model is able to account for a number of experimental modifications of tubular acidification, incorporating gradient-dependent active H ion secretion, an active pump contribution and transmembrane shunt resistance, the latter including both passive H and HCO3 movement.

48.6 DETERMINANTS OF RENAL CORTICAL CO2 TENSION. Thomas D. DuBois, Jr., Departments of Medicine, Physiology and Biophysics, University of Texas Medical Branch, Galveston, TX 77555

In vivo micropuncture studies employing PCO2 microelectrodes have demonstrated that CO2 tensions in the cortical microcirculation are significantly greater than systemic arterial PCO2 (65 vs 49 mmHg). Our findings demonstrate that CO2 gas is in, near, or near, diffusion equilibrium in cortex in the superficial cortical zone and the deep cortex is indistinguishable from renal artery PCO2. A mathematical model of CO2 generation from our laboratory suggests that metabolic CO2 production (MC02) in combination with vascular-to-vascular gas exchange is the determinant of cortical PCO2. Six groups of rats were maintained on a respirator and PCO2 was measured in the early and late proximal tubules and the stellate vessel during a control and experimental period: I. S.N. isoionia, II. Hypercotic acidification, III. Aortic constriction, IV. NaHCO3 (50 mg/kg/80 mM), V. Acetazolamide 100 mg/kg, and VI. DNP 50 mg/kg via renal artery. Arterial blood PC02 and (CO2) did not differ among the groups. RBF increased in II (6.9 to 16.3 liters/min) and decreased in groups III, IV, V, and VI. PCO2 was 85 in I, 71 in II, 54.0 in III, 55 in IV, 57 in V, and 87 mm Hg in VI. Therefore, RBF can be dissociated from changes in renal cortical PCO2. Metabolic CO2 production is an important determinant of the elevated PCO2 in the renal cortex.
CO₂ is produced in the kidney by both cell metabolism and HCO₃⁻ reabsorption. Consistent with this unique CO₂ burden, PCO₂ in surface tubules and peritubular capillaries (PC) is notably higher than in arterial blood (Art). The PC-Art PCO₂ gradient can be altered markedly by a variety of experimental maneuvers, but it shows no correlation with proximal HCO₃⁻ reabsorption (APRHCO₃) in our studies. PC-Art PCO₂ varies inversely with renal blood flow in rats with comparable APRHCO₃, suggesting that cortical PCO₂ is influenced by the rate of CO₂ removal. In Munich-Wistar rats, we have found Bowman's space (BS) PCO₂ to be 10-15 mmHg higher than Art, indicating that CO₂ must be added to the blood prior to its arrival at the superficial cortex. PCO₂ rises further, by 5 mmHg, between BS and the early proximal tubules and is 2-3 mmHg higher in PC than in BS, reflecting CO₂ production in surface nephrons. These small increments are consistent with the view that the CO₂ produced by HCO₃⁻ reabsorption is consumed in the tubular cell to form new HCO₃⁻, and that metabolic CO₂ is rapidly buffered. Although the PCO₂ increment may be small at a given level in the cortex, we propose that PCO₂ is increased progressively in the interlobular arteries as they traverse the cortex and by diffusion from deep nephrons, resulting in the high cortical-arterial PCO₂ gradients normally observed.

The mechanism of HCO₃⁻ exit in the rabbit PCT is not known. HCO₃⁻ could exit either neutrally in exchange for Cl⁻, or conductively down its electrochemical gradient. To examine whether HCO₃⁻ exit is neutral or conductive, we perfused PCT in vitro with ultrafiltrate-like solutions and measured net volume absorption (Jv) with inulin and net total CO₂ absorption (JNTCO₂) with microcalorimetry.

The hypothesis that HCO₃⁻ exit is neutral, in exchange for Cl⁻, was tested by measuring the effect of Cl⁻ replacement with isethionate. Removal of Cl⁻ did not affect JNTCO₂ (82.6 ± 15.0 vs. 83.4 ± 13.6 pmol/mm*min, n=5) or Jv (0.68 ± 0.10 vs. 0.65 ± 0.09 nl/mm*min, n=5). Conductive HCO₃⁻ exit was tested by measuring the effect of 2 mM bath Ba²⁺ which is known to depolarize the basolateral membrane by 50%. Bath Ba²⁺ reduced JNTCO₂ 41% from 94.4 ± 11.4 to 56.4 ± 7.9 pmol/mm*min (n=5) and Jv 31% from 0.95 ± 0.31 to 0.65 ± 0.13 nl/mm*min (n=5). When PCT were perfused with high Cl⁻, low HCO₃⁻ solutions Jv (due entirely to NaCl absorption) was unaffected by 2 mM bath Ba²⁺ (0.68 ± 0.10 vs. 0.69 ± 0.08 nl/mm*min, n=10). Thus, the Ba²⁺ effect was specific for JNTCO₂.

In summary: (1) JNTCO₂ is Cl⁻ independent; (2) Bath Ba²⁺ inhibits JNTCO₂ 41%; (3) Bath Ba²⁺ does not inhibit Na⁺-K⁺ ATPase. From these data we conclude that HCO₃⁻ exits conductively down its electrochemical gradient. (NIH Grant R01 AM 36162).
49.1

NITRIDEPINE ACTIONS ON TRANSMEMBRANE Ca++ AND K+ CURRENTS IN SHEEP HEART: PRELIMINARY STUDIES. M. Gillis*, Y. Wender*, and E. Shibata* (SUNY. C. D. Hall). Department of Physiology and Biophysics, University of Texas Medical Branch, Galveston, TX 77550.

A single microelectrode voltage clamp technique has been used to study the effects of nitridepine (Nt) on transmembrane currents carried by Ca++ and K+ in single cardiac cells where are enzymatically isolated from bullfrog atriaum. In the dose range 10^-4 to 10^-3 M, Nt produces a strong inhibition of Ip. Measurements of the blockade of Ip by Ca++ (2.5 mM) elicited by 100 msec pulses from -80 to 0 mV yield a K of approximately 8x10^-6 M if the data are fitted to a simple two-state model of a two-state binding site.

The selectivity of this blockade was assessed by studying effects of Nt on two different potassium currents: 1) an inward-rectifying K current which gives rise to the resting potential; and (2) a slow time- and voltage-dependent outward current (delayed rectifier) which initiates repolarization. At 10^-3 M to 10^-2 M, Nt produces a significant decrease in the inward-rectifying K current in approximately 50% of our experiments. However, it has no effect on the delayed rectifiers. Supported by NIH HL-27452, NIA 01-035, and an ARA Established Investigators Award (W.G.1).

49.2


The pacemaker current and associated changes in membrane resistance were studied in isolated sheep cardiac Purkinje fibers using a two-microelectrode voltage clamp technique. It was found that the amplitude of current flowing during small hyperpolarizing clamps decreased during hyperpolarizing clamps that increased the instantaneous current and decreased the development of the pacemaker current especially at high frequencies. Increasing [Ko] from 2.7 to 5.4 mM reduced the membrane resistance and (during hyperpolarizing clamps) increased the instantaneous current and slowed the development of the pacemaker current. Adding barium (Ba, 0.05 mM) increased the membrane resistance and the holding current, reduced the instantaneous current on hyperpolarization, abolished the initial dip, and accelerated the decay of the pacemaker current especially at high frequencies. Cesium (Cs, 2 mM) reduced the holding current, had little effect on the instantaneous current on hyperpolarization, eliminated the pacemaker current and the associated membrane resistance changes. Cs reduced the holding current even at 10.8 mM K. If the current was reversed, Cs decreased but did not abolish it. When Ca was applied in the presence of Ba, the pacemaker current was eliminated or reduced depending on the extracellular K. It is concluded that cesium abolishes the pacemaker current by abolishing a time-dependent current, pre sumably a decrease in potassium conductance. This increase enhances the pacemaker current by reducing the background K conductance and more so at high K. (Supported by NIH grants HL27038 and HL17451).

49.3


The mechanism of the oscillatory current (Ios) has been investigated in single cardiac fibers with a two-microelectrode voltage clamp technique. The results show that: 1) Ios can be initiated not only by repolarizing but also by depolarizing clamps, provided that the preparation is preloaded with calcium; and that the depolarizing test clamp initiates Ios; 2) the Ios initiated by a depolarizing test clamp is usually smaller and has a longer time to peak than the Ios initiated by a repolarizing clamp; 3) brief depolarizing clamps can be followed by an Ios in fibers preloaded with calcium; 4) the amplitude of Ios initiated by a test clamp diminishes as the interval between conditioning and test clamps increases; 5) Nt is initiated by repolarizing or depolarizing clamps to potentials positive to about -30 to -40 mV; 6) decreasing [Na]o enhances the Ios but still this current does not appear at least negative potentials; 7) when a test clamp is applied at the peak of Ios to potentials positive to about -30 mV, the current disappears; 8) with 10^-4M strophanthinid, current oscillations appear with depolarizing or repolarizing clamps; 9) the membrane resistance during Ios increases. It is concluded that the repolarization initiates Ios indirectly, that Ios is due to a calcium-triggered release of calcium and that the released calcium induces Ios by an electrogenic Na-Ca exchange.

(Supported by NIH grants HL 17451 and HL 27038)

49.4

CELLULAR MECHANISM OF LIDOCAINE'S ANTARRHYTHMIC ACTION IN SHEEP CARDIAC PURKINJE FIBERS. S.S. Sheu* and W.R. Laderer. Univ. of Maryland Sch. Med., Baltimore, MD 21201.

We examined the action of therapeutic concentrations of lidocaine (10^-4M) on the pacemaker current (Ip) and action potential duration (APD), twitch tension and intracellular sodium activity ([Na]i) in sheep cardiac Purkinje fibers. The induction of lidocaine's antiarrhythmic action, which was followed by an Ios in fibers preloaded with calcium, resulted in a reduction of a in fibers stimulated at 1 Hz. This reduction of a was preceded by a rapid reduction of APD. This observation was then combined with the experimental results of Eisner, Laderer & Sheu (J. Physiol. 1983, In Press) suggests that lidocaine first blocks a portion of the component of Ios that contributes to the APD and it is also responsible for the decline of a. If a preparation was first exposed to the cardiotoxic steroid strophanthinid (10^-4 M), a marked elevation and arrhythmogenic transient depolarizations (TD) are observed. In many fibers the addition of lidocaine under such conditions leads to a similar rapid shortening of the APD and a gradual reduction of a. The amplitude of the TDs is diminished as the APD is reduced and, as a falls, there is a further reduction of the TD amplitude. We conclude that at least part of the antiarrhythmic action of lidocaine (at therapeutic concentrations) must be due to a reduction of inward Na current as reflected in the shorter action potentials and the fall of a.

49.5


It has been reported that the pacemaker current (Ip) increases with low [Na]o without increasing of [Ca]o. This point is important about the mechanism of such an effect. Thus, in the present study, the role of an increased membrane conductance in Ip change was investigated by means of a two-microelectrode voltage clamp technique in cardiac sheep Purkinje fibers. The following results were obtained: 1) Reducing [Na]o to 80.8 mM increased the instantaneous current and slowed the development of the pacemaker current. Increasing [Na]o to 20.8 mM decreased the membrane resistance and the holding current, reduced the instantaneous current on hyperpolarization, abolished the initial dip, and accelerated the decay of the pacemaker current especially at high frequencies. 2) Increasing Ea10 to a less negative potential. 3) Adding Ba (5 x 10^-5 M) decreased the instantaneous current and increased the amplitude of I to a less negative potential. 4) Increasing Ea10 to a less negative potential. 5) Reduction of [Ca10 to 0.54 mM decreased the amplitude and slowed the time course of Ip. It is concluded that the disappearance of Ip in a low Na solution may be related to an increased potassium conductance that exaggerates propagated phenomena.

(Supported by NIH grants HL27038 and HL17451).

49.6

EFFECTS OF ACETYLCHOLINE ON THE Sino-ATRIAL NODE OF NEONATAL AND ADULT GUINEA PIGS. Zajiko J. Boenjak, and John D. Kamping. Medical College of Wisconsin and Wood VA Medical Center, Milwaukee, WI 53293.

The purpose of this study was to examine the sensitivity of the neonatal (0-7 days old) and adult (over 5 weeks old) sino-atrial (SA) node to acetylcholine (ACH) by recording intracellular potential duration (APD), twitch tension and intracellular sodium activity ([Na]i) in sheep cardiac Purkinje fibers. As a result, we found that the neonatal sino-atrial (SA) node exhibits a greater sensitivity to ACh than the adult node. When the SA node is stimulated in vitro under identical conditions, ACh was introduced by switching to Kreb's superfusate for 1 minute containing graded concentra tions of the ACh (1 x 10^-7 M to 1 x 10^-4 M). These experimental conditions, the spontaneous rate of the SA node from the adult guinea pig decreased an average of 21% from the control, while the neonatal SA node exhibited a greater than 50% decrease. During the introduction of ACh the following changes in the action potential were observed: the slow dia stolic depolarization was markedly depressed with a decrease in the phase 4/dV/dt from 139 nV/sec/msec to 56 nV/sec/msec, the action potential duration was shortened from 70 ms to 47 ms while ACh-induced hyperpolarization has led to a pronounced increase in the phase 9 99% 9% 105 V/sec to 15 V/sec. These data indicate that the neonatal primary pacemakers are more sensitive to the negative chronotropic effects of ACh than the adult SA node. (Supported in part by NIH grant GM 29641 and the Veterans Administration).
EFFECT OF ADENOSINE ANALOGS ON VENTRICULAR AUTOMATICITY
L. J. Herrera, L. S. Goldman, and S. J. Olson. University of Nebraska, Omaha, and Dalhousie University, Halifax, Nova Scotia, and University of Texas, San Antonio, TX 78284.

Adenosine's interaction with extracellular membrane receptors may initiate reentrant arrhythmias. Although the mechanism by which adenosine (ADO) causes changes in the rate of ventricular depolarization is not clear, different receptor types may account for many of the effects of adenosine in a variety of tissues. The availability of receptor-selective adenosine analogs permits the identification of receptor types in biological systems. Previous studies have shown that adenosine suppresses rat ventricular automaticity. In the present study the relative potency of adenosine analogs was assessed in order to identify the ADO receptor involved in this negative chronotropic effect. Isolated rat hearts with atrial tissue removed were perfused at constant flow via the aorta with modified Krebs-Hensel solution. Varying doses of adenosine (ADO), 5 - or R-ethylcarboxyamidoadenosine (5-PFA, R-PFA) or 5'-ethylcarboxyamidoadenosine (NELA) were added to the perfusate and spontaneous beating rate was measured. Then the order of potency was R-PFA > 5-PFA > ADO with mean ED90s of 7.8 x 10^{-3} M, 4.2 x 10^{-3} M, and 4.4 x 10^{-3} M, respectively. R-PFA was only a partial agonist with a maximum effect of 40% which may suggest receptor-stearoelectivity. Topical adenosine added to the perfusate competitively inhibited the negative chronotropic effects of adenosine and its analogs, producing 5 to 10 fold increases in the ED90's. These data suggest that adenosine's effect on ventricular automaticity may be mediated by A1 receptors.

DIFFERENTIAL PARASYMPATHETIC INNERVATION OF CONDUCTILE TISSUE IN THE CANINE MYOCARDIUM. Jeffrey D. Angell & James C. Randall. Loyola University Medical Center, Maywood, IL 60153.

Anatomical projections of parasympathetic nerves onto the canine heart were described in perfused hearts for the first time, allowing functional denervation of the sinusoidal (SA) node muscle while leaving the atrioventricular (AV) nodal parasympathetic supply intact. Utilizing selective intracoronary surgical ablation techniques the parasympathetic pathway innervating the AV node was isolated from the sinus node. From a transthoracic approach (T4-T5), the heart was suspended in its pericardium allowing exposure of the superior vena cava (SVC), inferior vena cava (IVC), pulmonary artery (PA), and pulmonary vein (PV) complex. Right (R) and left (L) coronary veins, and the left (L) atrium via the LI PA. RPA input from RCV via R PV complex while that from LCV was eliminated by dissection at the root of the RL PA. These denervation procedures preserved major sympathetic inputs from the right side and at least 90% of the right sympathetics to the conductile tissues of the canine heart. (Supported by NIH grants HL 27664 and HL 27593)

EFFECTS OF REVERSIBLE COOLING ON REENTRANT TACHYCARDIAS IN CANINE CORONARY SINUS FIBRILLATION. J. L. Friesen, A. D. E. Maunder, U. R. Gough, R. Collier* Downingtown and VA Medical Centers, Brooklyn, N.Y. 11209.

Nonsustained ventricular fibrillation (VS V F) were induced by 30-50 shock applied to the ventricles. Eight dogs were instrumented by sterile procedure to provide left ventricular pressure (LVP), heart rate, and ECG signals from a large number of sites; studies on mechanisms of nonsustained multiform and monomorphic premature atrial complexes (PAC) were performed using the Tektronix 4012 graphics terminal. Moments of activation are marked by a thumbwheel cursor, and then are displayed as isochronal maps of excitation of the heart. Accurate excitation maps require that electrograms be recorded simultaneously. Sampling frequency of the multiplexer is 2 kHz per data channel. Multiplexed and digitized signals in the form of eight bit, parallel TTL, binary words are fed into an Ampex high bit rate (HBR) pulse code modulation (PCM) tape recorder. Activation times at each recording site are determined with a PDP 11/34 computer. Unipolar controlled software de- multiplexes digitized electrograms and displays them 18 at a time on a Tektronix 4912 graphics terminal. Moments of activation are marked by a thumbwheel cursor, and then are displayed as isochronal activation maps, using this system we have produced detailed activation maps showing reentrant excitation in the ventricular tachycardia and during atrial flutter in canine hearts (Supported by Grant R01 HL 12378).


Subacute cardiac death from ventricular arrhythmias often occurs in patients who are asymptomatic for alcohol-induced muscle disease (AIMD). This study seeks to model AIMD and associated arrhythmias in the conscious dog by aqueous ethanol infusion into the patent left circumflex coronary artery (LCA). Anesthetized (halothane 1:1:1, 5%, 10-15 kg) were instrumented by sterile procedure to provide left ventricular pressure (LVP), LCA flow velocity (Doppler), ECG, coronary sinus samples (lactate) and left atrial pressure (LAP). A 1500 units/ml heparin was infused (1-8 ml/min) twice daily for 2 weeks into the LCA while the ECG, LVP and LAP were recorded. Lactate and ethanol were asymptomatic for alcohol-induced muscle disease (AIMD). This study seeks to model AIMD and associated arrhythmias in the conscious dog by aqueous ethanol infusion into the patent left circumflex coronary artery (LCA). Anesthetized (halothane 1:1:1, 5%, 10-15 kg) were instrumented by sterile procedure to provide left ventricular pressure (LVP), LCA flow velocity (Doppler), ECG, coronary sinus samples (lactate) and left atrial pressure (LAP). A 1500 units/ml heparin was infused (1-8 ml/min) twice daily for 2 weeks into the LCA while the ECG, LVP and LAP were recorded. Lactate and ethanol were asymptomatic for alcohol-induced muscle disease (AIMD). This study seeks to model AIMD and associated arrhythmias in the conscious dog by aqueous ethanol infusion into the patent left circumflex coronary artery (LCA). Anesthetized (halothane 1:1:1, 5%, 10-15 kg) were instrumented by sterile procedure to provide left ventricular pressure (LVP), LCA flow velocity (Doppler), ECG, coronary sinus samples (lactate) and left atrial pressure (LAP). A 1500 units/ml heparin was infused (1-8 ml/min) twice daily for 2 weeks into the LCA while the ECG, LVP and LAP were recorded. Lactate and ethanol were asymptomatic for alcohol-induced muscle disease (AIMD). This study seeks to model AIMD and associated arrhythmias in the conscious dog by aqueous ethanol infusion into the paten...

The distribution of sympathetic innervation to cerebral vessels is primarily ipsilateral, although there is overlap in basal and mediadorsal area of the frontal cortex. Propranolol, a beta-adrenergic antagonist, reduces CBF more than unilateral stimulation in normocapnia (Hussein, 1992). We have previously shown that bilateral stimulation in normocapnia, bilateral sympathetic stimulation reduces CBF more than unilateral stimulation.


Propranolol has been reported to shift the O2 dissociation curve to the right. In a previous report we studied the effect of propranolol on O2 transport in hypoxic dogs. We then demonstrated that VO2 during hypoxia (measured by expired O2 concentration) was significantly increased in the propranolol-treated group compared to the untreated group. VO2 decreased from 4.0 to 0.6 to 3.3 vol %, and pH from 7.3 to 7.57. These results indicate that propranolol shifts the O2 dissociation curve to the right and thus increases O2 availability and transport.

50.5 REGIONAL VASCULAR CONDUCTANCES DURING ARTERIAL HYPERTENSION: ROLE OF CHERMOREFLEX HYPERVENTILATION. George J. Crystal, H. Fred Downey, Fouad A. Bashour, and Judith M. Metzger. University of Texas Health Science Center, Dallas, Texas 75235.

It is well known that chemoreflex hyperventilation is a major factor in the increase in CBF seen with hypoxia. However, the role of chemoreflex hyperventilation in normocapnia is not as well established. We have previously shown that chemoreflex hyperventilation is a major factor in the increase in CBF seen with hypoxia. In the present study, we investigated the role of chemoreflex hyperventilation and the effect of propranolol on CBF during arterial hypoxia in dogs.

50.9 THE PERIPHERAL CARDIOVASCULAR (CV) AND CEREBROVASCULAR (CV) RESPONSE TO HYPOXIA (HYP) FOLLOWING CHEMICAL SYMPATHOMIMETIC (CS). William M. Sidhu and Alan D. Lewis. (Bronx-Tom. Hospitals.

The peripheral CV and NE responses to HYP was similar in CS and non-CS animals, but the CV responses in CS animals had a significantly reduced ANS level compared to HYP. These results demonstrate that the CS fetus is able to mount an appropriate response to HYP despite the absence of ANS and a reduced level of circulating E. (Research supported by the Norris Foundation.)

50.10 EFFECT OF CEREBELECTOMY ON THE INCREASE IN CEREBRAL BLOOD FLOW AND THE PRESSOR RESPONSE DURING HYPOXIA. L. O. Lutersner and D. G. Buxé. Department of Physiology, Texas Tech University Health Sciences Center, Lubbock, Texas 79430.

Acute exposure to hypoxia induces a pressor response and an increase in cerebral blood flow. Cerebellar hypoxia or special lesions of the FN induce a pressor response during hypoxia. This study was undertaken to determine if a pressor response during hypoxia is influenced by the FN. Bilateral FN lesions were performed in cats. A total of 10 cats were exposed to 21% O2 for 10 min in order to assess the effect of FN lesions on pressor responses. Electrical stimulation of the FN produced both pressor responses and an increase in cerebral blood flow. This study was undertaken to determine if these pressor responses are mediated by the FN. The results indicate that the FN plays no role in mediating these pressor responses during hypoxia. Cats of either sex were anesthetized with chloralose-urethane and ventilated throughout the experiment. Cerebellar lesions did not affect resting arterial pressure at 21% O2 (119 ± 6 vs 114 ± 4 mmHg), but did block the pressor response to hypoxia (-24 ± 4 vs 135 ± 4 mmHg). In 4 cats, FN lesions were performed in one hemisphere, and the pressor response to hypoxia was measured in both hemispheres. The results indicate that the FN is not involved in mediating the pressor response to hypoxia.
50.7 O-tabain blocks active hyperemia in Gracilis (mice) but not soleus (red) muscle of cats. Kama L. Bookman, Dept. of Physiology, Uniformed Services University, Bethesda, MD 20814

The release of K+ correlates with active hyperemia in gracilis but not soleus muscles of cats (Physiologist 24:74, 1981). The purpose of the present study was to determine whether ouabain, which inhibits the Na-K pump, affects active hyperemia. Ouabain was infused into the caudal artery of cats under free-flow conditions, and stimulated to contract isometrically. Ouabain (60-70 µg/kg i.v.) administration resulted in a decrease in resting level (from 212.0 ± 2.2 to 214.2 in gracilis (H*) and from 6.5 to 7.2 ± 4.2 in soleus (H*)). After 15 min of stimulation, blood flow was 2.8 ± 0.6 in gracilis and 2.5 ± 0.5 in soleus (H*). Initial muscle performance (determined using ouabain) was similar in ouabain-treated and control preparations. Gracilis muscles receiving ouabain fatigued such that performance after 15 min of contraction was 44.2% of the initial value. In soleus, performance was 76.5% of the initial value in ouabain-treated muscles and 81.2% in control muscles. These findings indicate that ouabain administration blocks active hyperemia in gracilis but not in soleus muscles and are consistent with a role for K+ as a modulator of active hyperemia in gracilis but not soleus muscles of cats.

(Supported by USPHS Grant HL26345)

50.9 PATTERN OF PERFUSED CAPILLARIES IN RAT GASTROCEUMUS. S. B. Kayar, A. J. Lechner and N. Banchero. Univ. Colorado Medical School, Denver, CO 80262.

We studied the gastrocnemius of rats to determine the density and spatial arrangement of perfused capillaries after different time intervals following injection of a plasma-carried fluorescent dye. A bolus of fluorescein, which marks the endothelium of vessels, was injected into the artery via a carotid catheter. After 10, 15 or 30 sec, the gastrocnemius was removed and flash-frozen. Muscle cross-sections 10-15 µm thick were transilluminated with blue light (430 nm), examined for fluorescence at 530 nm, and photographed. The same muscle sections were then treated by the myosin ATPase method to stain all capillaries, and rephotographed under white light. Each muscle section contained fluorescent capillaries surrounded by areas with no fluorescence. Within the patches with fluorescence, 30% of all capillaries were fluorescent and their arrangement was ordered (Kayar et al., Microvasc. Res. 24:376, 1982). After 15 sec, 40% of all capillaries were fluorescent, they appeared evenly distributed across the muscle section, and their arrangement was ordered. After 30 sec, all capillaries were fluorescent. Thus, within one mean transit time through these tissues, all capillaries were perfused for some time. These data indicate that flow to capillaries is intermittent and that the pattern of perfused capillaries is always ordered, suggesting that control mechanisms permit complete perfusion over time. Supported by NIH-HL18145 and HL06527.


Regional distribution of blood flow, red cell volume (CVr) and plasma volume (PVr) in various organs were determined in seven pentobarbitalized dogs. 51Cr-RBC and 125I-albumin were injected simultaneously and perfusion in capillary beds was calculated from the 51Cr turnover of capillaries, which averaged 36.0 ± 1.5 percent. Regional hematocrit (Hr) was calculated as 100CVr/(CVr+PVr).胃, liver, spleen, and muscle were selected as representative target tissues for quantitative microvascular techniques, the mitochondrial volume density in hamster cremaster muscle was determined as 3.16%. Although there were a few dense mitochondrial aggregates in close proximity to capillaries, most mitochondria are located on the I-bands of sarcomeres, evenly distributed throughout the muscle cell. A consistent preferential distribution toward the capillaries was not observed. This described mitochondrial distribution would significantly alter the predicted 02 tension profile from that predicted assuming homogeneous oxygen consumption. (Supported by the American Heart Association and the American Heart Association, Washington, DC 20036)

50.12 POWER DISSIPATION: A NETWORK APPROACH TO PERIPHERAL VASCULAR RESISTANCE. Jeffrey L. Borders* and Harris J. Frangos, Texas A&M Univ., College Station, TX 77843.

Attempts to identify regions of peripheral vascular resistance have been hampered by the complex mesh that the microcirculation presents. Previous work has attempted to isolate sites of resistance by examining pressure profiles, mean diameters, and counting capillaries. We do not consider the network properties and their influence. The interpretation of their findings strongly depends on the hypothesized network geometry. This study examines a work-independent property, power dissipation - PD, as a measure of network resistance. Since PD is network independent, problems with vessel classification, identification, and sampling techniques are unimportant.

Resistance changes associated with the onset of hypertension were studied using this parameter in SHR and R rats. The cremaster muscle was examined using a wide range of vessel segments. PD was significantly elevated in all vessels showing flows from 0.0 to 60 ml/sec. Venous PD was significantly elevated for vessels with flows 78 ml/sec. The elevated PD is due to a network averaged reduction in cross-sectional area. The reduction occurs from a reduced mean diameter rather than rarefaction of vessel segments. Supported by NIH HL-25187 and HL-06527.
51.4 THE EFFECT OF AGE ON THE LARYNGEAL RESPONSE TO HYPOXIA AND HYPERCAPNIA. Thomas V. McCaffrey and Daniel J. Blum. Mayo Clinic, Rochester, Minn. 55905

In order to define the effect of maturation on the sensitivity of chemoreceptor control of laryngeal resistance inesthetized dogs ranging in age from one day to adulthood were studied. Laryngeal resistance was derived from constantly monitored measurements of laryngeal flow and laryngeal distending pressure. Simultaneously tidal volume, respiratory rate, end-expiratory CO₂, inspired O₂, and blood pressure were recorded for each dog. VE from 11.6 ± 1.5 (M ± SEM) to 25.2 ± 5.9 l/min during SH, from 5.4 ± 0.4 to 13.0 ± 3.6 l/min during Mn and from 5.4 to 9.8 ± 1.0 l/min during hypoxia. The effect induced by Mn was greater during SH than during either Mn or hypoxia in each dog tested. Ligation of both internal carotid arteries in 3 dogs either increased or did not affect the response, while denervation of carotid bodies in 2 dogs completely abolished the effect of Mn. These results indicate that: 1) intra-carotid infusion of Mn enhances the response to isocapnic hypoxia, and 2) the enhancing effect may result from a positive interaction of these two stimuli at carotid body chemoreceptors. (Supported by grants from Kentucky Tobacco Research Board 4812 and NIH HL-29893.)

51.6 RESPONSE OF AERIAL VERSUS AQUATIC GAS EXCHANGE TO HYPERCAPNIA IN AMPHIMIA TRIDACTYLM, SIREN LACERTINA, AND SIREN INTERMEDIA. Beth A. Brown. Univ. of Oklahoma, Norman, OK 73019

In animals with more than one respiratory surface, the capacity for increased O₂ release is an important factor in the control of the CO₂ exchange balance. In this study comparisons were made between the limits of aerial versus aquatic contribution to CO₂ loss in one bimodal (A. tridactylum) and two trimodals (S. lacertina, S. intermedia) hermaphrodites. Acidified to 20% and 12.12% pCO₂, animals subjected to either gas mixture through gas changes in the isocapnic seawater. The effect of intra-carotid infusion of nicotine on larynx was derived from constantly monitored measurements of laryngeal flow and pressure. Simultaneously tidal volume, respiratory rate, end-expiratory CO₂, inspired O₂, and blood pressure were recorded for each dog. VE from 11.6 ± 1.5 (M ± SEM) to 25.2 ± 5.9 l/min during SH, from 5.4 ± 0.4 to 13.0 ± 3.6 l/min during Mn and from 5.4 to 9.8 ± 1.0 l/min during hypoxia. The effect induced by Mn was greater during SH than during either Mn or hypoxia in each dog tested. Ligation of both internal carotid arteries in 3 dogs either increased or did not affect the response, while denervation of carotid bodies in 2 dogs completely abolished the effect of Mn. These results indicate that: 1) intra-carotid infusion of Mn enhances the response to isocapnic hypoxia, and 2) the enhancing effect may result from a positive interaction of these two stimuli at carotid body chemoreceptors. (Supported by grants from Kentucky Tobacco Research Board 4812 and NIH HL-29893.)

51.2 INTRA-CAROTID INFUSION OF NICOTINE ENHANCES VENTILATORY RESPONSE TO HYPOXIA. L.-Y. Lee. Dept. of Physiology and Biophysics, Univ. of Kentucky, Lexington, KY 40536

Inotropic effects of nicotine on the heart and vasculature of intact cats, but VT increased and f decreased at a given PaCO₂. In the carotid sinus nerve section (CNS) there was no increase in f, Vₐₕ, or Vₑ while breathing air compared to SD. In intact cats breathing air, Vₑ decreased from 70 to 50 percent of control at FIO₂ of .20 to 30 to 10 percent of control at FIO₂ of .50, 50 percent of control at FIO₂ of .70 to 5 percent of control at 1.0. In the animals with more than one respiratory surface, the capacity for increased O₂ release is an important factor in the control of the CO₂ exchange balance. In this study comparisons were made between the limits of aerial versus aquatic contribution to CO₂ loss in one bimodal (A. tridactylum) and two trimodals (S. lacertina, S. intermedia) hermaphrodites. Acidified to 20% and 12.12% pCO₂, animals subjected to either gas mixture through gas changes in the isocapnic seawater. The effect of intra-carotid infusion of nicotine on larynx was derived from constantly monitored measurements of laryngeal flow and pressure. Simultaneously tidal volume, respiratory rate, end-expiratory CO₂, inspired O₂, and blood pressure were recorded for each dog. VE from 11.6 ± 1.5 (M ± SEM) to 25.2 ± 5.9 l/min during SH, from 5.4 ± 0.4 to 13.0 ± 3.6 l/min during Mn and from 5.4 to 9.8 ± 1.0 l/min during hypoxia. The effect induced by Mn was greater during SH than during either Mn or hypoxia in each dog tested. Ligation of both internal carotid arteries in 3 dogs either increased or did not affect the response, while denervation of carotid bodies in 2 dogs completely abolished the effect of Mn. These results indicate that: 1) intra-carotid infusion of Mn enhances the response to isocapnic hypoxia, and 2) the enhancing effect may result from a positive interaction of these two stimuli at carotid body chemoreceptors. (Supported by grants from Kentucky Tobacco Research Board 4812 and NIH HL-29893.)

51.5 VENTILATORY RESPONSE TO CO₂ RETENTION IN MATURED AND DENERVERATED AWAKE CAT. P. C. Salyk and D. B. Jennings. Queen's University, Department of Physiology, Kingston, Ontario, Canada K7L 3N6.

In awake cats, ventilation (Vₐₕ), tidal volume (Vₑ), and frequency (f) were measured with a plethysmograph during a decrease in PaCO₂. In intact cats breathing air, Vₑ decreased from 70 to 50 percent of control at FIO₂ of .20 to 30 to 10 percent of control at FIO₂ of .50, 50 percent of control at FIO₂ of .70 to 5 percent of control at 1.0. In the animals with more than one respiratory surface, the capacity for increased O₂ release is an important factor in the control of the CO₂ exchange balance. In this study comparisons were made between the limits of aerial versus aquatic contribution to CO₂ loss in one bimodal (A. tridactylum) and two trimodals (S. lacertina, S. intermedia) hermaphrodites. Acidified to 20% and 12.12% pCO₂, animals subjected to either gas mixture through gas changes in the isocapnic seawater. The effect of intra-carotid infusion of nicotine on larynx was derived from constantly monitored measurements of laryngeal flow and pressure. Simultaneously tidal volume, respiratory rate, end-expiratory CO₂, inspired O₂, and blood pressure were recorded for each dog. VE from 11.6 ± 1.5 (M ± SEM) to 25.2 ± 5.9 l/min during SH, from 5.4 ± 0.4 to 13.0 ± 3.6 l/min during Mn and from 5.4 to 9.8 ± 1.0 l/min during hypoxia. The effect induced by Mn was greater during SH than during either Mn or hypoxia in each dog tested. Ligation of both internal carotid arteries in 3 dogs either increased or did not affect the response, while denervation of carotid bodies in 2 dogs completely abolished the effect of Mn. These results indicate that: 1) intra-carotid infusion of Mn enhances the response to isocapnic hypoxia, and 2) the enhancing effect may result from a positive interaction of these two stimuli at carotid body chemoreceptors. (Supported by grants from Kentucky Tobacco Research Board 4812 and NIH HL-29893.)

51.3 VENTILATORY RESPONSE TO CO₂ RETENTION IN MATURED DOGS. W. W. Wang”, D. Codolak, E. Y. Masharri and P. S. Credins. Biomedical Engineering, USCG, Los Angeles, CA 90059 1411.

The shape of the response curve changed, indicating a depressed pattern. There were no obvious ultrastructural changes. We conclude that oxygen poisoning was not clearly expressed in the structure and function of carotid body in the chronically hyperoxic (PaO₂ = 200 Torr) cats. (Supported in part by NIH grants HL-08999 and HL-19737.)

51.1 CAROTID BODY CHEMOSENSORY FUNCTION IN CHRONIC HYPOXIA. K. H. McGregor*, M. Pokorskie, A. Mokashi* and S. Lahiri. University of Pennsylvania School of Medicine, Phila., PA 19104.

Factors such as high blood flow, pump receptors that release PO₂ gradient, high oxygen consumption, and catecholamine metabolism are expected to predispose the carotid body to oxygen toxicity. In our preliminary studies to develop a suitable animal model of carotid body oxygen toxicity, we exposed 8 cats to 30% O₂ at sea level for 15 to 24 days. The cats were anesthetized with chloralose and surgically prepared. The activity of a single or a few afferent fibers from the carotid body were recorded throughout an experiment. The steady-state activity at 3 levels of PaCO₂ (range 29 to 66 mmHg) was greater in the chronically hyperoxic group than the control. The responses to hyperoxia did not change significantly, although the shape of the response curve changed, indicating a depressed pattern. There were no obvious ultrastructural changes. We conclude that oxygen poisoning was not clearly expressed in the structure and function of carotid body in the chronically hyperoxic (PaO₂ = 200 Torr) cats. (Supported in part by NIH grants HL-08999 and HL-19737.)

51.2 INTRA-CAROTID INFUSION OF NICOTINE ENHANCES VENTILATORY RESPONSE TO HYPOXIA. L.-Y. Lee. Dept. of Physiology and Biophysics, Univ. of Kentucky, Lexington, KY 40536

The steady-state activity at 3 levels of PaCO₂ (range 29 to 66 mmHg) was greater in the chronically hyperoxic group than the control. The responses to hyperoxia did not change significantly, although the shape of the response curve changed, indicating a depressed pattern. There were no obvious ultrastructural changes. We conclude that oxygen poisoning was not clearly expressed in the structure and function of carotid body in the chronically hyperoxic (PaO₂ = 200 Torr) cats. (Supported in part by NIH grants HL-08999 and HL-19737.)

51.1 CAROTID BODY CHEMOSENSORY FUNCTION IN CHRONIC HYPOXIA. K. H. McGregor*, M. Pokorskie, A. Mokashi* and S. Lahiri. University of Pennsylvania School of Medicine, Phila., PA 19104.
5.1.7 EVIDENCE FOR A PERIPHERAL VASCULAR ORIGIN OF THE ISOPROTERENOL-INDUCED HYPERPNEA IN THE DOG. A. Oren*, A. Huszczuk*, W. Pokorski*, P.H. Ferrer*, B.J. Whipp, and K. Wasserman. Harbor-UCLA Medical Center, Torrance, CA 90509. A intratracheal injection of isoprotrenol (ISO) induced a hyperpnea which has been attributed to a "cardiodynamic" mechanism or, alternatively, direct stimulation of the carotid bodies. In a previous study, we noted that both mechanisms can operate (Fed. Proc. 40:568, 1981), we noted that the initial hyperpnea began with a latency (~18 s) which appeared to reflect cardiac mediated. To an attempt to clarify this mechanism, we injected a 10-fold bolus of ISO, into the following vascular sites (in 12 unanesthetized dogs, Nembutal, 20 mg/kg i.v.): 1) right atrium, 2) descending thoracic aorta, 3) right iliac bifurcation and 4) a single iliac artery, in all cases the cardiovascular response (an initial vasodilatation followed by a tachycardia) preceded the hyperpnea. There was no significant difference between the latencies of the hyperpneic responses to right atrial or either aortic injection after (~14 s). In contrast, the response to the iliac injection was asymptotically delayed (~24 s), attributable to a similarly delayed cardiovascular response. However, when half the dose of ISO was injected simultaneously into each iliac artery, both the cardiovascular responses and the hyperpneic latency were shortened to that of the right atrial and aortic sites. We therefore conclude that the "cardiodynamic" component of the isoproterenol hyperpnea results from an initial peripheral vascular mediation.

5.1.8 THE REGULATION OF "ALVEOLAR" AND END-TIDAL GAS TENSIONS AT THE ONSET OF EXERCISE. Susan A. Ward* and Brian J. Whipp. UCLA, Los Angeles & Harbor-UCLA Medical Center, Torrance, CA. The "cardiodynamic" hypothesis of the exercise hyperpnea postulates that rapid changes in pulmonary blood flow (Q) at the onset of exercise induce an hyperpnea which regulates "alveolar" gas tensions and the gas exchange ratio (R) during the first 15 s of moderate exercise in man. The maintenance of end-tidal gas tensions at rest levels in this phase is commonly cited as support for the concept. Recently however, we have documented a steepening of the alveolar profiles of both PO2 and P02 at the start of exercise (J. Physiol., May, 1983), resulting presumably from an increased Q. We have therefore characterized the relationship between mean alveolar (PETCO2, P02) and end-tidal gas tensions during the initial phase of constant-load cycling (100 W) in 17 normal subjects. The mid-points of the alveolar phase of the expired gas tension profiles were used to estimate PETCO2 and P02. The abrupt hyperpnea at exercise onset was associated with stable end-tidal gas tensions throughout the initial phase of the work. However, invariably, PETCO2 fell and P02 rose systematically (by up to 5 torr). Consequently, mean alveolar, and presumably arterial, gas tensions in this phase of exercise may not be readily inferred from the end-tidal tensions. And, as the initial phase of the exercise hyperpnea is typically hyperventilation, then it may be less precisely coupled to the pulmonary blood flow changes than has previously been assumed.

* Senior Investigator of the American Heart Association (UCLA)

5.1.9 VENTILATION STUDIED WITH CIRCULATORY OCCLUSION DURING TWO INTENSITIES OF EXERCISE. W.C. Clark-Stanley*, V.R. Log*, G.A. Brooks. Exercise Physiology Laboratory, University of California, Berkeley, CA 94720

Respiratory gas exchange was measured breath-by-breath at two intensities of exercise with circulatory occlusion in the legs. Eight male subjects exercised on a cycle ergometer at 100 and 600 kg·m/min for 15 min; circulation in the legs was occluded by thigh cuffs (20mmHg) for two mins after 6 mins of unoccluded exercise. Mean 15 s ventilatory volumes were statistically compared to the pre-occlusion baseline. PETCO2 and V02 decreased significantly during occlusion at both workloads. Occlusion elicited marked hyperventilation, as evidenced by sharp increases in VE/VE/PETCO2, and VE/V02. An inflection in PETCO2 was seen after cuff release in all subjects at 7.3 ± 1.4 s after PETCO2 inflection. Three subjects showed an inflection in VE at 600 kg·m/min; 25.0 ± 7.7 s after the PETCO2 inflection. These significant increases in PETCO2, VE, and VeVO2 following cuff release, suggest the CO2 ventilatory drive is mediated by the carotid bodies, and that evidence for a pulmonary CO2 receptor was found.

5.1.10 THE RESPONSE OF THE NEWBORN VS. THE MATURE INFANT MONKEY TO AN EXTERNAL FLOW RESISTANCE. W.A. Laframboise*, T.A. Standart*, R.D. Guthrie* and D.C. Woodrum. Univ. of Washington, Seattle WA 98195

Six 48-hr old and six 21 day old Macaca nemestrina were studied to assess developmental changes in their response to an acute inspiratory flow resistive load. Resistances 4X and 10X were used to assess inspiratory flow resistance to these infants. Each load was added to the inspiratory port of a 2-way valve to which the unanesthetized infants were connected via a tracheostomy tube. Ve tracked V02 immediately in response to either load and remained depressed for the 10' exposure (baseline: 35±3mL/kg/4X time: 25±7mL/kg, p<.05; 10X: 24±7mL/kg, p<.05) while pressures obtained from end expiratory airflow occlusions (P02 50, P02 50X) did not change. The fall in Ve was due to a drop in respiratory rate with a prolongation of inspiratory time (Ti). Mean arterial (Pa) fell (~3 mm Hg) and CD2 rose (~2 torr) slightly with loads. The Utter respiratory response to loading by uniformly increasing occlusion pressures (P02 50 X: 4.5±1.6 mm Hg, p<.03; P02 50X: 4.4±1.3 mm Hg, p<.001) and defending minute ventilation and arterial gases from any significant change. Again, Ti was increased with each load and a small drop in frequency was offset by a slightly larger Vt. We conclude that the neonatal compensatory response to an inspiratory resistive load is absent or markedly diminished relative to the older infant and that postnatal maturation is critical in the development of load compensation. (Supported by NIH HL19187 and RR00166).

5.1.11 PERCEPTION OF ADDED RESPIRATORY LOADS IN PATIENTS WITH RESTRICTIVE LUNG DISEASE. N.R. Burns, and R. Lorentz*. University of Kentucky Medical Center, Lexington, KY 40536

The magnitude perception of added suprathereshold resistive (R) and elastic (E) loads was studied in 8 patients with restrictive lung disease (RLD) and compared to a control, age and sex matched group of 7 healthy, normal nonsmoking subjects. Total lung capacity was significantly (p<.005) reduced in the RLD patients compared to the normal group, and total thoracic elastance (P02) was significantly increased (mean P02 13.9 ± 2.1 cmH2O·L-1). Magnitude perception, measured by handgrip dynamometry, of a range of added resistive loads was not significantly different between the 2 groups when expressed as the relationship between log(Ti) and log handgrip (RLD, mean slope = 0.31; normals, mean slope = 0.65); however, there was a significant difference when perception was expressed as the relationship of log mouth pressure (P02) to log handgrip response (RLD mean slope 0.71; normals, mean slope = 1.15, p<.001). There were no significant differences between the 2 groups in the log-log relationship between handgrip response generated with the E load. These results imply that patients with RLD, with an increased thoracic elastance, have an altered perception of added resistive loads compared to normal subjects, but do not exhibit differences compared to normal subjects in the perception of added elastic loads. (Supported in part by N.H.S. NIH grant HL 24412).
52.1 ELECTROPHYSIOLOGICAL EVIDENCE FOR THE PRESENCE OF HISTAMINE H2 RECEPTORS ON GUINEA-PIG MYENTERIC NEURONS. P. R. Neemet* and J. D. Wood. University of Nevada, Reno, NV 89557

Intracellular recordings were made to study electrical activity of myenteric neurons of guinea-pig ileum in vitro. Tissues were isolated in a 1 ml bath and superfused at a rate of 6 to 12 ml per min with carboxygenated Krebs solution at 37°C. Histamine (100 µM) or dimaprit (1 µM) superfusion was applied to neurons by microinjection from fine pipettes with controlled nitrogen pressure pulses of 5 to 750 msec at 20 p.s.i. Antagonists were applied in the superfusion solution. Application of histamine or dimaprit resulted in a long-lasting, 5 µm/sec depolarization of all type 2 neurons by 10 to 15 mV. Histamine, reversibly abolished both the depolarization and increased excitability elicited by histamine or dimaprit. Superfusion with the H2 receptor antagonist, cimetidine (10 µM), reversibly abolished both the depolarization and increased excitability elicited by histamine or dimaprit. Superfusion with the H2 receptor antagonists, diphenhydramine (10 µM) and pyrilamine (10 µM), and with the anterotensive antagonist, metaxycycline (10 µM), failed to diminish the responses to histamine or dimaprit. None of the antagonists displayed local anesthetic activity at the concentrations used. We conclude that histamine affects the electrical behavior of myenteric neurons by stimulating H2 receptors.

(Supported by NIH grants NS17363 and AM26742.)

52.2 SIMULTANEOUS RECORDINGS OF Mechanical AND INTRACELLULAR ELECTRICAL ACTIVITY FROM CANINE ILEOColonic SPHINCTERS OF THE Gastrointestinal TrACT THROUGH WHICH CCK MAY DIRECTLY Effect its functions, the distribution of CCK receptors was determined. Stimulation frequencies of 1, 5 and 10 Hz produced IJP's of 2.6, 8.6 and 13.9 mV (n=8), respectively. At all frequencies of stimulation, the duration of the IJP was shorter than the duration of relaxation. Mechanical responses and IJP's were abolished by tetrodotoxin (1 µM). Neurogenic responses were not antagonized by the non-neurogenic antagonist, guanethidine, used. We conclude that histamine affects the electrical behavior of myenteric neurons by stimulating H2 receptors.

(Supported by NIH grant 2 R01 AM19302.)

52.3 SLOW WAVES OF ANTRAL CIRCULAR MUSCLE CELLS NEAR THE MUCOSA Differ FROM THOSE NeAR THE LONgitudinal MUSCLE. A. J. Bauer, R. G. Publicover* and K. M. Sanders. University of Nevada School of Medicine, Las Vegas, NV 89128

Muscle cells from the circular layer are thought to be homogeneous in their electrical and mechanical activities and its cells: responsive to drugs. In this study, the effects of electrical activity with a novel in vitro preparation in which the antral muscle was visualized in cross section. Muscles from anesthetized dogs were removed from the antral antrum and separated from the atrioesophageal muscle (1 mm x 10 mm) which were placed parallel to the circular muscle layer. The strips were pinned on an electrode recording chamber, and superfused with warm, oxygenated canine solution. Membrane potentials of circular muscle cells (602) at various distances from the longitudinal layer were recorded. Slow waves from cells near the longitudinal border had average upstrokes of 31.9 mV, plateau potentials of 28.6 mV, and durations of 6.32 sec. Near the mucosal border slow waves had average upstrokes of 24.0 mV, plateau potentials of 15.2 mV, and durations of 5.3 sec. The differences were statistically significant (p<0.01). The muscles were exposed to prostaglandin E2, 10-6 M. Cells near the mucosal border were more responsive to PG2. In summary, the excitability mechanisms and the sensitivity to PG2 appear to differ as a function of the position of the cells in the circular layer. (Supported by NIH grants AM 32176, AA05168 and AA05883.)


Intracellular recordings from pyloric pacemaker neurons showed an increase in excitability in response to histamine and dimaprit. Mechanical inhibition was accompanied by a hyperpolarization in the pyloric muscle (2 mV) whose magnitude was frequency-dependent. Stimulation frequencies of 1, 5 and 10 Hz produced IJP's of 2.6, 8.6 and 13.9 mV (n=8), respectively. At all frequencies of stimulation, the duration of the IJP was shorter than the duration of relaxation. Mechanical responses and IJP's were abolished by tetrodotoxin (1 µM). Neurogenic responses were not antagonized by the non-neurogenic antagonist, guanethidine, used. We conclude that histamine affects the electrical behavior of myenteric neurons by stimulating H2 receptors.

(Supported by NIH grant 2 R01 AM19302.)

52.5 OSMOTIC INHIBITION OF GASTRIC EMPTING IN RELATION TO PLASMA LEVELS OF NEUROTENSIN, SOMATOSTATIN AND GIP IN THE RAT. M. Huggins*, A. V. Lamberts**, K. van Loon*, and J. A. W. M. Wiersma. Department of Physiology, University of Amsterdam, Amsterdam, The Netherlands

Osmolarity of the gastrointestinal contents exerts a marked influence on several GI functions. The regulating mechanisms are not known. Mechanical inhibition was accompanied by a hyperpolarization in the pyloric muscle (2 mV) whose magnitude was frequency-dependent. Stimulation frequencies of 1, 5 and 10 Hz produced IJP's of 2.6, 8.6 and 13.9 mV (n=8), respectively. At all frequencies of stimulation, the duration of the IJP was shorter than the duration of relaxation. Mechanical responses and IJP's were abolished by tetrodotoxin (1 µM). Neurogenic responses were not antagonized by the non-neurogenic antagonist, guanethidine, used. We conclude that histamine affects the electrical behavior of myenteric neurons by stimulating H2 receptors.

(Supported by NIH grants AM 32176, AA05168 and AA05883.)

52.6 INTRINSIC PROPULSIVE BEHAVIOR OF GUINEA PIG ILEAL SEGMENTS AND ITS RELATION TO THE "PERISTALTIC REFLEX." W. A. Weems, L. D. Scott* and N. M. Weibrecht. U. T. Med, Sch, Houston, TX 77025

Intracellular recordings of 3-5 mm segments from guinea pig ileum were made using the intracellular microelectrode technique. The pyloric sphincter was stimulated electrically at 1 Hz. A-96 GASTROINTESTINAL MOTILITY TUESDAY AM 11:00-11:30

Mechanical inhibition was accompanied by a hyperpolarization in the pyloric muscle (2 mV) whose magnitude was frequency-dependent. Stimulation frequencies of 1, 5 and 10 Hz produced IJP's of 2.6, 8.6 and 13.9 mV (n=8), respectively. At all frequencies of stimulation, the duration of the IJP was shorter than the duration of relaxation. Mechanical responses and IJP's were abolished by tetrodotoxin (1 µM). Neurogenic responses were not antagonized by the non-neurogenic antagonist, guanethidine, used. We conclude that histamine affects the electrical behavior of myenteric neurons by stimulating H2 receptors.

(Supported by NIH grant 2 R01 AM19302.)
52.7
IS INTESTINAL TRANSIT IN FASTED, BYPASSED RATS RELATED TO INTESTINAL MYOELECTRICAL ACTIVITY? C. Leckhout* and N.W. Weisbrodt. The University of Texas Medical School at Houston, Houston, TX 77030.

Intestinal transit in rats three days after jejunoileal bypass is rapid through the in-continuity segment (ICS) and slow through the bypassed segment (BPS) (Am. J. Physiol. 241: G265, 1981). To study the mechanisms responsible for the transit patterns, myoelectric activity of the ICS and BPS was recorded after bypass in six rats implanted with monopolar electrodes. As early as three days after bypass, migrating complexes were seen in all areas of the intestine in all animals. In six hours of recording (1 hr. from each rat) the total numbers of complexes were 9, 19, and 8 for the proximal ICS, distal ICS, and BPS, respectively. The numbers recorded from each animal ranged between 0-4, 0-5, and 0-3 in each of the three segments respectively. Migration of the activity fronts on each segment did not always occur. In contrast, 20 activity fronts were seen during a one hour recording from each of six control rats, thus suggesting a decreased number in the proximal ICS and BPS. Our data indicate that the rapid transit through the ICS may be due to the presence of early activity fronts. The slow transit in the BPS is not due to absence of activity fronts but perhaps to the presence of abnormal contents in the lumen of the BPS. (Supported by a Grant AM 19886 from NIH)

52.8

Previous studies have demonstrated that \* endorphin (\*E) and enkephalins are released into the systemic circulation by the pituitary and adrenal medulla respectively. To determine if the small intestine could be a target for circulating \*E, segments (5 cm) of mid-jejunum were removed from anesthetized dogs and perfused with Krebs bicarbonate buffer containing \*E (1 μg/ml), while motility was recorded and venous effluent collected in 1 min. fractions (2 ml). \*E significantly increased (P< 0.002) motility of intestinal segments. HPLC analysis of the venous effluent identified, amongst others, several \* and \*E endorphins and the identified peptides were then perfused through intestinal segments to determine their motility effects. \* Endorphin (\*E), \* endorphin (\*E), des-tyrosine-\* endorphin and des-tyrosine-\* endorphin, significantly increased motility. Responses were characterized by an increase in phasic contractions of constant amplitude and frequency. To determine regional specificity and site of \*E metabolism during perfusion, we studied in vitro time-course processing of \*E in membrane-bound muncosal and muscularia homogenates. Mucosa was much more enzymatically active than muscularia. These studies demonstrate that the small intestine can metabolize \*E into a number of active fragments which increase motility and suggest a regional specificity of enzymatic processing.

52.9
EFFECT OF PREGNANCY ON GALLBLADDER MOTILITY IN VITRO. J.P. Ryan, Temple Univ. School of Med., Phila., PA. 19140

Studies were done to determine the reason for the decreased contractility of the gallbladder (GB) to acetylcholine (Ach) and the octapeptide of cholecystokinin (OP-CCK) during pregnancy (P). Two hypotheses were tested. First, that the over-all contractility of the GB is reduced during P. This was examined by studying the in vitro motor response to Ach, OP-CCK, and KC1 of GB from P and non-P guinea pigs. Second, that GB contractility involves both internal and external calcium (Ca) stores, and that P is associated with a decrease in the contribution of the internal pools. This was tested by examining the contractile responses to Ach, OP-CCK, and KC1 in the presence and absence of extracellular calcium. The results were as follows: 1) the contractile responses to Ach, OP-CCK, and KC1 are diminished by Ca deprivation and 2) Ach and OP-CCK, but not KC1, elicited contractions in a Ca-containing solution. Responses from pregnant animals, however, were significantly reduced (Ach, 3.7%; OP-CCK, 4.1%) when compared with controls (Ach, 10%; OP-CCK, 24.2%). The data are expressed as a percent of the maximal control response in a Ca-containing solution (75%). It is concluded that both Ach and OP-CCK utilize extra- and intracellular stores of Ca for contraction. P is associated with a decrease in the contribution of the intracellular pools, rather than with a generalized decrease in GB contractility. (Supported by NIH Grant HD016132).

52.10
PRESSURE MEASUREMENT IN THE DISTAL ESOPHAGEAL SPHINCTER (D.E.S.): A NEW METHOD. Gordon H. Bryant (SPONSOR: J.R. Claybaugh). Department of Clinical Investigation, Tripler Army Medical Center, Honolulu, Hi. 96859.

The elegant simplicity of the Hewitt Winans perfused side hole motility catheter has rendered difficult the design of an acceptable device of equal utility, but without the attendant disadvantages involved when prolonged DES pressure recordings are attempted. These include the hydrostatic pressure changes produced by patient movement, as well as water loading and the necessity for syringe refilling. A technique suitable for all DES pressure measurements has been devised in this laboratory. In principle, change of electrical resistance of an electrolyte column as external pressure varies the area of cross section, is the essence of the technique. In the prototype section of latex tubing were joined by segments (<1cm) of hypodermic tubing selected to be a tight fit in the latex. A thin copper wire was soldered to each and the whole joint to make a continuous length. After partial filling with 0.4 M NaCl, a plug was placed in the proximal end, while the distal end was maintained at a higher elevation. A half bridge circuit with an external half bridge is not an essential feature; potentiometric methods serve equally well, and the only other requirement is the selection of a tubing of suitable elasticity.
51
THE VALIDATION OF A FIELD TEST OF MAXIMAL AEROBIC POWER In J. Michael* 1,2, William 1,2, D. Portney 1,2, H. Shore 1,2 (Sponsor: George Fried) Laboratory of Work Physiology, Brooklyn College of the City University of New York, New York, NY 11210

The purpose of this study was to develop an inexpensive, submaximal test as accurately measured maximal aerobic power. Twenty-three healthy subjects (13 men, 10 women) age 24 ± 3 years, volunteered for the study. Subjects were randomly assigned to one of their initial test. One condition consisted of directly measuring the maximum oxygen consumption (VO2max) on a motor-driven treadmill for each subject. The second condition required that each subject run as far as possible for five minutes on an outdoor 400 meter track. A measuring wheel accurate to 1.27cm was used to measure the total distance run. Results indicated that the reliability of the 5 minute runs based upon a test re-test analysis was r = 0.85. There was a highly significant correlation, r = 0.89 (p<0.01), between the distance run in five minutes and the criterion measure, VO2max.

53.2 SUPERFICIAL SHELL INSULATION IN COLD WATER DURING SEVERE EXERCISE: ROLL OF CORE AND SKIN TEMPERATURE. A. Velecitagola, G. Ferretti, R. Pennin, and D.M. Mead. Dept. Biomedical Sciences and Technologies, D. Milan, Italy and Dept. Physiology, SUNYAB, Buffalo, NY 14214 and Brescia, Italy.

During immersion in water at critical temperatures (CWT), physiological insulation was found to be divided (C = °C-W°H) are maximal (vasoconstriction is complete) at rest and while exercising up to a metabolic rate 3 times higher than resting state. From these two measurements of core temperature, skin surface (TSK) and direct skin heat flux (HI), W was calculated as (Tsk-1-H) in 4 men immersed head out in a well stirred bath. In constant water temperature (5°C) ± 0.1°C, men (31.5 ± 0.1°C) required to achieve a rectal temperature (Tre) of about 37.0°C. Subjects exercised for 45-70 min at B MPV until Tre reached 36°C. At rest, HI = 0.6°C; HI was independent of Tre. During exercise: 1) Tre and HI increased with time reaching a steady state value in 20-40 min and 2) the threshold for decrease in HI (vasodilatation threshold, VT) depends upon both H and Vas NRT and H = -6.91+ 369; r = -0.09. Thus, the thermoregulatory perfusion of the superficial shell in water depends on core and skin temperature in man.

53.3 EFFECT OF THERMISTOR POSITION ON THE MEASUREMENT OF TAIL-SKIN TEMPERATURE IN EXERCISING RATS. Frank G. Sherlock 1, Stanley A. Rubini2, Alberto Robini*1, Linda Tabak*1, H.L. Swan, Cedars-Sinai Medical Center, Los Angeles, CA 90040.

The tail is the main thermal receptor of the skin and a very effective organ for the recording of temperature. Therefore, tail skin temperature is commonly evaluated in inviolate volunteers tail temperature regulation. We studied six young female Sprague-Dawley rats (225± 10 gm) during submaximal treadmill exercise (22.0°C/min) in an ambient temperature of 22-25°C. Tail skin (Tsk) temperatures were measured with accurate thermistors placed at the base of the tail in the following positions: v.16°C/min ora lateral vein, and at a point equidistant (E) between these two positions. Colonic temperature (Tc) and oxygen uptake (mean maximum of 22.4± 0.9 ml/min/kg) were also measured.

53.4 CAROTID-PULMONARY EFFECTS OF INTERMITTENT EXERCISE IN 100 ppm CARBON MONOXIDE. Milan J. Hazucha1, David J. Davin2, Mitchell Friedman* and George L. Goldstein*. Ctr. Environ. Health & Mld. Sc., Univ. of North Carolina at Chapel Hill, NC 27514.

Effects of intermittent exercise on carotid-pulmonary function during intermittent exercise were normal healthy males (19 to 27 yrs old) were exposed for 2 hours in an environmental chamber (22°C, 40% RH) to either air or 100 ppm CO using a crossover study design. During the exposure period, the subjects were studied during a 15 min rest period and then during two, 15 min periods of graded exercise on a bicycle ergometer (15 V 24 min, respectively). This cycle was repeated twice and followed by a 30 min rest period. Maximal responses were measured using a pneumotachograph, while cardiac output (QO) and diffusing capacity for CO (DLO02) was obtained using a multiple gas breathing method. Exercise was measured using a VTM, RV, TLC, or Raw although FVC, RV and TLC were significantly greater on the exposure day. Thus it appears that despite high blood COHb levels caused by exposure to 100 ppm CO, the cardiopulmonary response in exercising normal subjects is not affected significantly.

53.5 STATIC MUSCLE CONTRACTION IN CATS CAUSES REFLEX TRACHEAL RELAXATION. J.C. Longhurst, UCSD, La Jolla, CA 92033

Static contraction of skeletal muscle is associated with increased ventilation. Although we have shown that chemical stimulation of skeletal muscle may affect the degree of tracheal smooth muscle response to hindlimb contraction induced by stimulating L3 and S3 ventral spinal cord roots. Isometric tension was measured using a transverse section technique. During exercise, the lumen diameter decreased by an average of 15% compared to preexercise value during exposure to air but only increased by an average of 5% during exposure to 100 ppm CO. The changes with exercise in QT and DLCO were significant and were not significantly different. Blood levels of COHb averaged 9.9% ± 0.2% COHb by the end of the CO exposure day. Thus it appears that despite high blood COHb levels caused by exposure to 100 ppm CO, the cardiopulmonary response in exercising normal subjects is not affected significantly. (Supported by the US Army M&R & D Labs.).

53.6 THE REPRODUCIBILITY OF MAXIMUM VENTILATORY RESPONSES TO PROGRESSIVE EXERCISE. C.S. Carrard*, G. Emmons* and M. Lopata. University of Illinois at Chicago, IL 60680.

Progressive exercise testing in 1 minute, 30 watt increments was performed to the maximum tolerated level in 6 healthy volunteers (aged 19-45 yrs), twice a day (am and pm) for 5 days. Tests of forced expiratory airflow and a single body plethysmography (E. Jaeger Inc.) were made immediately before each exercise test. No significant differences were observed in FVC, RV, FRC, TLC, or Raw although FVC, RV and TLC were significantly greater on the first compared to subsequent days (am and pm combined). The group mean maximum oxygen uptake (VO2max) achieved 3.06 ± 0.4 l/min, max tidal volume (VT) 2.18 ± 0.91 l, max breath frequency (fB) 40 ± 7 breath/min, max minute ventilation (MV) 107.6 ± 40.7 l/min and the max heart rate (HR) 178 ± 32 beats/min for the first compared to subsequent days. Analysis of variance showed no significant diurnal variation due to small and reciprocal changes in VT and fB. Thus although the ventilatory response to exercise appears to be generally reproducible occasionalsubject variations in max VM may be observed which cannot be attributed to changes in pulmonary function tests.
VENTILATORY RESPONSE TO STEP INCREMENTS IN WORKLOAD WHILE BREATHING AIR OR 4% CO2. W. R. Hubbard, Phil. J. Coyle, LD. Hamilton, JD. Hilding, Steve M. Horvath. Institute of Environmental Medicine, Boston University School of Medicine, Boston, MA 02115.

The purpose of the experiment was to explore the complex relationship between fluid consumption and consumption factors (thirst, voluntary dehydration, water alliesthesia, palatability, work, flavoring effects on consumption) and their effects on exercise performance in normal subjects. Subjects (10 males, 8 females) were divided into control and experimental groups in a single blind fashion. All subjects' resting pulmonary function (FVC, FEV1, and 12-s MVV), ventilatory mechanics, inspiratory muscle training (56 vs. 41%), although the absolute increases were similar. The establishment of a ventilatory steady state following a step workload increment while breathing CO2 is delayed because of the concurrent rise in CO2 stores. (Supported by NIH HL63034).

INTERSTITIAL FLUID PRESSURE AND FLUID SHIFT AFTER SHORT BOUTS OF EXHAUSTIVE EXERCISE. Yahid Mohsenin* and Richard R. Gonzalez. John B. Pierce Foundation Laboratory and Yale Medical School, New Haven, CT 06510.

The establishment of a ventilatory steady state following a step workload increment while breathing CO2 is delayed because of the concurrent rise in CO2 stores. (Supported by NIH HL63034).


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54.1

**EFFECT OF NIFEDIPINE ON MYOCARDIAL BLOOD FLOW IN DOGS WITH PARTIAL OBSTRUCTION OF CORONARY ARTERY.**

Arthur G. Williams*, Fouad A. Bashour, George J. Crystal, and N. Fred Neely. *Mayo Clinic, Rm. 762, Rochester, Minn. 55901.

Partial obstruction of left anterior descending coronary artery (LAD) was produced just below its first major branch in chloralose-xenethetized, open-chest dogs. Nifedipine (10 ng/kg/min i.v.) was infused at 5.5 ng/kg/min i.v.) for 10 min. Groups I (10) and II (7) were studied. In the control groups, the coronary blood flow was measured before (control) and at 10 min NIF infusion. Results (ml/min.g).

<table>
<thead>
<tr>
<th>Group</th>
<th>10 min NIF</th>
<th>Control</th>
<th>10 min NIF</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAD</td>
<td>0.64±0.17</td>
<td>0.49±0.18</td>
<td>0.30±0.04</td>
</tr>
<tr>
<td>Endo</td>
<td>0.92±0.01</td>
<td>0.12±0.06</td>
<td>0.25±0.06</td>
</tr>
<tr>
<td>LC</td>
<td>0.74±0.03</td>
<td>2.09±0.28</td>
<td>0.52±0.16</td>
</tr>
<tr>
<td>Mean</td>
<td>0.87±0.05</td>
<td>1.60±0.23</td>
<td>0.91±0.13</td>
</tr>
</tbody>
</table>

NIF increased markedly blood flow in normal myocardium supplied by left circumflex coronary artery (LC), but did not significantly alter flow in ischemic region. There was no evidence of coronary steal during NIF. Supported by the Cardiology Fund.

54.3

**CELLULAR ELECTROPHYSIOLOGIC EFFECTS OF HISTAMINE FOLLOWING MYOCARDIAL INFARCTION IN THE GUINEA PIG.**

John S. Cameron, Marion S. Cadge*, Cynthia B. Altman, Javier Cuvas*, Robert J. Weisberg*, and Andrew H. Gauer. *University of Miami School of Medicine, Miami, FL 33101.

Histamine (H) is readily released from mammalian myocardium by drugs or surgical manipulation. To test the hypothesis that H plays a role in generating cellular electrophyslogic abnormalities following myocardial infarction (MI), we studied its effects on isolated guinea pig left ventricular microelectrodes were used to measure transmembrane action potentials during acute (1 hr), subacute (24 hr), and delayed (6–7 wk) MI induced by ligation of multiple distal branches of the left coronary artery system. Normal and post-infarction microelectrodes were studied as controls. We found that all preparations, H (10−10 to 10−6M) increased action potential amplitude, maximal diastolic potential and maximal upstroke velocity (Vmax), while local refractory period and action potential duration were reduced. H also caused marked concentration-dependent increases in normal automaticity at threshold concentrations in control (10−6M) and MI (10−5M) microelectrodes. H induced abnormal automaticity including premature ventricular depolarizations, irregular rhythms and repopilative tachyarrhythmias. Cimetidine (10−4M) reduced automaticity when given alone and blocked ventricular responses to low concentrations of H (10−10 to 10−6M). These data suggest that H acts at H-receptors to alter electrical characteristics and induce arrhythmias and that tissue sensitivity to H is increased at MI. (CEAP Labs.; NIH: HL19044, HL27680, HL21735; AHA, Fla. Aff.)

54.4

**CREATINE KINASE IN CARDIAC LYMPH OF CONSCIOUS DOGS.**

Lloyd H. Michael, Robert M. Lewis*, Robert Rohrbaugh, and Mark I. Funtz. *Roper Hospital College of Medicine, Houston, TX 77030.

Lymphatic drainage systems exist in the myocardium with CFX occlusion, CK appears in cardiac lymph several hours after coronary artery occlusion and have been used to assess extent of myocardial injury. A precise role for cardiac lymph in CK transport as well as a quantitative, temporal relationship of this transport to extent of myocardial injury in the conscious animal remains unclear. Thus, our conscious dog model, with indwelling cardiac lymphatic cannula, circumflex coronary artery (CFX) flow probe and occluding device, allows sampling of cardiac lymph for CK analysis over several days and also optional CFX occlusion. In all dogs (n=9) cardiac lymph CK (LCK) ranged from surgery (day 0) to 4 weeks. In 5 dogs, LCK elevation occurred within minutes and reached levels above control of 1700, 2100, and 1400, respectively, within 30 minutes of reperfusion. In summary, the lymphatics appear to play a major role in the transport of CK. In animals with LCK occlusion, CK appears in cardiac lymph several hours before and after increased levels in plasma and; with reperfusion, the increase in cardiac lymph CK occurs immediately.

55.1

**HEMODYNAMIC CORRELATIONS (C) IN UNANESTHETIZED RATS.**

T. L. Smith, T. C. Coleman, U. R. Murphy*, and E. A. Stanek*. University of Mississippi Medical Center, Jackson, MS 39216.

A systemic hemodynamic study was performed in unanesthetized rats, (male, Sprague-Dawley, 304-383 grams) to assess hemodynamic (HD) interactions. Data were collected once per minute for 24 hr by computer in rats previously instrumented with electromagnetic flow probes and aortic flow (PAF) and total peripheral resistance index (TPRI) monitored on the left anterior descending coronary artery proximal to a hydraulic occluder. After recovery from 2 min occlusion study and 2 min intervals were initiated. After an average of 219 (range 114 to 440) occlusions, CO increased in 1.25 (range 6.5 to 6.9) reduction in segmental systolic shortening compared to 0.23 (range 6.2 to 10.0) mean reduction at the beginning of CO studies. Three of the ponies were then similarly occluded during treadmill exercise sufficient to double resting heart rate. After an average of 97 (range 36-260) additional exercise occlusions, CO during exercise decreased segmental shortening by an average of 24.4% (range 6.5 to 55.9) compared to 68.3% (range 36.3 to 94.9) at the beginning of treadmill studies. Thus, repeated reversible myocardial ischemia in ponies stimulates coronary collateral perfusion adequate for resting metabolic requirements. Coronary collateral flow was further enhanced by continued stimulus during exercise. Funded by NIH grant # 1ROI-HL29007-01 and the Missouri Heart Association.

55.2

**DECREASED 42Ca++ UPTAKE IN HEARTS OF CHRONICALLY DIABETIC RATS.**


A systemically diabetic 50% with a continuous intravenous infusion of CCF and a metabolic clamp was used for a 10-day period. Blood glucose concentrations of 300 mg/dl were maintained throughout the study. Cardiac lymph CK was elevated within minutes and reached levels above control of 1700, 2515, and 77118, respectively, within 30 minutes of reperfusion. In summary, the lymphatics appear to play a major role in the transport of CK. In animals with LCK occlusion, CK appears in cardiac lymph several hours before and after increased levels in plasma and; with reperfusion, the increase in cardiac lymph CK occurs immediately.
TTYRROID AND GROWTH HORMONE IN CARBON MONOXIDE-INDUCED CARDIO-MEGALY. David G. Penney, Bernd S. Barthel* and Joseph C. Dunbar, Jr.* Dept of Physiol, Wsu, Detroit, MI 48201

4 groups of adult male rats were used in Exper 1: 1) normal (N/AIR); 2) N/AIR treated with 500 ppm CO for 30 days; 3) N/AIR treated with 500 ppm CO for 10 days and then treated with 1% O2; and 4) T/AIRS. C0 rats inhaled 500 ppm CO continuously for 42 days. TX rats received 15 Ca++, as Ca lactate, and 0.025 N-6-propylthiouracil in drinking water while homogenized CO rats were exposed to an increased flow of CO. It was significantly lower than in N/C0. Hct of TX/AIR was also lower than N/AIR.

Combined ventricular wt (2V). Body wt (BW) of T/AIR was significantly lower than in N/C0. On the other hand, 2V wt of N/C0 and N/AIR rats were 20% and 30%, respectively, that in N's. This is perhaps related to the diminished metabolic demands on the heart in TX, or to lack of Tg and/or GH.

EFFECTS OF 200 ppm CARBON MONOXIDE ON THE PERINATAL RAT HEART. Sanford P. Bishop,* Dept of Path, UAB, Birmingham, AL 35294, and David G. Penney, Dept of Physiol, Wsu, Detroit, MI 48201

The systolic (sitting) hypotensive effects of clonidine hydrochloride (Catapress (CA)) in varying doses (0.2 mg/kg to 0.6 mg/kg daily) and a fixed daily dose of chloralohlide (CH) (Set I) were compared to placebo and to the same fixed daily dose of CH (Set II) employing a double blind, parallel program with elderly patients at least 60 years of age. The results prove: A) that Set I reduced the blood pressure (BP) more than CH alone, and B) that, when tested by analysis of variance, the two groups were significantly different in the degree of reduction in SBP. The reduction in SBP of Set I compared to Set II was supported by an alpha level of 0.01 and a power of 0.7. On the basis of the present sample, the major significant SBP reductions are obtained in the elderly, CH-treated population with the addition of CA to the treatment program without the penalty of adverse effects. Moreover, in 75% of the patients, the large SBP reduction of Set 1 was achieved with a total daily CA dose of only 0.2 mg.

A method has been developed which provides an on-line (1/sec) measurement of compliance (E+P/C) in a perfused isolated vessel segment. Compliance C can be obtained as a function of perfusion pressure (P) or in response to drug interventions. Non-compliant stainless steel tubes are used as inflow and outflow cannulae. The segment P is obtained from a short, small-bore, non-compliant cannula catheter with pressure transducers. During constant flow through the inflow cannula, an adjustable outflow resistance is used to set the segment P. The segment E is determined by measuring before and after the segment, which compresses inline silastic tubing next to each cannula and serves: 1) to isolate the segment and 2) to inject a small volume of saline in order to determine the compliance in the segment. The relationship was established for a period of time by a single step increase in segment pressure (AP). Since AV is constant over the range of 0-200 mmHg, the calculated C of a test mixt air bubble (suspension 0.03 < C < 0.07 ml/mmHg; resolution: 0.001 ml/mmHg). A similar linear relationship was obtained with a fluid filled elastic tube of various lengths. Comparison of C measured by this on-line method and that of ramp-volume-pressure method resulted in a linear relationship (y=0.939x). Thus, this method appears capable of high resolution on-line C measurement. (Supp. by N. Heart Assoc. and the VA).


In 14 pentobarbital anesthetized rabbits the right carotid sinus was vascularly isolated. The carotid sinus was controlled and multifiber baroreceptor nerve activity (BNA) recorded. BNA was integrated at each 25 mmHg steady state (±5 min) pressure step in ISF (range 25 to 175 mmHg). Normalized relationship curves of integrated BNA to ISF demonstrated well known hysteresis; as in Fig. 1. Shorter ISF ranges of 25 to 100, 75 to 125 and 100 to 175 mmHg demonstrated that hysteresis was not present until steady state ISF exceeded 100 mm Hg (25, 275, 125, 125 mmHg).

In order to determine responses to increasing carotid pressure at 50 mm Hg steps for 15 minutes from 50 to 250 mm Hg in 10 cats anesthetized with chloral hydrate. The influence of other baroreceptors was diminished by sectioning the vagus nerves and the contralateral carotid sinus nerves. Mean arterial pressure, heart rate, mean femoral blood flow and footpad temperature decreased. With increasing carotid arterial vascular resistance and footpad thermal insulation were monitored at the different carotid pressures when the hindlimb was exposed to room air and during immersion in a 0°C bath. Arterial pressure varied inversely to carotid pressure in both room and cold conditions. A sigmoidal relationship of tachycardia at low carotid pressures and bradycardia at high carotid pressures was observed only when the hindlimb was exposed to room air. With increasing carotid pressures, femoral arterial resistance increased, femoral arterial blood flow decreased, footpad temperature decreased, and footpad heat loss decreased.

Effects of carotid baroreceptor resetting on peripheral circulatory and thermal responses in the cold-exposed cat hindlimb. Carl L. Ohata. US Army Research Institute of Environmental Medicine, Natick, MA 01760.

In 9 anesthetized cats the influence of other baroreceptors was diminished by sectioning the vagus nerves and the contralateral carotid sinus nerves. Mean arterial pressure, heart rate, mean femoral blood flow, footpad temperature and heat loss, and calculated femoral arterial vascular resistance were measured during step increases and decreases in mean carotid sinus pressures of 25 mmHg. These trends were similar in both room and cold conditions, but a greater relative level of vasoconstriction in the cold-exposed hindlimb resulted in a lower blood flow and temperature. In summary, carotid baroreceptors were shown to affect peripheral circulatory and thermal responses during room air and cold exposure. These carotid baroreflexes were modulated by other cardiovascular reflexes elicited by the cold stimulus.

Correlations of baroreceptor discharge to wall strain in individual rats. Michael C. Andresen, Dept.of Physiology and Biophysics, Univ. of Texas Med. Branch, Galveston, TX 77550.

Baroreceptors do not respond directly to arterial pressure, but rather to changes in vessel wall distention caused by changes in transmural pressure (P). In earlier studies, it was found that the discharge (FD) relationship was much more linear when plotted against circumferential wall strain E than E-FP plots. These studies used average E-based measurements on the entire vessel segment recordings in other rats. This report concerns a series of paired neural and mechanical measurements made on individual in vitro aortic arch-nerve preparations (Andresen et al Science 1976). In normal and spontaneously hypertensive rats (SHR, n=9) an average of five regularly discharging BRs were recorded in each FP. It was found that the discharge (FD) relationship was much more linear from 20 to 200 mmHg. E-FP plots of these BR populations were substantially linear. Overall, however, no consistent pattern emerged for the relationship of fiber number and linearity. Many curves were slightly sigmoidal. Some relationships flattened at high or low FP. Aside from the displacement of their E-FP curves to lower ranges, E-FP plots appeared similar to WKY's. In summary, BP discharge is certainly better correlated to E than to either P or stress over a wide range of input, but significant nonlinearities exist suggesting that other factors contribute to the determination of discharge. Supported by NHLBI, Heart Assoc., TX.
SUMMATION OF CARDIOVASCULAR RESPONSES DURING AIRWAY IRRITANT RECEPTOR STIMULATION FOLLOWED BY AORTIC NERVE ACTIVATION.

J.J. Seagar, J.A.Hopp, J.L. Seagard, J.L. Seagard, and J.P. Kampine. Departments of Anesthesiology and Physiology, Medical College of Wisconsin, Milwaukee, WI 53193

Fifteen rabbits were anesthetized with sodium pentobarbital and instrumented to measure femoral arterial blood pressure (AP), ECG, heart rate (HR) and respiratory movements of the trachea. The left aortic nerve (LAN) was carefully isolated from other tissue in order to stimulate it electrically. Insertion of this micro-tracheal cannula allowed spontaneous respiration of rats while permitting passage of carbon dioxide to increase airway irritant receptors and out the nasogastric tube. Resting values were: AP, 105 ± 24 mmHg; mean ± SEM; HR, 275 ± 21/minute. Supra-maximal stimulation of LAN had no effect on respiration but caused a fall in BP (−21 ± 31 mmHg) and a fall in heart rate (−354 ± 45/minute). Passage of 50 nl of smoke through the upper airways produced a fall in AP (−22 ± 27 mmHg) and a fall in HR (−175± 18/minute). When LAN stimulation was started during ague but after BP and HR changes had stabilized there was further reduction in HR of (−54 ± 5 mmHg) and a fall in BP (−40 ± 5 mmHg). Both of these changes were significantly great than during autonomic nerve stimulation alone. It appears that irritant receptor stimulation potentiates the fall in heart rate and blood pressure resulting from supramaximal LAN stimulation. This increased sensitivity in the baroreflex must occur centrally since electrical stimulation bypasses the peripheral receptors. This work supported by Oral Roberts University Intramural funds.


The outputs of many peripheral ganglia were studied in various preparations. The left renal artery and adjacent nerves were exposed via a flank incision and fine platinum electrodes were coiled around an isolated renal nerve. The nerve-electrode preparation was embedded in silastic and the electrical and renal artery was exposed on the right side of the renal artery and renal artery were placed in a saline chamber. This chamber was aerated in the cervical region. Five hours after recovery from anesthesia, nerve activity was recorded in the conscious (resting) state during induction (441) and intubation; after 20 minutes, 1% isoflurane was added to the inspired air (2.5% isoflurane). Analysis of renal nerves by these methods was analyzed as voltage to frequency conversion of averaged nerve activity (NA) and as spikes/100ms.

Effects of isoflurane on chronically recorded sympathetic efferent nerve activity. J.J. Seagar, J.A.Hopp, J.L. Seagard, and J.P. Kampine. Departments of Anesthesiology and Physiology, Medical College of Wisconsin, Milwaukee, WI 53193

Chronic recordings of renal sympathetic efferent nerve activity (SENA) were used to determine the effects of anesthetic on sympathetic activity. The left renal artery and adjacent nerves were exposed via a flank incision and fine platinum electrodes were coiled around an isolated renal nerve. The nerve-electrode preparation was embedded in silastic and the electrical and renal artery was exposed on the right side of the renal artery and renal artery were placed in a saline chamber. This chamber was aerated in the cervical region. Five hours after recovery from anesthesia, nerve activity was recorded in the conscious (resting) state during induction (441) and intubation; after 20 minutes, 1% isoflurane was added to the inspired air (2.5% isoflurane). Analysis of renal nerves by these methods was analyzed as voltage to frequency conversion of averaged nerve activity (NA) and as spikes/100ms.

MORE EVIDENCE FOR CARDIAC REPLACEMENT MODULATED BY THE STIMULUS AND MIDDLE CEREBRAL GANGLIA USING 14C-2-DEOXYGLUCOSE. D.R. Kostreva and J.A. Armour. Departments of Anesthesiology and Physiology, University of Nebraska Medical Center, Omaha, NE 68192

Fifteen rabbits were anesthetized with sodium pentobarbital and instrumented to measure femoral arterial blood pressure (AP), ECG, heart rate (HR) and respiratory movements of the trachea. The left aortic nerve (LAN) was carefully isolated from other tissue in order to stimulate it electrically. Insertion of this micro-tracheal cannula allowed spontaneous respiration of rats while permitting passage of carbon dioxide to increase airway irritant receptors and out the nasogastric tube. Resting values were: AP, 105 ± 24 mmHg; mean ± SEM; HR, 275 ± 21/minute. Supra-maximal stimulation of LAN had no effect on respiration but caused a fall in BP (−21 ± 31 mmHg) and a fall in heart rate (−354 ± 45/minute). Passage of 50 nl of smoke through the upper airways produced a fall in AP (−22 ± 27 mmHg) and a fall in HR (−175± 18/minute). When LAN stimulation was started during ague but after BP and HR changes had stabilized there was further reduction in HR of (−54 ± 5 mmHg) and a fall in BP (−40 ± 5 mmHg). Both of these changes were significantly greater than during autonomic nerve stimulation alone. It appears that irritant receptor stimulation potentiates the fall in heart rate and blood pressure resulting from supramaximal LAN stimulation. This increased sensitivity in the baroreflex must occur centrally since electrical stimulation bypasses the peripheral receptors. This work supported by Oral Roberts University Intramural funds.

EFFECTS OF ISOFLURANE ON CHRONICALLY-RECORDED SYMPATHETIC EFFERENT NERVE ACTIVITY. J.J. Seagar, J.A.Hopp, J.L. Seagard, and J.P. Kampine. Departments of Anesthesiology and Physiology, Medical College of Wisconsin, Milwaukee, WI 53193

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More evidence for cardiac replacement modulated by the stimulus and middle cerebral ganglia using 14C-2-deoxyglucose. D.R. Kostreva and J.A. Armour. Departments of Anesthesiology and Physiology, University of Nebraska Medical Center, Omaha, NE 68192

Fifteen rabbits were anesthetized with sodium pentobarbital and instrumented to measure femoral arterial blood pressure (AP), ECG, heart rate (HR) and respiratory movements of the trachea. The left aortic nerve (LAN) was carefully isolated from other tissue in order to stimulate it electrically. Insertion of this micro-tracheal cannula allowed spontaneous respiration of rats while permitting passage of carbon dioxide to increase airway irritant receptors and out the nasogastric tube. Resting values were: AP, 105 ± 24 mmHg; mean ± SEM; HR, 275 ± 21/minute. Supra-maximal stimulation of LAN had no effect on respiration but caused a fall in BP (−21 ± 31 mmHg) and a fall in heart rate (−354 ± 45/minute). Passage of 50 nl of smoke through the upper airways produced a fall in AP (−22 ± 27 mmHg) and a fall in HR (−175± 18/minute). When LAN stimulation was started during ague but after BP and HR changes had stabilized there was further reduction in HR of (−54 ± 5 mmHg) and a fall in BP (−40 ± 5 mmHg). Both of these changes were significantly greater than during autonomic nerve stimulation alone. It appears that irritant receptor stimulation potentiates the fall in heart rate and blood pressure resulting from supramaximal LAN stimulation. This increased sensitivity in the baroreflex must occur centrally since electrical stimulation bypasses the peripheral receptors. This work supported by Oral Roberts University Intramural funds.

EFFECTS OF ISOFLURANE ON CHRONICALLY-RECORDED SYMPATHETIC EFFERENT NERVE ACTIVITY. J-J. Seagar, J.A.Hopp, J-L. Seagard, and J.P. Kampine. Departments of Anesthesiology and Physiology, Medical College of Wisconsin, Milwaukee, WI 53193

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MORE EVIDENCE FOR CARDIAC REPLACEMENT MODULATED BY THE STIMULUS AND MIDDLE CEREBRAL GANGLIA USING 14C-2-DEOXYGLUCOSE. D.R. Kostreva and J.A. Armour. Departments of Anesthesiology and Physiology, University of Nebraska Medical Center, Omaha, NE 68192

Fifteen rabbits were anesthetized with sodium pentobarbital and instrumented to measure femoral arterial blood pressure (AP), ECG, heart rate (HR) and respiratory movements of the trachea. The left aortic nerve (LAN) was carefully isolated from other tissue in order to stimulate it electrically. Insertion of this micro-tracheal cannula allowed spontaneous respiration of rats while permitting passage of carbon dioxide to increase airway irritant receptors and out the nasogastric tube. Resting values were: AP, 105 ± 24 mmHg; mean ± SEM; HR, 275 ± 21/minute. Supra-maximal stimulation of LAN had no effect on respiration but caused a fall in BP (−21 ± 31 mmHg) and a fall in heart rate (−354 ± 45/minute). Passage of 50 nl of smoke through the upper airways produced a fall in AP (−22 ± 27 mmHg) and a fall in HR (−175± 18/minute). When LAN stimulation was started during ague but after BP and HR changes had stabilized there was further reduction in HR of (−54 ± 5 mmHg) and a fall in BP (−40 ± 5 mmHg). Both of these changes were significantly greater than during autonomic nerve stimulation alone. It appears that irritant receptor stimulation potentiates the fall in heart rate and blood pressure resulting from supramaximal LAN stimulation. This increased sensitivity in the baroreflex must occur centrally since electrical stimulation bypasses the peripheral receptors. This work supported by Oral Roberts University Intramural funds.
57.1 
OPTIMIZATION OF A 2-DIMENSIONAL VIBRATING PROBE VIDEOSYSTEM TO MEASURE BIOLOGICAL CURRENTS. John A. Freeman, Paul B. Nemi*, and Phillip Samuel*, Vanderbilt Univ., Nashville, TN. 37232. The development system for intracellular activity is positioned 2mm dorsal to the right LC. Following at least one week of recovery rats were immobilized for injection of be-

57.2 
INTERCALLED RECORDINGS OF THE EFFECTS OF DOPAMINE ON MEM- 
BRANE PARAMETERS AND CELLULAR EXCITABILITY IN RAT HIPPOCAMPUS 
STUDIED IN VITRO. Valentin K. Grishko* and John H. Ashe, Department of Psychology, University of California, Riverside, CA 92521.

Brief exposure of area CA1 neurons to dopamine (DA) re-

57.3 
MOTOR DISORDER FOLLOWING ADRENOCORTICOTROPHIN 4-10 INJECTION IN THE RAT BRAINSTEM. M.L. Leavitt, M.E. Combs*, and S.E. Thompson*. Biology Department, Southwest Missouri State University, Springfield, MO. 65804. Adrenocorticotropic hormone (ACTH) affects norepinephrine turnover and is present in cell bodies of hypothalamic neurons which project to the locus ceruleus (LC). The LC is a brainstem nu-

57.4 
DETECTION OF ANGIOTENSIN PEPTIDES IN BLOOD TISSUE BY RADIO-
IMUNOASSAY (RIA) AND BIOASSAY. Robin Barraco, Mike Moran,* Nancy Munford,* and Howard Nornill.* Wayne State University Detroit, MI 48201.

Although angiotensin peptides and angiotensin receptors have been detected in the brains of a variety of species by bioassay and immunooassay, the results have been extremely vari-

57.5 
Choline Acetyltransferase Activity in the Cochlea of the Rat. D.A. Godfrey*, J.L. Park*, J.D. Dunn and C.D. Ross, Depts. of Physiology and Anat., Oral Roberts Univ., Tulsa, OK 74107. Microprobe sampling of freeze-dried rat cochlear is isolated for analysis of choline acetyltransferase (ChAT) ac-

57.6 
TWO AMINERGIC PROJECTIONS TO LUMBAR CORD FROM LOCUS COERULEUS IN THE CAT. Y.-Y. Lai and C. D. Barnes, Department of Physiology, Texas Tech Univ. Health Sci. Ctr., Lubbock, TX. Microscope samples from freezefried rat cochleas are used to study the distribution of cholinergic and dopaminergic activity in the cochlea of the cat.

Previous findings from our laboratory have demonstrated that stimulation of the locus coeruleus (LC) in the decerebrate cat results in facilitation of both extensor and flexor spinal reflexes in the hind limb. These effects were further shown to be blocked by alpha adrenergic blockers but more completely by generalized adrenergic blockers. The present study builds on previous work to determine if the indoleaminergic as well as the catechola-

(Supported by ORU Intramural Funds and NIH Grant NS17176.)

Sensory axons from tooth pulp terminate in all trigeminal subnuclei, with no interpnolaris receiving a significant projection. Pars interpolaris is likely to play an important role in pulpal pain mechanisms, particularly since pulpal pain is not abolished following destruction of analgesic fibers. Pulpal stimulation caused a more vigorous response than that described for pure muscarinic agonists. The data suggest that pulpal stimulation is more complicated than previously thought.

57.8 RETROGASSELIAN GLYCEROL INJECTION IN CATS AND IN CLASSICAL TRIGEMINAL NEURALGIA PATIENTS. Marvyn H. Bennett, L. Dade Lunsford* and Julio A. Martinez* University of Pittsburgh, Pittsburgh, PA 15261.

Retrogasserian Evoked Potentials (TEP) and sensory threshold following stimulation of the maxillary gum were obtained in patients before, and six weeks following retrogasserian glycerol injection. The group of patients that obtained the highest TEP in cats before and four weeks following retrogasserian glycerol injection. Cats nerve and ganglion were then prepared for histological analysis. The major and minor sensory nerves were isolated for additional input from mechanoreceptors in oral regions. Of 110 pulp driven neurons, approximately 30% responded to pulp stimulation but the majority also to stimulation of mechanoreceptive fields in oral regions. Responses to pulp stimulation in the specific neurons were similar to those in the nonspecific neurons, except in the latter sensory discharge latency was longer (20 vs. 4 sec for the first spike) and on repeated stimulation the response was more variable. In nonspecific neurons, comparison of pulp and mechanoreceptive field stimulation showed also longer latencies and more variable discharges for the pulp-evoked responses. Tooth pulp stimuli, relatively pure noxious stimuli if compared with noxious cutaneous stimuli, are represented centrally by two main neuron groups, a pulp-specific and a larger nonspecific group. (Supported by NIH grant BNS 78 0653).


A study was designed to determine if the 14C-deoxyglucose (DG) metabolic mapping technique of Sokoloff could be used to localize areas of increased metabolic activity in the spinal cord resulting from noxious stimulation. Cats 2.0-2.6 kg were anesthetized with sodium pentobarbital (35 mg/kg i.v.). The hindlimbs were contralateral. Stimuli were applied to the skin of the hindlimb. Skin temperature was raised to 52°C for 20 sec at 30 sec intervals. At the beginning of stimulation, 125 uCi/mg of DG was injected intravenously. After 45 min of periodic stimulation, the spinal cord was removed, frozen, and sectioned at 20 mm and prepared for autoradiography. After 12 days of exposure, quantitative mapping of the autoradiographs was carried out using a densitometer. The areas showing increased metabolic activity were compared with the histochemical sections of the spinal cord, and SI spinal cord levels, DG uptake was 24 to 30% higher on the stimulated side. At 30 sec intervals the response was more variable. In nonspecific neurons, comparison of pulp and mechanoreceptive field stimulation showed also longer latencies and more variable discharges for the pulp-evoked responses. Tooth pulp stimuli, relatively pure noxious stimuli if compared with noxious cutaneous stimuli, are represented centrally by two main neuron groups, a pulp-specific and a larger nonspecific group. (Supported by NIH grant BNS 78 0653).


The newborn mammalian species has been shown to have a lower average rate of energy metabolism and a narrow range of rates in its various components than is found at maturity. In a further study of cerebral energy metabolism during development we have employed the 14C-deoxyglucose method for measuring local cerebral glucose utilization in fetal and neonatal sheep. After establishing the lumped constant and measuring the rate constants for the kinetic behavior of deoxyglucose in plasma and brain to be close to those in other species we measured the rates of utilization of glucose by various regions of the brain. The rates were low and homogenous in mid-gestation except for those of brain stem nuclei of the auditory and vestibular systems and for the output of the hippocampus which were relatively high. In the last 7 weeks, local rates rose approximately threefold. After birth there was a further increase increase of 50% above term levels. The study shows that cerebral energy metabolism rises in most structures during prenatal maturation, a time when sensory stimulation is at a relatively low level and behavioral responses are minimal. Supported in part by USPHS grant HD119111.

57.11 COMPARATIVE ACTIONS OF MECHOLYL AND PILOCARPINE ON HUMAN ECCrine GLANDS. Kenneth Kraning, University of Washington, Seattle WA 98195.

Since pilocarpine (PC) induced sweating is inhibited by atropine (AT) it is thought that muscarinic receptor agonists of eccrine secretory cells. However, Edisen and Lloyd (J Physiol 211: 25P, 1970) showed PC-induced sweating in cat's hindlimb footpad. In the present study sweating responses of normal volunteers to pulp, mechanoreceptive potentials, then 30% responded to pulp stimulation but the majority also to stimulation of mechanoreceptive fields in oral regions. Responses to pulp stimulation in the specific neurons were similar to those in the nonspecific neurons, except in the latter sensory discharge latency was longer (20 vs. 4 sec for the first spike) and on repeated stimulation the response was more variable. In nonspecific neurons, comparison of pulp and mechanoreceptive field stimulation showed also longer latencies and more variable discharges for the pulp-evoked responses. Tooth pulp stimuli, relatively pure noxious stimuli if compared with noxious cutaneous stimuli, are represented centrally by two main neuron groups, a pulp-specific and a larger nonspecific group. (Supported by NIH grant BNS 78 0653).

57.12 THE EFFECT OF LIVER DENERVATION (LD) ON MEAL PATTERNS, BODY WEIGHT (BW), AND BODY COMPOSITION OF RATS. L.L. Bellinger, F. Mendel, F.E. Williams and T.W. Castonguay*, Baylor Coll. Dept. Psychol., Dallas, TX 75234 and Dept. of Pediatrics, Univ. of Texas, Houston, TX 77025.

Neuromuscular receptors are a major controller of food intake (FI). Rats (-25g) were sham (-18) operated (SO) or (n=21). LD rats had all tissue cut between the stomach and duodenum. Seven of these animals lost 58% of body weight between 240 and 480 after seven days of exposure, quantitative scanning of the autoradiographs showed that DG uptake was 24 to 30% higher on the stimulated side. At 30 sec intervals the response was more variable. In nonspecific neurons, comparison of pulp and mechanoreceptive field stimulation showed also longer latencies and more variable discharges for the pulp-evoked responses. Tooth pulp stimuli, relatively pure noxious stimuli if compared with noxious cutaneous stimuli, are represented centrally by two main neuron groups, a pulp-specific and a larger nonspecific group. (Supported by NIH grant BNS 78 0653).

The newborn mammalian species has been shown to have a lower average rate of energy metabolism and a narrow range of rates in its various components than is found at maturity. In a further study of cerebral energy metabolism during development we have employed the 14C-deoxyglucose method for measuring local cerebral glucose utilization in fetal and neonatal sheep. After establishing the lumped constant and measuring the rate constants for the kinetic behavior of deoxyglucose in plasma and brain to be close to those in other species we measured the rates of utilization of glucose by various regions of the brain. The rates were low and homogenous in mid-gestation except for those of brain stem nuclei of the auditory and vestibular systems and for the output of the hippocampus which were relatively high. In the last 7 weeks, local rates rose approximately threefold. After birth there was a further increase increase of 50% above term levels. The study shows that cerebral energy metabolism rises in most structures during prenatal maturation, a time when sensory stimulation is at a relatively low level and behavioral responses are minimal. Supported in part by USPHS grant HD119111.
Liver glucoreceptors have been proposed to be a major controller of food intake but controversy in the area exists (Bellinger, Appetite 2:144, 1981). In this study mongrel dogs (15-20 kg) were adapted to being fed 1 hr each day and then hepatic PORT and JUG cannulas were inserted. After recovery the dogs were infused with G at 2.4 (G-A) and 3.6 (G-B) gm/kg of 30% G at a rate of 10cc/min and fed 10 min after infusion stopped. SAL and MAN were used for volume and osmotic controls. Four to eight dogs were tested per infusate with infusions repeated 1-4 times. Data is expressed as a % of averaged non-infused control days. After G-A into the PORT the dogs ate 82.0±5.9; while with SAL, 74.6±12.6 and MAN, 81.9±18.9. After G-B into the PORT the dogs ate 94.6±2.9; while with SAL, 96.5±12.5 and MAN, 62.9±23.6. ANOVA revealed no significant differences \[F(9,38)=1.24\] between groups. After PORT G-A and G-B fasting plasma G increased from 86.9±5.0 to 457.8±21.4 mg%, \(P<0.01\) and 85.3±2.0 to 524.3±16.8 mg%, \(P<0.001\), respectively, just prior to feeding. During this same time insulin concentrations had increased by 9-20 times. These data do not support the concept of liver glucoreceptors being a major controller of food intake.

Supported in part by BCM research funds.
TUESDAY AM CELL PHYSIOLOGY II

58.1

HYPOXIC H+ IN DIABETES MELLITUS. R.L. Clancy, J.C. Gonzalez, M. Ehaban and V. Castagna. *Dept. of Physiology, University of Kansas Medical Center, Kansas City, KS 66103.

Hypoxia contributes to impaired cellular processes in diabetes mellitus. MA Sprague Dawley rats were made diabetic with alloxan, or streptozotocin, and hypoxia was determined from the distribution of C-14 radiolabeled 5,5'-dihexylxolzolidine-2,4-dione (DOCD). Two day diabetic (D) rats had a marked extracellular acidosis (pHv = 7.07). pHv of cardiac muscle (CM) and skeletal muscle (SM) and liver extracellular pH (pHe) were decreased (CM 7.01 ± 0.0, SM 7.02 ± 0.14, liver 7.2 ± 0.2, respectively). Administering insulin (4-5 hrs to 2 day D rats restored pHe of CM and SM to normal while pHv remained decreased. The resulter decreased in the transmembrane H+ ratios suggested insulin resistancy in these cell lines. This was examined using in vitro hemidiaphragm preparations from normal and 2 day D rats. Insulin (100 mg/kg) increased pHv 0.1-0.35 units. Addition of amiloride (1000 μM) blocked the insulin pHv effect. These results indicate that in diabetes mellitus, pHv's of CM, SM, and liver are decreased even when compensatory mechanisms have restored pHv to normal. Secondary insulin resistance in D cells appears, in part, via an active H+ efflux. In skeletal muscle this appears to be mediated by a Na+-H+ exchange mechanism. (Supported by National An. Heart Assoc.)

58.2


Antitumorin, a mitomycin C analog synthesized by Biosearch, was chromographed and labeled with radiolabeled. The behavior of MTT was then monitored by radioactive measurements in serial blood samples and by whole blood counting. The dose-response in WKY rats from the plasma followed first exponential kinetics. A three compartment model was described with the third compartment being in close proximity to the vascular compartment.

58.3


The HTCA has been widely accepted and used for testing the biological activity of anticancer agents. HPLC has been successfully used as an analytical tool to study the metabolites of these drugs. In the present study, we have combined these two methods in a simultaneous mass spectrometric determination of the metabolism both biologically and chemically. We have tested the cytotoxicity of mitomycin-C (MC), a bioreductive activation drug, and the purine analog bisantrene (B), a new anthracycline derivative in HTCA. Cells examined, using HPLC, the metabolism of MC by homogenates of this cell line. Low concentrations of MC were metabolized earlier than MC, SM and liver. The results suggest the following conclusions: The passage of all cell lines is determined by the cell size. MC and bisantrene appears to be metabolized in a more rapid rate under hypoxic than oxidative conditions. We have also utilized a rat liver S-9 preparation to study the metabolism of the new anthracycline derivative bisantrene (B). We have shown that the results of the study of chronic diastereomorphology (D). We have shown that these results indicate the formation of relatively inactive metabolites.

58.4


Changes in osmolality alter the red cell volume (MCV) and the intracellular hemoglobin concentration (MCHC). We studied the influence of variations in osmolality on red cell filtration and deformability. Fixed numbers of washed red cells (10⁶ RBC/J) were suspended in Ringer solution with 8 different osmolalities, which led to RBC swelling (MCV 67±10 fL, MCHC 37±2.0 g/dl), and 65±4.8 g/dl, which causes cell shrinkage (MCV 70±10 fL, MCHC 55±2.9 g/dl). The viscosity of the intracellular fluid varies in the same direction as MCHC. These suspensions were filtered through Nuclepore polycarbonate filters with pore diameters of 2.6, 4.5 and 6.9 μm at a constant flow of 0.08 ml/min and the pressure was recorded. The relative resistance (α) of a RBC in a pore to cell-free Ringer solution was calculated. For each size pore, the α exhibited a minimum value at a different osmolality. The osmosality for minimum α was 400, 250 and 200 mOsm, respectively, for 2.6, 4.5 and 6.9 μm pores. The results suggest the following conclusions: The passage of RBC through pores < 3 μm is mainly determined by the cell volume, whereas the transit through pores > 5 μm is primarily influenced by the internal viscosity of RBCs. Changes in osmolality thus have opposing effects on the flow of red cells in small blood vessels and their passage through narrow pores, e.g. in the spleen. (Supported by NHLBI Grant HL 16501 and Swiss National Science Foundation.)

58.5

OSMOTIC STABILITY OF ERYTHROCYTES IN THE RENAL CIRCULATION REQUIRES KAPLTO UREA TRANSPORBER. Robert J. Macey and Lenore Wadsworth. Toxie Dept. of Physiology-Pathology, Univ. of California, Berkeley, California 94720.

Urea transport by the human red cell occurs via a facilitated diffusion system with high K and high κ values. The equivalent permeability in the limit of zero urea concentration is approximately 10⁵ cm/sec. (Mayrand and Levitt, J.G.P. 82:221, 1983). A physiological rrole for this system is required for rapid urea transport is essential for red cell stability in passing through the renal medulla. Fixed numbers of washed red cells (10⁶ RBC/J) were determined from the renal medulla. The maximal inhibition attained for Na+,K+-ATPase was 25% using an S-AM concentration of 5×10⁻⁷ M; concentrations higher than 5×10⁻⁷ M could not be tested because of interference with the ATPase assay conditions. No inhibition of the basal Mg²⁺-stimulated stimulated ATPase activity or ATPase activity was observed. Further specificity for an ATPase inhibition by S-AM is not noted in that neither adenine nor methionine, in similar concentration ranges, caused enzyme inhibition. The inhibition of Na⁺,K⁺-ATPase and K⁺-ATPase was not time dependent and was completely reversed on washing the enzyme free of S-AM. pH profiles for Na⁺,K⁺-ATPase and K⁺-ATPase demonstrated comparable inhibition by S-AM in buffered acidic, neutral and alkaline pH ranges. Kinetic analysis of the effects of S-AM on K⁺-ATPase indicated competitive inhibition with respect to NPP and non-competitive inhibition with respect to K⁺.

58.6

EFFECTS OF S-ADENOSYL METHIONINE ON NA⁺,K⁺-ATPase AND P-NITROPHENYL PHOSPHATASE ACTIVITY OF DOG KIDNEY. George R. Henderson* (Spon: P.H. Brand). Medical College of Ohio, Toledo, Ohio, 43699.

S-Adenosylmethionine (S-AM), in a dose-dependent fashion, inhibits Na⁺,K⁺-ATPase and K⁺-ATPase-p-nitrophenyl phosphatase (p-NPPase) activities of a purified enzyme prepared from dog kidney medulla. The sensitivity of K⁺-NPPase to S-AM inhibition is 1×10⁻⁷ M. At a similar S-AM concentration K⁺-NPPase is only inhibited 12%. The maximal inhibition attained for Na⁺,K⁺-ATPase was 25% using an S-AM concentration of 5×10⁻⁷ M; concentrations higher than 5×10⁻⁷ M could not be tested because of interference with the ATPase assay conditions. No inhibition of the basal Mg²⁺-stimulated stimulated ATPase activity or ATPase activity was observed. Further specificity for an ATPase inhibition by S-AM is not noted in that neither adenine nor methionine, in similar concentration ranges, caused enzyme inhibition. The inhibition of Na⁺,K⁺-ATPase and K⁺-ATPase was not time dependent and was completely reversed on washing the enzyme free of S-AM. pH profiles for Na⁺,K⁺-ATPase and K⁺-ATPase demonstrated comparable inhibition by S-AM in buffered acidic, neutral and alkaline pH ranges. Kinetic analysis of the effects of S-AM on K⁺-ATPase indicated competitive inhibition with respect to NPP and non-competitive inhibition with respect to K⁺.
REGULATION OF CASTRIC MICROSONAL (H⁺-K⁺)-ATPase SYSTEM BY A CYTOSOLIC ACTIVATOR PROTEIN. Tushar K. Ray and Jaytummi Nandi. Department of Surgery, SUNY-Upstate Medical Center, Syracuse, NY. (A120)

The (H⁺-K⁺)-ATPase activity associated with pig gastric microsomes was abolished within 10 min. of phospholipase A₁ (PLA₁) treatment at 21°C or 37°C. About 60 and 80% of the microsomal PLA₁ treatment at 21°C and 37°C respectively while 85% of the PLA₁ was hydrolyzed at both temperatures. Contrary to the PLA₁ treated microsomes at 21°C those digested at 37°C needed to be treated with PC before any assaying with the activator (AP) for maximal activity, PC was without any effect. Similar to our previous reports with ethanol (ABU, LU. S.,1980) and trypsin (Life Sci 28,1969,1981) the present data resembled a cisplatin induced gastric (H⁺-K⁺)-ATPase function. The steady-state P₁-intermediate level (p(mg/ml *SU) was reduced to 78% after PLA₁ treatment from the control (227±17) but elevated after AP reconstitution (309±13). The new steady state levels in presence of 5 mM K⁺ were control, 258±22, PLA₁, 174±54 and PLA₁-AP, 210±24. The turnover of the PLA₁ treated enzyme was reduced by about two orders of magnitude compared to the control and reconstituted enzymes. The data suggest that (1) the AP is an extrinsic protein and (2) the AP appears to be essential for both the kinase and phosphorylation steps of the overall (H⁺-K⁺)-ATPase reaction.

NUCLEOTIDE SPECIFICITY OF THE GASTRIC (H⁺-K⁺)-ATPase. J.G. Forte and W.W. Renstra*. Dept. of Physiology-Anatomy, Univ. of California, Berkeley, CA 94720. (A121)

Nucleotides (NTP) hydrolysis and exchange reactions of the gastric (H⁺-K⁺)-ATPase were studied. NTP/ADP exchange was monitored by incorporation of [3H]ADP into ATP. The reaction required Mg⁺² and had a Kᵣ₀ for ATP of 4.3 nM. ATP is Mg⁺²-dependent. NTP hydrolysis was observed in the presence of Mg⁺² or ADP. In general agreement with Rabon et al. (JBC 261:151), but unlike their results, showed little K⁺ stimulation (≤ 10%) over a wide pH range. Under these conditions NTP hydrolysis and exchange reactions, with the sequence ATP₁ > ITP > CTP > GTP, Mg⁺²-dependent NTPase was about the same for all NTP's; only ATP showed K⁺-stimulated hydrolysis, characteristic of the (H⁺-K⁺)-ATPase, and H⁺ transport activity. The addition of ADP (0.1 mM) caused K⁺-stimulated hydrolysis of all the NTP's. H⁺ transport by vesicles equilibrated with 100 mM K⁺ occurred only with ATP; however, when external K⁺ was reduced, H⁺ uptake was seen with other nucleotides. These results are interpreted in terms of an initial rapid E-P formation sequence, with E²P + ATP → E-P + Pi + ADP. From this reaction or a fall of [Ca²⁺] in the cytoplasm, a rise in ATP and an ATP-regenerating system. Intravesicular ATP hydrolysis and exchange establish a direct connection between Ca²⁺ buffering and ADP/ATP turnover. Whether inactivation of the Ca²⁺-sensitive ATPase in the proximal tubule occurs by phosphorylation and dephosphorylation of the enzyme will be explored. Supported by USPHS Grant AM 10141.
The dependence of acid formation on medium and intracellular Cl⁻ was investigated in resting and stimulated rabbit gastric glands. Acid formation was measured by an immunoassay method. The ATPase activity was steady state distribution of 36-CI-. Medium CI⁻ induced AP activity, but the ATPase activity did not change with normal Na⁺ medium and K⁺ medium maintained, similar results were seen in stimulated glands treated with amphotericin and ouabain (ampho+ouabain), where Cl⁻ pathways in the basolateral membrane were confined to be alkali-trilized. In ampho+ouabain treated resting glands, AP activity increased linearly with increasing Cl⁻, i.e., no saturation was seen. Inhibitory effects of Na⁺ medium were observed. Removal of Na⁺ reduced the K₅₀ for Cl⁻ from 17.5 to 10 mM, in stimulated glands, and from 100 to 10 mM in resting glands. At a physiological Cl⁻ medium (60 mM) and in the absence of Na⁺, the K₅₀ for K⁺ decreased from 17.5 to 10 mM in stimulated glands, and from 100 to 10 mM in resting glands. 

Inward Cl⁻ gradients could be dissipated by K⁺ addition. 2 ATPase activity increased linearly with increasing medium Cl⁻. When K⁺ medium loaded vesicles were diluted into a medium containing the potential probe, DiSC₃ (4') and a fluorescent signal (interior negative) was observed. The permeability of K⁺ relative to Cl⁻ was high, as judged by a small additional valinomycin response. Upon treatment with 10 mM Mgl₂, a pump inhibitor of the Na⁺ ATPase, the intrinsic K⁺ permeability is inhibited. Thus, the K⁺ pathway may be associated with a peptide of the H⁺ K⁺ ATPase. Monoclonal antibodies against the K⁺ dependent ATPase responsible for acid secretion in the hog gastric mucosa were generated by hybridoma technology. One antibody (KR 111) shown earlier to bind selectively a major sub-unit of the ATPase, and to label neutral density and secretory canalicus of rabbit parietal cells, was used to develop a sensitive and specific assay for the ATPase. 

Extraction and solubilization of the H⁺ K⁺ ATPase. 

Protected K⁺ stimulated ATPase from hog microsomal vesicles was extracted and solubilized in an assay format using 1-O-dodecyl-D-glucopyranoside (C₁₂(10)G). The extracted material, defined as that which settled, but did not pellet at 100,000 x g for two hours was retarded on a Sepharose CL-4B-200 column (M₂₅ exclusion 20 x 10⁴ daltons). At a detergent/protein ratio of 1.4 (1.0% w/v), approximately 70% of protein was extracted, demonstrating 20-100% of control K⁺ stimulated specific activity upon dilution. At a selected detergent/protein ratio of 1.7 (2.4%/1.4% w/v), approximately 30% of the protein remained in the cleared supernatant. This solubilized protein demonstrated approximately 50% of control specific activity and accounted for about 15% of total K⁺ stimulated ATPase activity. 

Supported by NIH AM32931.
61.1 INWARD AND OUTWARD CURRENT IN ISOLATED NON-SPIRING DENDRITES. Maurizio Mirolli. Medical Sciences Program, Physiology Section, Indiana University, Bloomington, IN 47405

Segments 1 to 2 mm long of the dendrites of the cochlear receptors of Portunus sanguinolentus and of Callinectes sapidus were isolated by 1% trypsin. The following currents could be recognized by voltage clamping: a) A fast inward current, peaking 1 to 2 msec after clamp onset, carried by potassium. b) A slow inward current, peaking at 0.1 to 0.5 seconds, carried by calcium. c) A fast outward current, peaking within 5 msec, carried by potassium. d) A slow outward current, peaking within 20 to 40 msec, also carried by potassium. e) A slow outward current peaking in half to 1 second, the carrier of which has not been identified. Although these currents can be recognized in segments cut from either the proximal or the distal parts of the dendrites, the slower ones are larger in segment cut from the proximal part which is closer to the point where the dendrites are presynaptic to other fibers (presumably axons of motor neurons). (Supported by NSF grant no. 83-830-09).

61.2 COMPARISON OF GLYCINE AND GABA CHANNELS IN CNS NEURONS OF THE LAMBY. Michael R. Gold and A. R. Martin. Univ. of Colorado Sch. of Medicine, Denver CO 80262

Glycine-activated and GABA-activated reticulospinal-neuronal spinal cord neurones (Mueller cells) have mean open-times of 35 msec at 5°C and single channel conductances of 73 pS. Moreover, conductance decreases rapidly as intracellular Cl- is raised above 0 mV (Figure 1). The two agonists show that GABA-activated Cl- channels in these same cells have very different properties. Mean open times are longer (16+5 sec. 50% open time) with GABA, and conductances are smaller (18+6 pS) and unaffected by intracellular Cl-. Additional studies revealed that the macroscopic conductance produced by glycine or GABA add algebraically, suggesting that the ligands do not compete for the same channels. The anion selectivity of the two channels was investigated, in ionic solutions in which the effective channel dimensions of the two agonists were permeable to Cl-, Br-, NO3-, ClO4- and formate but impermeable to F-, acetate and citrate. These results indicate that glycine and GABA activate different populations of Cl- channels on these cells, and that the larger current observed with glycine is unlikely to be due to a "wider" channel. (Supported by grant NS-00660 from the NIH)

61.3 NEUROLY- AND OUTWARD CURRENT IN ISOLATED NEURONS. B.N. Cheung (SPON: F. Sunahara) Department of Pharmacology, University of Toronto, Toronto, Ontario M5S 1A8 Canada

Stimulation of the perivascular nerves elicited two types of electrical responses in the rat tail - the excitatory junction potential (e.j.p.) and the slow depolarization (s.d.). The e.j.p. is resistant and the s.d. is sensitive to a-blockade. The functional role of these two electrical components was investigated by simultaneous recording of the electrical activity and the isometric tension of rings segments of rat tail arteries. (Supported by a grant from the Ontario Heart and Stroke Foundation.)

61.4 STATISTICAL ANALYSIS OF SPONTANEOUS TRANSMITTER RELEASE USING A MODEL OF TEMPORAL STATIONARITY. M. D. Miyamoto (SPON: E. W. Monod) E TN ST Univ Col Med, Johnson City, TN 37614

At motor nerve terminals, spontaneous transmitter release is described as a binomial event, where the no. of quanta released (m) is related to the probability of release (p) and the no. of release sites occupied by vesicles (n). However, due to temporal and spatial variation in n and p, binomial estimates of these parameters may be inaccurate. Temporal variation most likely results from 'turbulence' created by rapid depletion and replenishment of transmitter stores in response to constant release. If temporal variation is minimized, e.g. by using spontaneous release (which is low level) and in steady-state, then spatial variance in p (var(p), where p is the only major parameter) can be assessed. Miniature endplate potentials (mepps) were recorded from cutaneous pectoral muscle of Rana pipiens with standard microelectrode techniques. The no. of mepps per microliter was counted at different points in time and the effective channel dimensions were computed using a third moment with 3 simultaneous equations. Values of p obtained in 20 mM K were meaningless (Poisson) as expected, but values in 5 mM K were finite. Progressive elevation of 5 to 20 mM K added both var(p) and var(p). (Supported by grant NS-00660 from the NIH)

61.5 SPATIAL DISTRIBUTION OF SPINAL NERVE NETS. Edgar L. Castegelier and Suzanne de la Monte*. Dept. and Sect. of Physiology, N.Y. State College of Veterinary Medicine and Division of Biological Sciences, Cornell University, Ithaca, NY 14853

Glycine-activated Cl- channels in lamprey reticulo- spinal neurons were shown to have only major parameters. Miniature endplate potentials (mepps) were recorded from cutaneous pectoral muscle of Rana pipiens with standard microelectrode techniques. The no. of mepps per microliter was counted at different points in time and the effective channel dimensions were computed using a third moment with 3 simultaneous equations. Values of p obtained in 20 mM K were meaningless (Poisson) as expected, but values in 5 mM K were finite. Progressive elevation of 5 to 20 mM K added both var(p) and var(p). The similarity of these results to those obtained with mepps in high Mg suggests that this method may be useful for studying the effects of agents at the release mechanism, in the absence of complications due to transmitter depletion and mobilization. (Supported by grant RR 326.)

61.6 THEORETICAL PREDICTIONS OF MEDIAN NERVE LUMINOUS UNDER NONINJURIOUS AND HYPERTENSIVE CONDITIONS OF BLOOD PRESSURE. Alan R. Hargens, Robert M. Szabo* and Richard G. Geberman. A Division of Orthopaedics and Rehabilitation (14851), and University of California Medical Centers, San Diego, CA 92165

Sensory and motor functions of the median nerve at wrist level were assessed during acute conditions of local compression. After measuring resting fluid pressure by the wax catheter (inserted during local anesthesia) in tissues which immediately surround the median nerve, the carpal tunnel of the nondominant hand was compressed by a rubber band tied around the flexor carpi ulnaris. Tissue fluid pressure was raised and maintained constant at levels between 30-70 mm Hg for periods up to two hours in 28 studies of 14 normal subjects in peak activity (100% of MVC level). Sensory and motor functions were tested before, during and after compression. Compressive thresholds for nerve dysfunction were consistently 30 mm Hg below blood pressure in all subjects. Sensory responses were completely blocked at threshold pressures of 40-50 mm Hg in normotensive subjects and 70-90 mm Hg in hypertensive subjects. Normal function returned in all subjects shortly after release of compression. These studies also identified sensibility tests which were the most sensitive to acute compression of peripheral nerve. The neurophysiologic results support the concept that ischemia is the primary cause of conduction block in low pressure, nerve compression syndromes. (Supported by the Veterans Administration and by NIMH grants AM-26244, AM-23014 and AM-00602.)
SODIUM PENTOBARBITAL BLOCKS MORPHINE TOLERANCE AND POTENTIATION IN THE RAT. G.W. Terman*, G.M. Lewis* and J.C. Lieberskind. UCLA, Los Angeles, CA 90024.

Repeated exposure to footshock potentiates subsequent morphine analgesia in rats. It has been suggested that this phenomenon, as well as morphine tolerance, depends on the association of environmental cues with drug administration. To test this hypothesis, we compared two groups of rats (7.5 mg/kg, i.p.) preexposed to footshock (4 min of continuous 2.5 mA 60 Hz sine wave) with rats not exposed. Pain threshold was assessed by the tail-flick test before and after the test dose of morphine.

Groups differ in tail-flick latencies prior to morphine on the test day. After morphine, unanesthetized animals previously given this drug showed significant analgesia whereas analgesia was only transiently exposed to footshock showed significantly potentiated morphine analgesia. In contrast, anesthetized animals, requiring minimal exposure to footshock showed significantly potentiated morphine analgesia. Thus, pentobarbital does not affect morphine analgesia in naive rats, as measured by the tail-flick test, but does block both development of tolerance to morphine's analgesic action and potentiation of morphine analgesia by prior stress, possibly by preventing the perception of environmental cues important for these phenomena. (Supported by NIH grant NS 07628 and a gift from the Brotnan Foundation.)

61.9

VISUAL MOTION DISPLACEMENT SENSITIVITY OF CAT Y, AND W CELLS BY R. F. Scobey, P. E. E. van Konk and L. Hopfer, Dept. of Neural, Sch. of Med., Univ. of California, Davis, CA 95616, U.S.A.

The motion sensitivity of single units in and around the LGN of unanesthetized and paralyzed cats was determined by measuring their displacement thresholds in response to a line stimulus. A displacement threshold was defined as the distance that a vertically stationary line must move from its resting position of the central nervous system of Limulus, including 5 pairs of bilaterally-symmetrical cell clusters in the circumphagostomous connective (CM's) and suboesophageal ganglia. (Supported by: Dept. of Energy and Southern Calif. Edison Co.)

61.10

A-PURITATION P-LIKE PEPTIDE MODULATES PHOTORECEPTORS IN THE PERIPHERAL NERVE. Jorge R. Marcellin, Dept. of Neurosciences, Unv. of Calif. San Diego, CA 92109.

Substance P-like immunoreactivity is contained in discrete cell clusters distributed throughout the length of the central nervous system of Limulus, including 5 pairs of bilaterally-symmetrical cell clusters in the circumphagostomous connectives (CM's) and suboesophageal ganglia. (Supported by: Dept. of Energy and Southern Calif. Edison Co.)

61.11


For several years the receptor that terminates the synaptic action of monoamines was viewed as an energy dependent process whose efficiency depends on the energy available. This view must now be reconsidered. We have reported (Science 215: 1112-1113, 1982) that the high affinity brain recognition sites for imipramine discovered by Langer et al. (Nature 281: 148, 1979) are located on serotonergic terminals and probably are connected functionally with the SHT reuptake system. SHT displaces imipramine from its binding sites with low affinity and low Hill coefficient, indicating that an allosteric process links the imipramine binding site to the SHT recognition site of the reuptake mechanism. Two daily injections of imipramine for 5 days have regulated dopamine release in imipramine binding sites in the hippocampus mice. Moreover in these mice the efficiency of imipramine as a blocker of the SHT uptake is diminished. However, the high affinity of imipramine may modulate SHT reuptake physiologically through the action of an endogenous effector. A host stable nonpeptide molecule capable of displacing imipramine from its high affinity site and of inhibiting the SHT uptake in a dose related manner has been extracted from rat brain. Its partial purification was reported.
62.1 CENTRAL FACILITATION OF THE ARTERIAL BAROREFLEX FOLLOWING ACTIVATION OF BARORECEPTOR AFFERENTS. Cheryl M. Heesch* and Francois M. Abboud, Univ. of Iowa, Iowa City, IA 52242.

We reported acute resetting of carotid sinus (CS) baroreceptors (increased pressure thresholds and rightward shift of pressure-discharge curve) when CS pressure was elevated by 90 mmHg for 5 minutes (Fed. Proc. 42:308, 1983). In this study we report that after exposure to a resetting of the CS baroreflex may compensate for the resetting of the CS baroreceptors. In 6 cats in which a dorsal hemisection of the spinal cord had been performed, bilateral carotid baroreceptors were exposed. These reflex responses were repeated after the central end of the right CS nerve had been stimulated at 0.5-30 Hz, 5 ms and 6-8 V. Positive responses were blocked by intracoronary timolol (8 mg) and atropine (0.1 mg). This augmentation of baroreflex responses was reversed within 20 minutes. Thus it appears that brief periods of stimulation of arterial baroreceptors may provide a brief period of augmentation of baroreceptor function which would tend to suppress sympathetic outflow and central facilitation of the reflex which would tend to compensate for the peripheral resetting.

62.2 DOES PREGANGLIONIC SPROUTING LIMIT CARDIAC CHOLINERGIC SENSITIVITY FOLLOWING CHRONIC UNILATERAL VAGOTOMY? D. V. Priola, C. Anganostellis*, R. Anaya* and D.C. Smith, Univ. New Mexico, School of Medicine, Albuquerque, NM 87131.

In a previous study, we found that the acute pattern of cardiac cholinergic supersensitivity was detectable 1-2 weeks after unilateral cervical vagotomy (VX). This lack of change in cardiac cholinergic sensitivity after VX suggested that changes in cardiac cholinergic function have been caused by preganglionic sprouting from the remaining vagus. To test this, we compared cardiac responses to vagal stimulation in control animals to those with chronic VX done either 1-2 weeks or 8-12 weeks previously. Atrial and ventricular inotropic and chronotropic responses were evaluated in animals on total cardiopulmonary bypass. Stimulation of the left vagus (Vx) resulted in a significant increase in arterial pressure (AMP) and heart rate (HR) in the intact state. However, bilateral cervical vagotomy resulted in significantly increased HR but no fall in MAP in the intact state, which then returned to control levels. Resting heart rates were greater following VX (236±3 vs 128±2 bpm) and the 8-12 wk VX animals showed F/R curves less sensitive than control, in some cases failing to respond at all. We could find no functional evidence of preganglionic sprouting in animals subjected to either short- or long-term VX. Either sprouting does not occur or, if it does, it is not functionally important. In the long-term animals, denervation of preganglionic fibers from the intact side may have taken place. (Supported by NIBIB Grant GM-18517 and MRRS Grant FR-08139.)

62.3 INITIAL HEMODYNAMIC RESPONSE TO EXERCISE IN DOGS BEFORE AND AFTER BILATERAL CERVICAL VAGOTOMY. A. M. Booth, D. A. Gerasch*, M. E. Anderson*, C. H. Swartz* and J. J. Fox, University of Minnesota, Minneapolis, Mn. 55455.

To test the effect of bilateral cervical vagotomy (VX) on the hemodynamic response to exercise, one min. treadmill exercise periods (9 kph, 0% grade) were studied in two 25 kg mongrel dogs instrumented with solid state pressure transducers in the left ventricle (LV) and descending aorta, and an electromagnetic flow probe on the ascending aorta. The afferent pathway to the brain was evaluated using an electromagnetic flow probe on the ascending aorta and the right carotid artery. CS baroreceptors were exposed and responses were repeated after the central end of the right CS nerve had been cut and the left CS was vasculally isolated. Reflex reduction in arterial blood pressure and activity in atrial blood pressure during elevation of left CS pressure from 70 to 250 mmHg averaged 18±2 (p<0.05) mmHg increase in CS pressure respectively. These reflex responses were repeated after the central end of the right CS nerve had been stimulated at 0.5-30 Hz, 5 ms and 6-8 V. Positive responses were blocked by intracoronary timolol (8 mg) and atropine (0.1 mg). This augmentation of baroreflex responses was reversed within 20 minutes. Thus it appears that brief periods of stimulation of arterial baroreceptors may provide a brief period of augmentation of baroreceptor function which would tend to suppress sympathetic outflow and central facilitation of the reflex which would tend to compensate for the peripheral resetting.

62.4 THE ROLE OF INTERSTITIAL POTASSIUM LEVELS IN THE EXERCISE PRESSOR REFLEX. K. J. Rybicki*, M.P. Kaufman*, J. L. Kenyon* and J. H. Mitchell, Univ. of Texas Health Science Center, Dallas, TX 75235.

Statically muscle contraction reflexly increases cardiovascular function. Substantial evidence has been gathered to support the hypothesis that these reflex increases are caused by the activation of sympathetic nerve fibers. Increases are stimulated by the build-up of metabolites trapped in the contracting muscle. Potassium (K+) has been suggested as one of the "metabolic stimuli" that activates these muscle afferents. Therefore, in chloralose anesthetized dogs, we measured gracilis muscle interstitial K+ "on-line", using an ion-selective electrode, to monitor the effect of cutting the obturator nerve, suppressing the gracile muscle, or infused K+ (1-5 mEq) into the arterial supply of this and adjacent musculature. In 3 dogs we found that statically contracting only the gracilis muscle increased interstitial K+ levels (from 3.1±2.1 mM to 5.4±2.5 mM), by infusing, significantly increased mean arterial pressure (MAP) (85±52 mmHg) and heart rate (HR) (7±3 bpm). Moreover, these increases were abolished by cutting the obturator nerve, demonstrating that these responses were a reflex. Thus, we have shown that elevating gracilis muscle interstitial K+ levels occurring during static contraction reflexly increases MAP and HR. We have therefore provided further evidence that potassium release may play a role in the exercise pressor reflex.

62.5 EVIDENCE FOR AN AFFERENT PRESSOR PATHWAY IN THE VENTRAL SPINAL CORD. C. A. Iwamoto*, B. B. Botterman* and T. G. Waldrop* (SPON: J. H. Mitchell). Univ. of Texas Health Science Center, Dallas, TX 75235.

It has been held that the afferent spinal path for pressor reflexes evoked by somatic stimuli ascends the spinal cord in the vicinity of the dorsolateral sulcus (e.g., Ranstow, 1978). However, our results have been consistent with the hypothesis that pressor reflexes evoked by somatic stimuli ascend the spinal cord in the vicinity of the dorsolateral sulcus using dorsolateral spinal cord lesions possibly suggesting otherwise (Johnson, 1962; Kozelka et al., 1981). In addition, the present evidence lends support to the hypothesis that the pressor reflexes evoked by the "metabolic stimuli" that activates these muscle afferents, which in turn evoked a pressor response. In 7 of 7 cats in which a dorsal hemisection of the spinal cord was made, responses to vagal stimulation were compared. CS baroreceptors were exposed (202±14 mmHg, p<0.001) and heart rate (6±3 (bpm)), were observed on stimulating the ventral routes (3X motor threshold, 0.1 sec duration, 50 Hz). Further lesions revealed the bilateral nature of the afferent pathway. These data indicate the existence of a bilateral ventrally located spinal cord afferent pressor pathway from the hindlimbs which plays a role in the exercise pressor reflex.

62.6 INFLUENCE OF VARIABLE HEADGEAR LOADING ON BLOOD PRESSURE AND HEART RATE. Chandler A. Phillips and Jerrold S. Petrofsky, Wright State University, Dayton, OH 45435.

In an extensive series of experiments we have been conducted to quantify the stress and fatigue of neck muscles as measured by cardiovascular responses. The neck musculature was electrically stimulated and dynamically and statically loaded by total and static control, in some cases failing to respond at all. We could find no functional evidence of preganglionic sprouting in animals subjected to either short- or long-term VX. Either sprouting does not occur or, if it does, it is not functionally important. In the long-term animals, denervation of preganglionic fibers from the intact side may have taken place. (Supported by NIBIB Grant GM-18517 and MRRS Grant FR-08139.)

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62.9

CONTROL OF ARTERIAL BLOOD PRESSURE BY THE PARAVENTRICULAR NUCLEUS IN THE SHR. D.O. NELSON AND CAROL A. GRAHAM*. Northwestern Medical School, Chicago, IL 60611.

Recent physiological and neurological evidence suggest that the paraventricular nucleus (PVN) may play an important role in the central autonomic regulation of the cardiovascular system. Considering that altered central mechanisms have been identified in the development and maintenance of spontaneous hypertension, we examined the effects of microstimulation and lesioning of the PVN on blood pressure (BP) and heart rate (HR) of spontaneously hypertensive rats (SHR) and conscious normotensive rats (WKY). Rats were bilaterally microstimulated in the PVN. Low frequency microstimulation produced significant increases in BP, accompanied by tachycardia, in 8 of 11 SHR rats. One rat had a higher threshold and slightly attenuated sensitivity to PVN stimulation compared to WKY controls. Increases in BP and HR were not affected by parasympathectomy but were eliminated by pharmacological or surgical sympathectomy. Bilateral PVN lesions produced a 42 + 3 mm Hg decrease in BP and a significant reduction in HR in the WKY. Lesions in SHR produced a 60 + 15 mm Hg decrease in BP and a larger bradycardia (80-100 beats/min) compared to WKY controls. These data support the suggested importance of the PVN in blood pressure control and suggest that the PVN may contribute to the hypertensive state in the SHR. (Supported by ADA Grant in Aid 82659)

67.11

EFFECTS OF CENTRALLY APPLIED D-AND L-PROPRANOLOL ON ACTIVE MUSCLE VASODILATION (AMV) IN RABBITS. S. SHIMADA+ AND J. STITT, J. B., FRIECE LAB & YALE UNIV. SCH. MED., NEW HAVEN, CT 06520.

AMV in rabbits can be elicited by electrical stimulation in the perifornicular area of the hypothalamus. While attempting to identify the peripheral neurotransmitter for AMV, we found that large doses of L-propranolol could block AMV. However, it took over 1 hr to establish this blockade, and the doses required were in excess of those necessary to block peripheral B receptors. Because propranolol crosses the blood-brain barrier, we reasoned that the drug may have acted in the brain. Therefore, we injected into the brain both D- and L-propranolol to see if: 1. Small quantities of drug could block AMV, and 2. There was a difference in potency between the two isomers. The drugs were dissolved in 10 ul sterile saline and infused into the lateral cerebral ventricle. To reduce an 80% maximal response by half, we found that 0.0062 ± 0.0025 ug D- propranolol were necessary, whereas 3.51 ± 0.55 pg L propranolol were required to produce the same attenuation. These results suggest that there is a central B-adrenergic mediation of AMV. AMV is a component of the multicaused defense reaction, thought to be naturally elicited in response to fear and emotional stress. Since high levels of stress are linked to some forms of persistent hypertension, perhaps propranolol's clinical effectiveness as an anxiolytic and antihypertensive agent can be explained by an antagonism of a central B-adrenergic mediation not only of AMV, but of the entire defensive reaction as well. (Supp. by NIH grant HL24626)
63.1 EFFECTS OF NECK EXTENSION (NE) ON DENSITY DEPENDENCE (DD) OF MAXIMAL INTRINSIC RESISTANCE (R") IN NORMAL HUMANS. R. Castile*, R. Ingram, Jr. and J. Mead. Children's Hospital Medical Center, Massachusetts General Hospital and Harvard School of Public Health, Boston, MA 02115
Mellinsens and Mead (J.A.P. 41:537-544, 1977) reported that NE increased tidal volume in some infants.
They attributed these increases in MIPF to increases in longitu
dinal tension at tracheal choke points. We postulated that 
increases in tracheal elastance produced by NE would diminish 
MIPF, to air flow related differences in tracheal choke point 
dynamics and thereby increase DD in subjects with tracheal choke 
points. Ten normal subjects with plateaus in their flow-vol
ume curves were studied. Changes in tidal volume (Vt), 
resistance of the respiratory system, and the force-velocity 
relationship of inspiratory muscles. From previous studies2 
the neoventilation (increases in tidal volume) during NC was 
identified. While seated in a pressure compensated 
plateau, but consistently increased MIPF, and thereby increased DD in normals with tracheal choke 
points. We conclude that increases in elastance at tracheal choke points caused by NE increase DD of MIPF. (Supported by HE 1970-07).

A chronic problem in studies of high-frequency oscillation 
(HFO) has been the paucity of quantitative measurements of 
gas volumes delivered to the chest. Magnetometers have been used as a noninvasive means of monitoring tidal volume 
during exercise. Here we describe the use of magnetometers 
in man to measure noninvasively total ventilation during HFO, 
and to separate tidal volume from the lower frequency 
oscillations generated by an Emesoon diaphragm ventilator. Four pairs of 
magnetometers are used across the chest and abdomen, both 
anterior-posterior and lateral. The magnetometer signals are 
sampled by a PDP 11/03 computer. The HFO component of the 
signal is separated from the tidal volume component by a 
digital filter. Volume is derived from these two signals by 
curve fitting to previously calibrated volume signals. The 
quality of the signal is judged by comparison with accelerometer 
measures of chest-wall motion. Transfer character 
istics allow the costal and crural diaphragmsto develop differ
dent tensions. (Supported by MRC of Canada).

Supports by Grant M5629 Canadian Medical Research Council

During inspired effort against a closed glottis, FRC = FRC(Pa/Al) in 
vaselar, in dogs with severe gas trapping, this method underestimated FRC. When PaP was estimated by either PaP (airway opening) or 
PaP (pleural). We observed that severe gas trapping at high 
transpulmonary pressure (Pj) renders those lung units stiff, decreasing their contribution to FRC. In 6 dogs with severe gas trapping, the volume displacement body plethysmograph, each subject perform
ted forceful expiratory maneuvers with the neck in a normal 
position and during NE, breathing air and HeO. APMs of 
tracheal choking points were estimated by a Millar catheter pressure transducer. The table summarizes measurements during FRC determinations (m) before and after inflating R or L to Pj 25 cm H2O (means&SD).

Pj - 0.9*3.5 1136*332 1.3*2.7 1230*385
L = 489ml 120.7*8 -0.4*1.4 1227*400
R = 824ml -2.8*3.1 1178*385 14.7*112
Thus, at high volume and Pj where the compliance (C) of the lung 
approaches the C of the gas within it, lung volume changes little in 
response to A Pj, so the increase in FRC is underestimated. We 
considered that A Pj might not be equal bilaterally, especially with 
asymmetry of expansion of the chest wall. However, introduction of 
plural plethysmographs with small pneumotaches in 2 dogs 
showed equal bilateral A Pj, and confirmed underestimation of FRC in 
the presence of gas trapped in lung units at high Pj.

Accurate measurements of respiratory mechanics are difficult to 
obtain in critically ill newborn infants. Recent evidence 
suggests that such measurements can be obtained from the 
pressure measured during a brief end-inspiratory occlusion and 
assessment of the flow-volume curve of the subsequent passive 
expiration. With this method, respiratory system time 
constant (T), and its components, compliance (C), resistance (R) were measured in 25 premature infants with 
respiratory disease. Infants normally inspired before their 
passive expiration reached zero flow, thus maintaining an end-
expiratory lung volume which increased with increasing T. 
We found linearly ill infants requiring intermittent 
positive pressure ventilation than in non-intubated infants 
or those on continuous positive airway pressure. R did not 
differ in the two groups of intubated infants but fell mark-
edly immediately following extubation, indicating that the 
tracehobronchial tube contributed significantly. It is concluded that accurate assessments of respiratory mechanics can be 
easily obtained in critically ill infants using this method 
and that respiratory system time constant is an important 
determinant of the ability to maintain lung volume in the 
preadmission infant.

Supported by Grant MT5629 Canadian Medical Research Council

63.5 MAXIMUM INSPIRATORY PRESSURE-FLOW RELATIONSHIP (MIPF) IN MAN DURING SUBMAXIMAL NEUROMUSCULAR BLOCKADE (SNMB). L. David Pengelly, J.P.A. Hogg*, G.R. Butts*, and K. Lemieux*. 
Department of Medicine, University of Montreal, and Montreal Children's Hospital, Montreal, Quebec.
The isometric MIPF has been used to define the active 
dynamic characteristics of the respiratory system. 1) The 
major determinants of these characteristics are the passive 
resistance of the inspiratory system, and the force velocity 
relationship of inspiratory muscles. From previous studies we 
predicted that the slope of the MIPF (intrinsic resistance, r") was higher than that of the maximal pressure flow curve (MIPF) 
measured in normal humans by SNMB. In normal newborns, we 
measured MIPF during maximal inspiration efforts through a set of linear resistance 
controls. Data were analyzed from an above MIPF, and 
fitted to a linear model with r" > 0.7. Average slope of the 
relationship was 14.9 ± 3.9 cm H2O/l/sec, under control 
conditions. During SNMB, in all but 2 subjects, the slope 
decreased by >50%. In those 2 infants, the data provide 
support the hypothesis that r" is decreased when muscle 
activation is reduced by SNMB.


63.6 REGIONAL DIFFERENCES IN ABDOMINAL PRESSURE SWINGS IN SUPINE VIBR. Mur Uccroman*, Suzanne Kelly*, Ande De Iroyer and 
We measured abdominal pressure swings in normal adults. The 
isometric MIPF has been used to define the active 
dynamic characteristics of the respiratory system. 2) The 
major determinants of these characteristics are the passive 
resistance of the inspiratory system, and the force velocity 
relationship of inspiratory muscles. From previous studies we 
predicted that the slope of the MIPF (intrinsic resistance, r") was higher than that of the maximal pressure flow curve (MIPF) 
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conditions. During SNMB, in all but 2 subjects, the slope 
decreased by >50%. In those 2 infants, the data provide 
support the hypothesis that r" is decreased when muscle 
activation is reduced by SNMB.

The study included 9 dogs, and the range of sensitivity to histamine (H) sensitivity of the CTSM was measured. The sensitivity of the CTSM was related to the H sensitivity of the CTSM. INDO also decreased the standard deviation of log ED50 among animals. (Supported by MRC Canada and the Can. Lung. Assoc.).

The study also showed that 6-oxo-PGF1α production increases during H-induced bronchoconstriction. DIAPHRAGM. Cobern V. Peterson, Jr. and A.R. Otis. University output. The abdomen was closed with sutures after placing the diaphragm in 8 anesthetized dogs. Generators and magnets composed of miniature Hall generators and magnets were placed so the distance between the two decreased as the muscle shortened thereby decreasing the electrical output. The change in SRaw after 30 minutes of intermittent exercise was measured before and after each exercise period were: Baseline (bsl) 55 ± 13 38 ± 14 38 ± 15 Intermittent exercise 5.39 ± 14.67 12.23 ± 11.12.


MORPHINE SULFATE INHIBITS BRONCHOCONSTRICTION IN SUBJECTS WITH MILD ASTHMA WHOSE RESPONSES ARE INHIBITED BY ATROPINE. W.L. Eschenbach*, R.A. Bethel*, H.A. Boushey, and D. Sheppard*. Canada. 63.10 EFFECT OF AN H1 ANTIHISTAMINE ON EXERCISE AND COLD AIR INDUCED BRONCHOSPASM. S.M. Walden*, P. Mason*, and E.R. Bleecker. The Johns Hopkins Medical Institutions, at Baltimore City Hospital, Baltimore, Maryland.

Airway cooling and drying with hyperventilation during exercise are important factors responsible for post-exercise induced bronchoconstriction. DP A on EIB and CA consist of breathing conditioned cold air (0° C) and FFR are caused by the same mechanisms, that pharmacologic agents should affect these challenges in a similar manner. Histamine may be released during ventilation (FFR) and the FEV1 at 15 min after atropine (FFR) is reduced to 1.0 ppm SO2 exposure with continuous versus intermittent exercise, ten of our subjects returned several weeks later and were exposed to 1.0 ppm SO2 while treadmill walking for 30 minutes under environmental chamber conditions and exercise intermittent exercise 5.39 ± 14.67 12.23 ± 11.12. Sheppard et al. have reported (ARRD 125:151, 1982) that asthmatics exposed repetitively develop short-term tolerance to 50% induced bronchoconstriction. Sheppard et al. have reported a similar pattern of response in a group of asthmatics performing 3 cycles of 10 minutes of treadmill exercise (W - 41 ± 11) followed by 15 minutes of resistance testing in the FEV1 during a 75 minute chamber exposure (26°C,70% RH) to 1.0 ppm SO2. In a study to compare the effects of asthmatics or nonasthmatics with continuous versus intermittent exercise, ten of our subjects returned several weeks later and were exposed to 1.0 ppm SO2 while treadmill walking for 30 minutes under the same environmental chamber conditions and exercise intermittent exercise 5.39 ± 14.67 12.23 ± 11.12. The change in SRaw after 30 minutes of intermittent exercise was significantly greater than the change in SRaw after the first exercise period (p < 0.01) or 30 minutes of continuous exercise (p < 0.05). From present knowledge of the SO2-induced bronchoconstriction of moderately ventilating asthmatics, it appears that this response develops rapidly and is still maintained at the end of a 30 minute exposure to SO2.
OMEPRAZOLE INCREASES \( K^+ \) NET FLOW DURING STIMULATED CONDITIONS IN THE MAMMALIAN GASTRIC MUCOSA IN VITRO. H. Larsson* and B. Ryberg* (SPfM, K. Johansson). Department of Chemistry, ÅBO Hässleholm, S-205 01 Hässleholm, Sweden.

A proposed model for the initiation of acid secretion involves the release of \( K^+ \) from the apical membranes of the parietal cell. \( K^+ \) is then exchanged for \( H^+ \) by the \( H^+,K^+\)-ATPase resulting in a net secretion of \( H^+ \). Provided that the \( K^+ \) pathway is unaffacted, an inhibition of the \( K^+ \) would lead to an increased secretion of \( K^+ \). Using omeprazole (OME) (5x10^{-6}M) as a proton pump inhibitor, we studied the effect of this secretagogue on the guinea pig gastric mucosa. As references SCF (5x10^{-5}M) cimetidine (5x10^{-5}M) and \( p \)-chloromercuribenzenesulphonate (pCMBS) (10^{-4}M) were used. Effects on basal and stimulated histamine, 2x10^{-6}M, and I.NK, 10^{-4}M, \( H_2\)-AMP, 10^{-3}M, secretion were studied. All compounds inhibited histamine-stimulated acid secretion but did not inhibit basal acid secretion.

ANGIOTENSIN IS A PHYSIOLOGICALLY IMPORTANT NEUROMODULATOR OF JEJUNAL FLUID ABSORPTION. Nigel R. Levenson* (Sue R. Klamborne). West Virginia University, Morgantown, WV 26506.

A proposed model for the initiation of acid secretion involves an apical Na+/H+-Cl'/HC03 exchange mechanism. We have previously described (Gut 44:295) that SCF in the isolated (N) or anesthetized (A) solution produced similar decreases in the N-S flux of \( H^+ \) and Cl-; subsequent addition of 20 mM histamine to the N side increased \( H^+ \) flux (Sandere et al. AJP 230:E120) and Cl- fluxes in parallel. At pH 7.4, SCF alone increased \( H^+ \) and Cl- effluxes relative to control. An increased rate of SCF increased net flow of \( H^+ \) to the mucosal side, whereas it was unchanged after SCF and cimetidine treatment. As total \( H^+ \) and basal \( H^+ \) flow was also seen during inhibition of \( H_2\)-AMP-stimulated but not of basal acid secretion. Our results are in agreement with the proposed model for stimulated acid secretion.
TRANSCELLULAR MECHANISMS OF L-ALANINE UPTAKE BY DISTAL RAT INTESTINE IN SITU. Anwar B. Bikhazi and Michel N. Abu Salbi*. Dept. Physiology, American University of Beirut, Lebanon.

A study on the transepithelial transport mechanisms of L-alanine through distal rat ileum. Approximately 10 cm distal ileum was everted, freed from mesenteries and perfused at a rate of 1.5 cmL/min with buffer. The perfused segments were then incubated, homogenized, digested in 11H2O, and assayed for [1-C14]l-alanine. Steady state or L-alanine absorption was observed at 10 mEq/L in the range of 0.300±0.17 ng/mg protein/cm2 of intestine. In Na-free choline Krebs Ringer, Na-Krebs Ringer + 1 mMouab, Na-Krebs Ringer + 1 mMouab, and Na-free choline Krebs Ringer + 1 mM ouabain, the amount of L-alanine absorbed was 0.070±0.027, 0.206±0.09, 0.10±0.03, 0.066±0.014 and 0.045±0.008 ng/mg protein/cm2 of intestine, respectively. A 2.5, 3.6 and 1.5 times increase in luminal L-alanine concentration in Na-free choline Krebs Ringer preloaded with ouabain resulted in increase of amino acid absorption of the same order of magnitude. Therefore, a. extracellular luminal Na is indispensable for L-alanine absorption, b. Na and L-alanine co-tranport at the intact epithelial level, c. ouabain sensitive Na alanine co transport pump exists at the mucosal site, d. the L-alanine pum at the apical site is Na-independent and yet ouabain sensitive. 15% of absorbed L-alanine is passively transported. (Supported by Grant 11-1455 from the Faculty of Medicine Research Funds.)


To study the relationship between dietary-induced increase in intestinal disaccharidase activities and disaccharide absorption, adult male rats were either fed a high starch low fat diet (HS) or a high fat low starch diet (HF) for 12 weeks. In the 12-week period, body weight changes, and amount of protein per intestinal segment were similar in the two groups of animals. The intestinal sucrase and lactase activities were significantly higher (p < 0.01) in the HS group than in the HF group. This was reflected in the significantly higher absorption of sucrose and lactose (p < 0.01) by the rats fed the high starch low fat diet (HS) than by the rats fed the high fat low starch diet (HF). In the HS group, the total TV decreased 0.164 cm3/cm L; mucosa decreased 0.147 cm3/cm L; muscle decreased 0.014 cm3/cm L; and the tissue matrix increased 0.07 cm3/cm L. The ratio of tissue volume to unit intestine length (TV/L) cm3 cm/L decreased significantly in the HS group compared to the HF group.

Supported by grants from Natural Sciences and Engineering Council of Canada (A6249), and NIH (AM52642).

CARMINATE UPTAKE BY SMALL INTESTINE OF RAT. Oleese S. Sack*, Robin A. Ruark* and Gary W. Randall*. (Span: 64.11, 64.9)

brand . Marketing, University of British Columbia, Vancouver, Canada, and Department of Pediatrics and Physiology, University of Arizona, Tucson, Arizona.

To investigate the carminate uptake by the small intestine of the rat, a biopsy was taken from the ileum of the rat. The biopsy was incubated in HN03 and assayed for carminate. The results showed that the carminate uptake by the small intestine of the rat was significantly higher for the rats fed the high starch diet than for the rats fed the high fat diet. The carminate uptake by the small intestine of the rat was also significantly higher for the rats fed the high starch diet than for the rats fed the high fat diet.

Supported by the Natural Sciences and Engineering Council of Canada (A6249), and NIH (AM52642).
65.1 SALIVA FLOW IN HEAT-STRESSED RATS DURING BEHAVIORAL THERMOREGULATION. Ingrid Schmidt*, Randy Kaul* and Richard Simon, Max-Planck-Institute of Chemical Ecology, Jena, Germany. Saliva flow has been measured in rats stressed by whole-body heating. The results show that saliva flow increases with body temperature, reaching a peak at around 40°C and decreasing thereafter. This increase is believed to be due to the release of neurochemicals that stimulate the salivary glands.

65.2 ROLE OF BROWN ADIPOSE TISSUE (BAT) ON THE HYPERTHERMIC RESPONSES OF RATS TO MORPHINE. J.A. Thornhill and M. Desautels*, University of Saskatchewan, Saskatoon, Sask., Canada. A model has been developed to determine how BAT contributes to the hyperthermic response of rats to morphine. The model predicts that BAT contributes significantly to the hyperthermic response, with the contribution increasing with increasing morphine dose. This suggests a role for BAT in thermoregulation in response to morphine.

65.3 THE EFFECT OF AMBIENT TEMPERATURE ON THE FEBRILE RESPONSES OF RATS TO ENDOTOXIN PYROGEN (ED) John T. Stitt and Steven C. Shimada* John B. Pierce Fdn Lab. Yale Univ. Sch. of Med. New Haven, CT 06510. Rats generally exhibit poor febrile responses to pyrogens at ambient temperatures (Ta) above thermoneutrality, and it is believed that at low Ta's, they are incompletely capable of generating any fever-like response. Indeed, we have shown that i.v. doses of ED that can elicit fevers in rats stressed at Ta-26°C, have no effect on body temperature (Tre) when administered to rats at Ta-2°C, indicating that the fever-like response is not due to specific activation of BAT. Supported by MRCCanada (PAS Project No. 10.4). 

65.4 Diurnal rhythm of menstrual hot flashes: Subjective report and physiological correlation. Fredi Kronenberg* and John A. Downey, Dept. Rehab. Med., College of Physicians and Surgeons, Columbia University, New York, NY 10032. Patterns of hot flashes in post-menopausal women with frequent flashes were studied to see if there is a diurnal rhythm of flares. Frequency (vaginal or rectal) and skin temperatures were recorded with an ambulatory temperature monitor at 30-min intervals for 24-hour periods during the last hour of each menstrual cycle. A high correlation was found between core and skin temperatures, as well as of autonomic and behavioral interaction. Supported by NIH grant AG 03367.

65.5 SIMULATION OF SHIVERING THERMOGENESIS: A MODEL BASED ON THE ACTIVITY OF THERMOSENSITIVE NEURAL STRUCTURES. Duu B. Hekjyvic* and James B. Morrison*, ( upon: E. W. Smith) Dept. Kinesiology, Simon Fraser University, Burnaby, B.C., V5A 1S6, Canada. The model simulates shivering thermogenesis based on the activity of thermosensitive neural structures. The simulation shows that shivering thermogenesis is not due to specific activation of BAT but rather to the activation of other thermosensitive neural structures.

65.6 BODY TEMPERATURE ELEVATION TO REPEATED EXERCISE IN DOGS: ADRENERGIC IMPLICATIONS. J. E. Greenleaf, A. Kuciba Uczekels, K. Krug, A. Hazet, and S. Kozlowski*, Polish Academy of Sciences, Institute of Experimental Medicine, Warsaw, Poland and NASA, Ames Research Center, Moffett Field, CA 94035. The effect of i.v. propranolol (0.25 mg/kg) on the inter-relationship of metabolic variables (blood lactate [LA], glucose, plasma free fatty acid [FFA], and osmotic concentrations), with the progressive elevation of muscle (TM), rectal (Tc), and hypothalamic (Th) temperatures, was measured in 9 male mongrel dogs (14.4 to 21.0 kg). Each dog performed 4 consecutive 30-min treadmill exercise-bouts (1.3 m/s, 12° slope) separated by 30-min rest periods that allowed temperatures to return to resting levels. Bout I to bout IV increased (P<0.05) Th, from 0.8 to 1.0°C (NS). In the 4 exercise-bouts heart (HR) and respiratory (RR) frequencies were increased (P<0.05) in units of 5.0 and 10/min, respectively. Plasma glucose progressively (P<0.05), [glucose] decreased progressively (P<0.05), and unattractability was unchanged. The only significant (P<0.001) correlations among the body temperatures and metabolic variables were between [FFA] and resting [FFA] (r=0.68). During subsequent exercise bouts, adrenergic blockade with propranolol completely inhibited the normal increases in Th, Tm, and TA and post-exercise [FFA] (r=0.59). These results suggest that the adrenergic pathway is involved in the control of body temperature during exercise and the subsequent decrease in plasma FFA.

We have demonstrated previously that certain blood chemical changes characteristic of the acute-phase reaction (APR) to systemic endotoxin (LPS) or intracerebral endogenous pyrogen (P) are not mediated by the 4-hour but rather by the 24-hour response. To determine whether the activation of the thermoeffectors of fever production per se, i.e., without a concomitant fever, could mediate these changes, we exposed New Zealand white rabbits for 3.5 h to a cold environment (Tc = 34.1°C) and measured their colonic (Tco) and ear skin (Tsk) temperatures, arterial (PaO2) and venous (PvO2) oxygen concentrations, and the succinoxidase (SO) activity of heart and liver mitochondria. The Tco of these animals was maintained at 39.9 ± 0.7°C, while the Tsk fell to 37.1 ± 0.7°C. However, the difference between the colonic and ear skin temperatures, and the levels of oxygen in the arterial and venous blood, became PO2 dependent. The Tco of these animals was maintained at 39.9 ± 0.7°C, while the Tsk fell to 37.1 ± 0.7°C. However, the difference between the colonic and ear skin temperatures, and the levels of oxygen in the arterial and venous blood, became PO2 dependent. Group I animals were kept at 37°C and Group II animals were cooled to 30-31°C and maintained at pH 7.5 (constant relative alkalinity) using combined systemic endotoxin (LPS) or intracerebral endogenous pyrogen (P). The APR induced significantly increased fluid loss (.49 g/min vs .32 g/min). The pH optimum for SO was 6.2, and the APR induced lactic acid production was noted. These data suggest that at low T the APR induced lactic acid production was greater in the P than in the R groups, indicating greater involvement of anaerobic energy sources in the APR of the P animals. Supported by NIH Grant No. PCM80-21895.


Circulatory adjustments occur at term of pregnancy which optimize the growth and survival of the offspring during this critical time before birth. To determine whether a subcutaneous infusion of P, a point source of hypothermia, would affect the regional blood flow, we measured the regional blood flow of nonpregnant (NP) and pregnant (P) does with 15-20 microspheres and calculated the blood flow rate to each organ. The P group was injected with 2 µg/kg of LPS 30 min before and during the onset of fever, 35 min after the iv injection of 2 µg/kg of S. enteritidis endotoxin (LPS). LPS induced decreases in the blood flow to brain, skin, liver, lungs, and kidney. However, the reduced blood flow to the placenta also occurred in the P rabbits. Peak heights and courses and mean arterial blood pressure in pregnant and nonpregnant animals were not significantly different in different vascular beds, the pattern of which is not altered at term of pregnancy in rabbits. We conclude that this redistribution of cardiac output during fever might cause fetal stress. (Supported by F.O.E. of Illinois, BRSG 01RCFSP-001, and HL 30260 and 30271)


To determine the effects of various levels of plasma cholinesterase inhibition on the ability to work (level treadmill, 9.10% min/min in the heat (35°C), adult, male rats were treated with malathion (M) or pyridostigmine (P). Treatment with M elicited a 35% inhibition of circulating cholinesterase levels while P elicited a 64% decrement. M treatment had no significant effects on endurance when the rats were run thermoneutrally (Tre = 43°C) while endurance was decreased by 33% (23.09 min vs 36.85 min) in P-treated rats. In M-treated animals and saline-treated controls, rates of heat gain were similar, but P treatment elicited significant increments in rates of heat gain (2°C/min vs .19°C/min) during exercise in the heat. While weight (water) loss during exercise in the heat was unaffected by M administration, P induced significantly increased fluid loss (1.09 g/min vs .32 g/min). Following exercise in the heat, significantly increased elevations in several clinical chemical indices of heat/exercise injury were noted in P-treated rats. We concluded from these studies that moderate cholinesterase inhibition, both thermoregulation and endurance are compromised. We hypothesize that the increased cholinergic activity due to the more intense cholinesterase inhibition resulted in increased fluid loss and more rapid onset of hyperthermic exhaustion.

IMMUNOHISTOCHEMICAL LOCALIZATION OF HIBERNATOR'S SUCCHONIDASE ACTIVITY IN HIBERNATING AND ACTIVE HAMSTERS AND GROUND SQUIRRELS. Jane L. Roberts, Dept. of Biology, Creighton Univ., Omaha, NE 68178.

To determine the effects of various levels of plasma cholinesterase inhibition on the ability to work (level treadmill, 9.10% min/min in the heat (35°C), adult, male rats were treated with malathion (M) or pyridostigmine (P). Treatment with M elicited a 35% inhibition of circulating cholinesterase levels while P elicited a 64% decrement. M treatment had no significant effects on endurance when the rats were run thermoneutrally (Tre = 43°C) while endurance was decreased by 33% (23.09 min vs 36.85 min) in P-treated rats. In M-treated animals and saline-treated controls, rates of heat gain were similar, but P treatment elicited significant increments in rates of heat gain (2°C/min vs .19°C/min) during exercise in the heat. While weight (water) loss during exercise in the heat was unaffected by M administration, P induced significantly increased fluid loss (1.09 g/min vs .32 g/min). Following exercise in the heat, significantly increased elevations in several clinical chemical indices of heat/exercise injury were noted in P-treated rats. We concluded from these studies that moderate cholinesterase inhibition, both thermoregulation and endurance are compromised. We hypothesize that the increased cholinergic activity due to the more intense cholinesterase inhibition resulted in increased fluid loss and more rapid onset of hyperthermic exhaustion.


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A microsomal membrane fraction was prepared by different techniques from cells isolated from the medullary thick ascending limb of Henle’s loop (TALh) from rabbit kidney. Chloride uptake by plasma membranes was measured by a rapid filtration technique. At 25 mM NaCl, 25 mM KCl, and 6 mM Cl⁻, chloride uptake at 25°C was 1.93 pmol/ml protein and was linear up to 35°C by physiological chloride. Removal of sodium resulted in a 10% inhibition of chloride uptake. Addition of bumetanide to sodium-free media had no effect on chloride uptake. When potassium was removed, chloride uptake also decreased to the level obtained in the presence of bumetanide. Again, no effect of bumetanide was seen in the potassium-free media. Addition of 10⁻⁴ M STS (a-catenadom-4'-isothiocyanato-stilbene-2,2'-disulfonic acid) to the medium produced no change in chloride uptake. These experiments provide the first direct evidence that the movement of chloride into TALh plasma membrane vesicles can be driven by sodium and potassium and inhibited by bumetanide. A conclusion hereof reached only indirectly in sodium and rubidium flux and tracer exchange experiments using the same vesicle preparation. These data strongly support the operation of a sodium, potassium, chloride cotransport system in active chloride reabsorption in the thick ascending limb of Henle’s loop. Supported by NIH AM29927, NIH GM307288, and the Max Planck Institute.

66.2 ACIDIC SODIUM AND PASSIVE CHLORIDE ION TRANSPORT IN PROXIMAL CONVOLuted TUBULES PERFUSED UNDER OIL. Deon W. Burhans, WRT, Dept of Physiology and Biophysics, University of Alabama in Birmingham, 35294.

Proximal convoluted (PCT) and proximal straight (PST) tubules perfused under oil with artificial ultrafiltrate (AUF) or simple electrolyte solution (SES) develop transcellular gradients for Na⁺ and Cl⁻. An ultrafiltrate (AUF) which allowed for rapid absorption of fluids (red froc 42304, 1983). To determine if these ion gradients demonstrate active Na⁺ and Cl⁻ transport, the electrical potential (P) was measured (Langf reference)...

66.3 OSMOTIC WATER PERMEABILITY OF THE IN VIVO RAT PROXIMAL CONVOLUTED TUBULE (PCT). Patricia A. Preisch and Christine A. Berry. Univ. of Calif., San Francisco, CA 94143.

Recent studies in the rabbit PCT find the transepithelial osmotic water permeability (Pₛₒ₆) is high (1960 ± 240) and that spontaneous volume absorption (Jᵥ) can be explained by less than 6 mOsm of luminal hypotonicity. The purpose of our studies was to determine the Pₛₒ₆ and driving force needed to explain Jᵥ in the rat PCT. Pₛₒ₆ was determined from Jᵥ and the mean isometric gradient (6.5). Rat PCT were perfused at 99 nl/min with an ultrafiltrate which was a 45% artificial hypoosmotic to rat plasma by the removal of 50 mM NaCl. This solution also contained 8.33 mM NaCl-γyand which we found to inhibit active transport along the entire perfused segment. Jᵥ was measured with H₂-insulin and Δ was calculated from measured osmolarities, obtained with a Ramsay-Brown type osmometer, of perfusate, collected fluid, and plasma. The Pₛₒ₆ was 1196 ± 196 mOsm and was dependent on the mixture of CO₂ in inspired air. The effect of acute hypocapnia and hypercapnia on urinary acidification processes participate in renal responses to acidosis, and ammonia was also measured with H inulin and A 71 was calculated from measured...
66.7 NEURAL REGULATION OF FLUID AND BICARBONATE ABSORPTION IN THE RAT KIDNEY. P.P. Shah*, M. LaPorte*, C. Sabo*, M. Laski* and Y.I. Chen. Univ. of IITinos Col. of Medicine, Chicago, IL. 

Previous studies in this laboratory have shown that noradrenergic receptor mechanisms could stimulate bicarbonate and fluid reabsorption in the rat proximal convoluted tubule (PCT) through alpha adrenergic receptor mechanisms. This study was designed to examine the effect of acute denervation on fluid and bicarbonate absorption in the rat PCT and cortical Na-K-ATPase. In situ microperfusion of the left kidney of pentobarbital-anesthetized, mannitol-treated dogs only 2.9±0.3-fold (N=3E) H-PAH/C-In ratios, in comparison to 20% polyacrylamide equilibrated with 100 mM NaCl and 5 mM NaHCO3 serves as a salt bridge between a Ag/AgCl reference electrode and the pH glass surface. The 90% response time of the silicon membrane yields a pH electrode which can continuously measure blood pH. Without the carbonic anhydrase enzyme the response times are approximately doubled. Removal of the silicon membrane yields a pH electrode which can continuously measure blood pH. When joined with a PO2 electrode (J. Appl. Physiol. 30:909, 1971) continuous rapid blood PCO2, pH and PO2 may be recorded. (Supported by NIH Grant AM27691). 


A newly synthesized prostaglandin analog, 5-(N-acetyl-DL-norvalincarbamoyl) furyl methyl 4-oxo-2-thiazolidinyl propyl benzoic acid, increases renal blood flow without increasing sodium excretion. To investigate the role of renal interstitial hydroxy carbonate (HCO3-), in this dissociation, comparisons were made with prostaglandin (PGE2), a natural prostaglandin that increases renal blood flow and is mililutec. Renal blood flow (RBF), interstitial pressure, fractional sodium excretion (FE Na%) and blood pressure (BP) were measured before and after sequential intrarenal infusion of PGE2 and the prostaglandin analog (0.15 µg/kg/min), 

<table>
<thead>
<tr>
<th>Treatment</th>
<th>RBF (ml/min)</th>
<th>BP (mm Hg)</th>
<th>IP (mm Hg)</th>
<th>FE Na%</th>
<th>BP (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>125±15</td>
<td>7.2±1.4</td>
<td>0.3±0.2</td>
<td>141±6</td>
<td>154±6</td>
</tr>
<tr>
<td>PGE2</td>
<td>168±12</td>
<td>12.0±1.7</td>
<td>3.6±1.0</td>
<td>135±6</td>
<td>133±5</td>
</tr>
<tr>
<td>PG Analog</td>
<td>216±21</td>
<td>6.0±1.6</td>
<td>1.0±0.4</td>
<td>136±9</td>
<td>133±9</td>
</tr>
</tbody>
</table>

The prostaglandin analog is similar to PGE2 in that it increases RBF, but differs in that it does not increase renal interstitial pressure or sodium excretion. This observation suggests that renal interstitial pressure is a crucial factor linking renal hemodynamics to sodium excretion in the dog.

Endoxin shock was produced in rabbits with 7 mg/kg E. coli endoxin. Sham group rabbits received vehicles for both endoxin and nordihydroguaiaretic acid (NDGA), a lipooxygenase inhibitor. Eight of 8 endoxin rabbits receiving the vehicle died. Preperitoneal injection of rabbits with a 7 mg/kg iv bolus plus a 5 hr constant infusion at 2 mg/kg/hr post-endoxin did not improve survival. Prostacyclin and thromboxane concentrations in venous plasma were (ng/ml): Minus after endoxin 1. 6-keto-PGF1α 1.60 ± 0.30 0.96 ± 0.23 0.95 ± 0.21 0.8 ± 0.17 0.9 ± 0.17 1.1 ± 0.1 1.2 ± 0.1


Isolated, perfused hearts and left-ventricular (LV) papillary muscles were used to evaluate cardiac effects of endoxin (ET) shock in guinea pigs. In vivo administration of ET (50mg/kg) 1 hr prior to sacrifice produced LV contractile depression and anotropic dysfunction of hearts perfused using a modified Langendorff technique. Shock hearts (n=8) exhibited decreased contractile force, decreased heart rate, and increased control heart rates. LV performance of shock hearts remained depressed as LV end-diastolic pressure (EDP) was incrementally increased (isovolumic LV balloon technique) from 4 to 10 mmHg. At EDP=10 mmHg, control and shock hearts generated peak systolic pressures of 85.0±21.6 and 53.3±7.6 mmHg, respectively. These data suggest that lipooxygenase inhibition in the rabbit model of endoxin shock has no effect on the rate of survival. Were was no statistically significant indication that the shock may be responsible for a variety of metabolic alterations reported to occur during sepsis and shock.


Using a model of canine anaphylaxis produced by Ascaris endotoxin, we examined lymph flow and protein flux in endoxin shock. This specific experimental model developed an increased cardiac output, increased total peripheral resistance, increased heart rate, normal or slightly decreased mean arterial blood pressure and increased body temperature. All animals became anorectic and exhibited signs of decreased hemodynamic function. The mean arterial pressure increased in the first 2 h of shock and returned to baseline values by 3 h. After 5 min, the mean arterial pressure increased and returned toward baseline values by 3 h. After 5 min, the mean arterial pressure increased and returned toward baseline values by 3 h.

67.5 BLOOD VOLUME CHANGES IN ANAPHYLACTIC SHOCK. W.H. Wagner*, W.A. Miller*, P.L. Smith* and E.R. Blocher, Johns Hopkins Med. Inst., at Baltimore City Hospitals, Baltimore, MD 21224

To study the role of complement in endoxin shock, we used a model of canine anaphylaxis produced by Ascaris endotoxin (Ag). We examined the lymphatic circulation of the abdominal lymph nodes. Our results suggest that lymphatic circulation is normal in the abdominal lymph nodes after endoxin injection. The thoracic duct was cannulated prior to injection of endotoxin. This study attempted to determine the rate and extent of these changes in the dog following a bolus injection of E. coli endotoxin. The thoracic duct was cannulated in 5 animals. The lymphatic duct was opened in the 8th intercostal space. An experimental group (n=6) received 0.5 mg/kg endotoxin in saline via the femoral vein. In control group (n=6) received only saline. Within 10 minutes post-endoxin, LF rate in the thoracic duct had increased five-fold, returning toward baseline values by 3 h. By 5 min, after endoxin injection, there was an increase in total protein lymph/plasma (L/P) ratio, plasma protein clearance (ml/min), and plasma albumin protein flux (mg/min). Serum and endotoxin levels increased to 20 times baseline within 2 min of endoxin injection. Serum albumin, albumin concentration, and plasma albumin concentration were increased in endoxin shock. This study suggests that endoxin injection increases LF and increases L/P protein ratio suggesting increased protein permeability in the hepatosplanchnic vasculature.


Arterial electrolytes and enzyme profiles were monitored during a chronic (14-21 days) hyperdynamic peritonitis model. This specific septic model developed an increased cardiac output, increased total peripheral resistance, increased heart rate, normal or slightly decreased mean arterial blood pressure and increased body temperature. All animals became anorectic and exhibited signs of decreased hemodynamic function. The mean arterial pressure increased in the first 2 h of shock and returned to baseline values by 3 h.

Recent reports from this laboratory have described glucose and insulin alterations associated with acute endotoxin shock. The present study was undertaken to document the glucose and hormone changes which occur in the dog during the development of atelectasis without an appreciable low VA/Q region. Sustained sepsis increased in conscious unrestrained rats by IP administration of a pooled fecal microbial extract (as estimated by the coronary blood flow (CBF) and urinary volumes measured in vivo on days 1-4 postinfection, using radioactive microspheres. Sepsis rats had a consistently elevated (52%) CBF which was not linearly related to the CBF of gram-negative septic rats. A similar study of 400 rats with comparable septicosis also showed a consistently elevated CBF over a range of sepsis-induced CBF levels (estimated as CO x MAP). A similar study of 400 rats with comparable sepsis-induced CBF levels (estimated as CO x MAP) failed to show any evidence of enhanced CBF in a range of sepsis-induced CBF levels (estimated as CO x MAP). A similar study of 400 rats with comparable sepsis-induced CBF levels (estimated as CO x MAP) failed to show any evidence of enhanced CBF in a range of sepsis-induced CBF levels (estimated as CO x MAP). A similar study of 400 rats with comparable sepsis-induced CBF levels (estimated as CO x MAP) failed to show any evidence of enhanced CBF in a range of sepsis-induced CBF levels (estimated as CO x MAP). A similar study of 400 rats with comparable sepsis-induced CBF levels (estimated as CO x MAP) failed to show any evidence of enhanced CBF in a range of sepsis-induced CBF levels (estimated as CO x MAP).
8.5 THE ALVEOLAR UPTAKE OF HALOTHANE USING HIGH FREQUENCY OSCILLATION. E. Jane McCarthy*, R.H. Abbrecht, J. Langton*, W.G. Keefe*, S. Muldoon. Departments of Physiology, Medicine, and Anesthesiology, Uniformed Services University, Bethesda, Maryland 20814.

The objective of this study was to determine the effect of high frequency oscillation (HFO) on the alveolar uptake of halothane. HFO (400 cycles/min) was administered to six awake sheep using a double-lumen endotracheal tube. Blood halothane concentrations were measured at frequent intervals during a 20 min period following onset of HFO administration. Halothane content was determined by gas chromatography. In each sheep, drug was withdrawn from a single lung at frequent intervals during the 20 min period.

The results showed that HFO significantly reduced the alveolar uptake of halothane. In all sheep, Pa_Hal increased progressively (P < 0.05) with increasing frequency at each time studied. The results of this study show that alveolar uptake of halothane increases with increased frequency. This study supports the hypothesis that HFO operates via the mechanism of enhanced diffusivity. (Supported by U.S. NIH Grant No. HL-25316)

8.6 PULMONARY VENTILATION, AIRWAY EPITHELIAL FUNCTION AND LUNG GENERAL TUESDAY PM


Stimulation of bronchial C-fibers evokes reflex increase in secretion by tracheobronchial glands. We have carried out experiments to determine whether pulmonary delivery of low frequency HFO (10-15 Hz) results in increased secretion by tracheobronchial glands.

Afferent pulmonary C-fibers reflexly increase secretion from the submucosal glands of the trachea. However, HFO (10-15 Hz) does not increase the maximum rate at which hillocks appear when applied to the submucosal glands of the trachea. We therefore carried out experiments to determine whether pulmonary C-fibers reflexly increase secretion from tracheal glands. (Supported by National Institutes of Health Grant HL-24136 and HL-07192 and a grant from Cystic Fibrosis Research Inc.)


The purpose of this study was to determine alveolar permeability (AP) in awake newborn and adult sheep, and to assess longitudinal growth in AP. We studied the effects of capsaicin (10-20 mg/kg) on AP in newborn and adult sheep. Capsaicin (10-20 mg/kg) increased the maximum rate at which hillocks appeared to 35.3 ± 10.6 hillocks/min (P < 0.05). The results of this study show that alveolar permeability increases with increased frequency. This study supports the hypothesis that HFO operates via the mechanism of enhanced diffusivity. (Supported by U.S. NIH Grant No. HL-25316)


The electrical properties of monolayer cell cultures of dog tracheal epithelium were studied in a 50/50 mixture of Dulbecco's modified Eagle medium and Ham's nutrient F12, containing 3% fetal calf serum, and cultured on porous polycarbonate filters in a humidified, 5% CO2, 95% air atmosphere at 37°C. The cultures were examined using the method of Jones et al., 2) newborn lambs have a significantly lower AP ratio, 3) AP increases with age and with nutritional status. In conclusion, AP can be measured in awake sheep using the method of Jones et al., 2) newborn lambs have a significantly higher AP ratio, 3) AP increases with age and with nutritional status. (Supported by National Institutes of Health Grant HL-24136 and HL-07192 and a grant from Cystic Fibrosis Research Inc.)


The purpose of this study was to determine the effect of bradykinin (Bk) on canine tracheal epithelium, possibly due to an increase in prostaglandin production. (Supported by USPHS PPG HL-24136)

The alveolar epithelium may play a major role in lung water homeostasis by actively transporting electrolytes across it. Some factors controlling this process are unknown. As an in vitro model, alveolar type II cells are used to study the surface activity. The addition of 10-4 M 8-bromo-adenosine 3':5' cyclic monophosphate (8-Br-cAMP) resulted in increased Isc from 2.9 + 0.79 u/cm2 (Mean ± S.E.) to 6.9 + 0.67 u/cm2 at 35 minutes (P<0.05). After an initial rise in Isc, values fell back to 2.9 ± 0.23 u/cm2 at 60 minutes (P<0.01). The addition of agents that increase intracellular cAMP resulted in similar changes. 3-Isobutyl-1-methyl xanthine produced the largest response and abolished the hysteresis of the membrane. However, inhibiting cAMP synthesis with adenosine 3'-phosphoribosyl transferase (AICAR) abolished the hysteresis of the membrane. Additionally, estrogen and sabotage inhibition abolished the hysteresis seen with 8-Br-cAMP and agents thought to increase intracellular cAMP.

68.12 SURFACE TENSION ACTIVITY OF COTTON DUST COMPONENTS. G. Gossypol, rutin and catechin (major components of the cotton plant) resulted in minimal changes when the addition of histamine, bradykinin, and carbamylicholine produced no effect. In summary, we have demonstrated an increase in Iac and a decrease in the yield of high purity Type II alveolar epithelial cell suspensions from rat lungs that does not require adherence to a surface. The technique involves buoyant density gradient separation (1.025-1.070 g/ml) followed by unit gravity velocity sedimentation. Briefly, isolated, lysed and perfused rat lungs are inflated first with frog Ringer's solution containing 8% dextran and then washed in saline solution (37°C, 20 min each). The lungs are minced and sequentially filtered through gauze, 175 μm and 35 μm nylon cloth. This results in a cell suspension containing about 10^7 cells/rat of 90% type II cells which are 90% viable by trypan blue dye exclusion. The major contaminant is small fragments. These type II cells form domes in 3 days when plated on plastic. This preparative method results in high purity, adequate yield, viable Type II cell suspensions, and has the advantage of not requiring adherence to a surface. (AHA-BlAA 101-703, IL 26203.)

Intravenous administration of oleic acid is known to impair the capillary endothelium and cause pulmonary edema. Kinins are potent edemagenic agents in systemic tissues, producing an increase in vascular permeability to proteins and water. We therefore decided to investigate the relationship of kinins and CE during oleic acid induced pulmonary edema in the dog. Mongrel dogs of either sex were anesthetized with pentobarbital sodium, mechanically ventilated, and catheters placed into the carotid artery, pulmonary vena cava, and femoral vein. Oleic acid (35 mg/kg) was infused into the femoral vein, and arterial and venous blood samples removed at 30 min intervals. Plasma kininogen levels were measured as an index of the rate of kinin production. The base line arterial plasma kininogen values were 3.04 ± 0.25 pg bradykinin (BK)/ml (mean ± S.D.). Within 30 min of oleic acid infusion, plasma kininogen depletion reached 0.59 ± 0.09 pg BK/ml. The levels of plasma kininogen stayed close to 0.3 pg BK/ml for the rest of the experiment. The arterial serum CE value prior to the treatment was 1.76 ± 0.46 units and increased to 118% after 30 min treatment. These findings suggest increased liberation of kinins into the circulation — and increased CE activity may play a role in the development of acute lung injury.

68.18 LIPOPROTEIN DISTRIBUTION IN SHEEP LUNG LYMPH. T.M. Forte*, C.E. Cross*, R.A. Gunther* and G.C. Kramer* (SPON: J.C. Schooley). Dormer Laboratory, Univ. of Calif., Berkeley 94720 and Departments of Physiology, Medicine, and Surgery, Univ. of Calif., Davis 95616

Lipoprotein distribution in lung lymph was studied in order to determine whether there was selectivity of lipoprotein transport across the lung capillary bed and whether modification of lipoproteins occurred in the lymph. Mature sheep lung lymph was collected over several hours and lipoproteins recovered from lymph compared with those of plasma. Lymph and plasma triglyceride levels were 6.1 ± 1.2 and 12.0 ± 3.0 mg/dl, respectively, with a lymph to plasma (L/P) ratio of 0.50. Lymph and plasma cholesterol values were 18.8 ± 5.8 and 42.1 ± 10.5 mg/dl, respectively, L/P ratio = 0.45. Very low density lipoproteins were absent from both plasma and lymph. High density lipoproteins (HDL), d = 1.063-1.21 g/ml and low density lipoproteins (LDL), d < 1.063 g/ml were isolated from lymph and plasma. lymphp HDL and LDL levels were approximately 50% those of plasma but were present in the same general proportion. lymph HDL = 47 ± 8 mg/dl and LDL = 52 ± 17 mg/dl. The LDL fraction of lymph contained particles which were enriched in phospholipid and free cholesterol. These particles had unusual electron microscopic morphologies and were not seen in plasma. Studies suggest that lipoproteins transported in the lung lymph undergo physical and chemical modifications in this fluid compartment.

68.19 UNRELIABILITY OF THE THERMODILUTION MEASUREMENT OF LUNG WATER IN HYDROCHLORIC ACID LUNG INJURY. P.V. Carlisle*, P.M. Butler*, M. Hojarad* and B.A. Gray, Dept. of Medicine, VA Med. Ctr. and Univ. of Oklahoma, Oklahoma City, OK 73104

We investigated the relationship between the extravascular volume of distribution for thermal indicator (ETV) and extravascular lung mass (ELM) in dogs with focal lung injury produced by the bronchial instillation of hydrochloric acid (group I) or diffuse injury produced by alloxan or CINTU (group II). Lung injury in group I was either bilateral (IC) or restricted to one lung with a tracheal divider (ICT) to permit measurement of the percentage of blood flow to the injured lung (QI) with 99Tc labelled macroaggregated albumin. ETV was determined from the difference in mean transit times of thermal and dye dilution curves recorded in the aorta after right and left atrial injections. ETV and shunt were measured four hours after lung injury. ELM and extravascular wet to dry weight ratio (W/D) were determined postmortem. The W/D was 9.15 ± 1.29 (SD) for Group I and 10.98 ± 2.2 for Group II. The ETV/ELM ratio was 0.31 ± 0.14 for Group I and 1.09 ± 0.16 for Group II (P < 0.01). Shunt was 18 ± 12% for Group I and 44 ± 22% for Group II (P < 0.01). We conclude that the thermal dilution method fails to detect edema in focal lung injury characterized by redistribution of blood flow and low shunt. (Supported by Medical Research Svc. of the V.A., N.I.H. Grants Ml 07207, Ml 07524 & Ml 30450 and the Parker B. Francis Fndn.)

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6.01 TUBULOGLOMERULAR FEEDBACK MEDIATED REDUCTIONS IN DIRECTLY MEASURED GLOMERULAR CAPILLARY PRESSURE IN RESPONSE TO INCREASED DISTAL VOLUME DELIVERY. L.G. Navar, M. Reddington*, P. Bell and D. Rhode. Univ. of Alabama in Birmingham, Birmingham, AL 35294

Increases in flow rate to the macula densa segment stimulate tubuloglomerular feedback to reduce glomerular filtration rate. While it is generally thought that there are associated decreases in glomerular capillary pressure (GP) resulting from increases in efferent arteriolar resistance, our recent study (Am J Physiol 253:F746-52) indicated that directly measured GP in Munich Wistar rats (MWR) does not decrease as long as the filtration process is not interrupted. To evaluate this issue further, GP was measured in MWR during increases in flow rate achieved by perfusing an isotonic electrolyte solution into an unblocked late proximal convolution. Arterial pressure averaged 1155 ± 5 mmHg and proximal tubule hydrostatic pressure (PSP) averaged 141 ± 5 mmHg. In 21 tubules from 10 rats, perfusion at 24 ± 2 μl/min decreased GP from 3513 ± 74 to 4722 ± 102 mmHg. Upon cessation of perfusion, GP returned to 5621 ± 5 mmHg. The statistically significant decrease in GP averaged 1021 ± 77 mmHg. These results demonstrate that GP does decrease during increased distal delivery even when the tubule is not blocked and support the hypothesis that changes in different arteriolar resistances are primarily responsible for feedback mediated reductions in GFR. (Supported by NIH Grant HL18416)

6.02 TUBULOGLOMERULAR FEEDBACK RESPONSES DURING CALMODULIN INHIBITION WITH TRIFLUOPOREFAZINE IN THE RAT. P. Urwin Bell and Mary Reddington*. University of Alabama in Birmingham, Birmingham, AL 35294

In recent studies, we have suggested that cytosolic calcium within the macula densa cells serves to transmit signals from distal tubules to the glomerulus via tubuloglomerular feedback. Since calcium binding proteins, such as calmodulin, have been implicated in the intracellular actions of calcium, we tested the effects of inhibition of calmodulin activity with trifluoperazine (TFP) on tubuloglomerular feedback responses. In the rat, SPF was measured during retrograde microperfusion for up to 5 minutes at 15 ml/min. Perfusion with a isotonic Ringer's solution (IRS) resulted in a decrease in SPF of 10.7±0.9 mmHg (n=18). With the addition of 50 μM TFP to IRS, SPF was decreased by 11.1±2.9 mmHg (n=8); with 75 μM TFP, SPF feedback response was 1360±5 mmHg (n=8). The rate of decrease in SPF in response to the initiation of perfusion with TFP was the same as with IRS alone. After cessation of perfusion, however, recovery of SPF to preinfusion values was significantly prolonged in tubules perfused with TFP (69% vs 100% at 30 min). Accordingly, these results suggest that calmodulin does not directly mediate the effects of macula densa cytosolic calcium to transmitafferent arteriole signals. In contrast, since calmodulin can stimulate transport, the delay in the return of SPF to control values may be due to an impaired ability of the macula densa cells to lower cytosolic calcium.


Captopril administration inhibits angiotensin II (AII) formation and produces natriuresis and hypotension in sodium deficient dogs. Angiotensin II infusion (3 ng/kg/min) into dogs treated with captopril restored urinary sodium excretion and arterial pressure within 3 days to levels observed in untreated sodium deficient dogs. In the present study we evaluated the effects of des-aspl-angiotensin II (AIII) on arterial pressure, plasma aldosterone concentration (PAC), plasma renin activity (PRA), urinary sodium excretion (UnaV), effective renal plasma flow (ERPF), fractional Na reabsorption (FNaR), sodium reabsorption (NaRe), fractional Na excretion (FNaE), fractional Na excretion (FNaE), renal blood flow (RBF), glomerular filtration rate (GFR), and plasma renin activity (PRA). The results indicate that AIII infusion at rates of 5 to 12 ng/kg/min decreases arterial pressure within 3 days to levels observed in untreated sodium deficient dogs. However, PRA, PRA, and PRA and PRA did not change significantly. While UnaV decreased from 1.94 to 1.18 mEq/day, ERPF decreased from 201 to 160 ml/min, and GFR decreased from 84 to 76 ml/min. These data demonstrate that, like AII, AIII stimulates tubuloglomerular feedback. However, unlike AII, AIII has little or no effect on arterial pressure or aldosterone secretion. (Supported by NIH grants HL09971


The aim of this study was to determine the role of changes in renal artery pressure (RAP), renal hemodynamics, and tubular reabsorption in mediating the natriuretic and antinatriuretic actions of AII. AII formation was blocked with SQ-14225 and AII was infused iv at rates of 5, 15, 45, 135, 405, and 1215 ng/kg/min for 30 min at each dose while RAP was either servocontrolled or permitted to increase. To examine the effects of inhibition of calmodulin activity with trifluoperazine (TFP) on arterial pressure, aldosterone secretion, Renin Renin activity (PRA), urinary sodium excretion (UnaV), effective renal plasma flow (ERPF), and glomerular filtration rate (GFR) in sodium deficient dogs. The results indicate that AII infusion rates of 45 ng/kg/min and below, urinary Na excretion increased, while fractional Na excretion (PRA) and RBF were not significantly different from the values observed when RAP was allowed to increase. These data indicate that the effect of the intact kidney, even very large doses of AII cause antinatriuresis when rap is prevented from increasing. The natriuretic effect of high doses of AII is caused by increased RAP which appears to decrease proximal tubular Na reabsorption. (Supported by NIH grants HL 23502, HL 11678 and the miss. Heart Assoc.).

6.05 ANGIOTENSIN II (AII) CONSTRISTS PGLOMERULAR VESSELS IN THE PRESENCE OF ADENOSINE. John E. Hall, Joey P. Granger and Andre P. J. Preston. Univ. Miss. Med. Ctr., Jackson, Miss. 36216

The present study was designed to test the hypothesis that high renal levels of adenosine (Ado) may greatly enhance the vasoconstrictor action of AII primarily in preglomerular vessels. In normal dogs, Ado infusion (20 ng/kg/min) iv with renal artery pressure (RAP) maintained constant decreased renal blood flow (RBV) to 61% of control, increased filtration fraction (FF) to 173% of control, and did not change GFR. After intrarenal infusion of 1 ml/min of Ado, RAP (20 ng/kg/min) decreased RBP and CFP to 61% and 61% of control, respectively, due to large decreases in preglomerular (BPc) after inhibition of tubuloglomerular feedback (TOBF) by occluding the ureter during mannitol diuresis, AII increased RAP markedly but did not alter RBP, however, after intrarenal Ado infusion and inhibition of TGF, AII raised RAP, decreased RBP, and Pco2 to 102 ± 7 and 155 ± 7% of control, respectively, while decreasing RBP to 59 ± 5% of control. These data indicate that while the effect of Ado on tubuloglomerular feedback is not significant per se, the high levels of Ado that are normally localized in postglomerular vessels, Ado may increase RAP markedly when renal levels of Ado are elevated. These results also suggest that Ado and AII could play a role in lowering GFR when renal Ado and AII levels are both elevated, as in renal ischemia. (Supported by NIH grants HL 23502 and HL 11678 and by the miss. Heart Assoc.)


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DOSE RESPONSIVENESS OF THE RENAL VASCULAR TISSUE TO SELECTIVE ADENOSINE RECEPTOR AGONISTS. Robert D. Murray and Paul C. Churchill, Hypertension Research Lab., Henry Ford Hospital and Dept. of Physiology, Wayne State University, Detroit, Michigan 48202.

We have previously reported (Fed. Proc. 42(5):1201, 1983) that 1 μM 2-ethylcarboxyalkyladenosine (NECA) increased flow rate when infused into isolated canine renovascular preparations. We now have evidence for dose-dependent stimulation of constant pressure. 1 μM cyclicadenosine (CHA) had no effect on flow rate. In the present studies, we have determined the dose-dependency of total renal resistance to CHA, a selective A1 adenosine receptor agonist, and to NECA, a selective A2 adenosine receptor agonist. Kidneys isolated from female Sprague-Dawley rats were perfused at a constant flow rate (initial perfusion pressure of 90 mm Hg) and increasingly higher doses of agonist (10-9 through 10-4 M). Perfusion pressure was monitored for 4 minutes following initiation of each dose. CHA (n=7) in doses of 10-9 to 10-7 M caused increases in perfusion pressure (vasoconstrictor) in most of the experiments, but was vasodilatory at doses of 10-8 M and higher. These results support the hypothesis that both A1 and A2 adenosine receptors are present within the renal vasculature and that adenosine receptor agonists may either increase or decrease renal vascular resistance in a dose-dependent manner.

Supported by NIH grant HL-20802-01.

ACTION, AND MECHANISM OF ACTION, OF VERATRINE ON RENIN RELEASE. F. C. Churchill, M. C. Churchill, and F. D. McDonald, Wayne State University, Detroit, Michigan 48202.

It is known that increased activity of the renal nerves stimulates renin secretion by a beta-adrenergic mechanism. The goal of these experiments was to develop an in vitro model of neurally-mediated renin secretion. Veratrine produces a dose-dependent depolarization of nerve terminals resulting in neurotransmitter release. Rat renal cortical slices were incubated at 37°C in a buffered, oxygenated, physiological salt solution containing various concentrations of veratrine. As can be seen in the table below, veratrine increased renin secretion in a concentration-dependent manner. Denervation of the kidneys 3-5 days prior to the experiments nearly abolished the stimulatory effect of 10-7 M veratrine (6.4 ± 0.5 μU/g/30 min versus 5.4 ± 0.4 for 0 veratrine). These results are consistent with the hypothesis that veratrine stimulates renin secretion by inducing release of norepinephrine from nerve terminals in the preparation.

Veratrine, M
Renin Secretory Rate, μU/g/30 min
0 5.4 ± 0.4
1 x 10-5 5.9 ± 0.4
2 x 10-5 6.8 ± 0.6
5 x 10-5 10.4 ± 0.8
1 x 10-4 10.9 ± 0.6

EVOLUTION AND REGRESSION OF JUXTAGLOMERULAR HYPERTROPHY FOLLOWING CAPTOPRIL ADMINISTRATION. Bailey D. Sibbens, Baylor College of Medicine, Houston, Texas 77030. Merritt L. Opdenorth and Sharon E. Smith, University of Texas Medical School, Houston, Texas 77025.

Morphologic analysis of the kidneys was done on control rats and on rats given normal saline plus 4.7 mg/kg captopril daily for up to 7 months. Blood pressure, plasma renin activity (PRA) and angiotensin I converting enzyme (ACE) were determined at monthly intervals for 6 months. Renal tissue was examined by light and electron microscopy. Hypertrophy of the juxtaglomerular apparatus (JGA) was prominent at 3 months. At 7 months, the JGA rectangular area averaged 10,342 ± 2,731 μm2 which was statistically greater than normal postnatal control. The size of the JGA was noted as early as 2 months after cessation of captopril but slight hypertrophy was still occasionally seen at 4 mo. post-procedure. These results indicate that veratrine inhibits the normal inhibitory feedback of the renin-angiotensin system resulting in marked stimulation of the JGA with consequent hyperplasia and hypertrophy which can be reversed by cessation of captopril.

HEPATIC EXTRACTION OF RENIN (R) ALLOTTED BY CAPTOPRIL (C). Joan A. Keiser, Terry J. Oppenorth, and Juan C. Romero, Mayo Clinic and Foundation, Rochester, Minn. 55902.

It is hypothesized that hepatic extraction of R by the liver may be regulated by circulating angiotensin II (AII). In the present study hepatic extraction of R was measured in anesthetized dogs before and after administration of captopril. During 1 hr post-surgical stabilization a sulfobromophthalein (BSP) infusion was initiated. Hepatic extraction by the liver was used to calculate hepatic plasma flow (HPF). In 3 dogs plasma renin activity (PRA) averaged 9.0±3.1 μU/ml/hr during the control period and rose to 20.5±4.4 after 1 hour of C infusion. Hepatic renin extraction increased from 7.4±2.7% to 17.6±4.9% during treatment conditions. Administration of C resulted in a significant fall in R extraction to 31.9±4.4 (P<0.05), however, HPF was unchanged (21.5±2.7 to 22.9±4.9 ml/min). Mean arterial pressure (MAP) fell from 85±10 to 68±9 mmHg after administration of C. During treatment the post-CAPACOCANGE of C was no different than that of C alone. During the two periods, respectively. In several dogs AII was infused in addition to C at a dose sufficient to resolve MAP to pre-C levels, samples were collected after an additional 30 min. The AII infusion did not alter HPF but did dose-dependently increase PRA and AII values (9.0±2.8), however, R extraction remained blunted (36.9±4.2%). From the present experimental data we conclude that compensatory enzyme inhibition following C administration in dogs anesthetized with sodium pentobarbital, blood viscosity was altered either by changes in red blood cell concentration (hematocrit, Hct) or by changes in plasma viscosity (P). PGE2 administration in dogs perfused with heparinized blood up to 65 percent Hct can also be correlated with renal vasoconstriction. The renal release found following extreme levels of hemocoencentration (above 65 percent Hct) and hemodilution (below 25 percent Hct), despite the renal vasoconstriction, reflects the overriding effect of non-augmented activation. (Supported by NHLBI Research Grant HL-18195 and NRSA Grant HL-07114)
69.13  
PLASMA RENIN ACTIVITY (PRA) AND ANGIOTENSIN CONVERTING ENZYME (ACE) LEVELS ARE DETERMINED BY THYROID FUNCTION L.M. Reznick* and J.M. Laragh, Cardiovascular Center, Cornell University Medical College, New York, NY 10021.

In order to study thyroid function and the renin-angiotensin system in human hypertension (HiBP), we measured PRA, T3(h), T4, and ACE before and after 300 mg. of thyrotropin-releasing hormone (TRH) in 20 euthyroid normotensive (NL-BP) and 24 HiBP subjects. Mean arterial pressure was normal for NL-BP (107±10 mmHg) and 145±26 mmHg in HiBP. T3(h) and T4 were normal for NL-BP (1.1±0.1 pmol/l) and 3.2±0.6 pmol/l in HiBP (P<0.005). ACE levels were normal for NL-BP (272±20 U/ml) and 157±11 U/ml in HiBP (P<0.001).

Results (mean±SEM) for HiBP were:

- T3(h) (nmol/l) and T4 (pmol/l)
- ACE (U/ml)

<table>
<thead>
<tr>
<th>T3(h)</th>
<th>T4</th>
<th>ACE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1±0.1</td>
<td>3.2±0.6</td>
<td>157±11</td>
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69.14  

Experiments were designed to develop a method to produce chronic selective pharmacological blockade of brain angiotensin II (AII) receptors or brain angiotensin converting enzyme (ACE). The pressor responses to infusions of AII were measured and to an intraventricular (ivt) bolus injection of AII (100 ng) were recorded in conscious Sprague-Dawley rats that had been instrumented with a femoral vein and a femoral artery catheter inserted transitorily into the lateral ventricle (LV). After a 5-day ivt infusion of 3 Barb-AII (barbital), pressor responses were retested. In a separate group of rats, the pressor responses to ivt ivt injection of AII was totally blocked while the dose response curve to iv AII was slightly diminished. Teprotide (10 ng/hr ivt) for 5 days produced significant depression of the pressor response to ivt AII but had no effect on the dose response curve to iv AII. ACE levels were measured before and after 5-day ivt infusion of the ACE inhibitor teprotide.

69.15  
EFFECT OF ELEVATED BLOOD PRESSURE, ALDOSTERONE AND RENIN ON RENAL SODIUM RETENTION. Janal N. Bitar*, Ammar A. Rizkallah and Ali D. Dhib*, Dept. Physiology, Faculty of Medicine, American University of Beirut, Lebanon.

Aortic stenosis produces a fluid and salt retaining state in 3-kidney salt hypertensive rats. The technique involves retrograde kidney perfusion from the renal veins via the kidneys, and then through the renal arteries and dorsal aorta. Sodium retention in 7 and 30-60 days post-stenoscopic hypertensive rats was 70% greater than in normotensive rats. A significant change was observed in Na retention in the clipped kidney of the 1 day post-stenosus. However, the去年同期 elite kidney showed similar aldosterone concentrations than the control and the post-60 days post-stenoscopic rats had higher aldosterone plasma concentrations than the controls. Therefore, the post-60 days post-stenoscopic rats had higher plasma aldosterone concentrations than the controls and the 60 days post-stenoscopic rats showed lower aldosterone plasma levels. The plasma renin activity of the 1 day post-stenosus rats showed 66% higher activity than that of the sham operated control rats with no significant change in the 30-60 days post-stenosus. Therefore Na retention may be mediated by aldosterone in the 7 days post-stenoseus period but pressure autoregulation was abolished during UO, UO+Ch, respectively.

69.16  
EFFECTS OF CAPTOPRIL ON THE GENESIS OF NOREPINEPHRINE-INDUCED MALIGNANT HYPERTENSION. Thomas E. Lohmeier, Robert G. Carroll, Allison J. Brown* and Larry J. Tillman*, Univ. of Miss. Med. Ctr., Jackson, MS 39216.

Infusion of progressively higher rates of norepinephrine (50 ng/min) for 6 days--

69.17  
NATRIURETIC RESPONSE TO 5-BLOCKADE IN DOCA-SALT HYPERTENSIVE DOG. T.J. Burke, H.R. Walker, and A.L. Erickson* Univ. Colorado, Boulder, CO 80302.

A study on the effect of elevated blood pressure, insulin and aldosterone on renal Na retention in 5-kidney salt hypertensive rats. The technique involves retrograde kidney perfusion from the renal veins via the kidneys, and then through the renal arteries and dorsal aorta. Sodium retention in 7 and 30-60 days post-stenoscopic hypertensive rats was 70% greater than in normotensive rats. A significant change was observed in Na retention in the clipped kidney of the 1 day post-stenosus. However, the去年同期 elite kidney showed similar aldosterone concentrations than the control and the post-60 days post-stenoscopic rats had higher aldosterone plasma concentrations than the controls. Therefore, the post-60 days post-stenoscopic rats had higher plasma aldosterone concentrations than the controls and the 60 days post-stenoscopic rats showed lower aldosterone plasma levels. The plasma renin activity of the 1 day post-stenosus rats showed 66% higher activity than that of the sham operated control rats with no significant change in the 30-60 days post-stenosus. Therefore Na retention may be mediated by aldosterone in the 7 days post-stenoseus period but pressure autoregulation was abolished during UO, UO+Ch, respectively.

69.18  
Histamine H-1 Receptors and Ureteral Occlusion-Induced Renal Vasoconstriction in the Dog. R.O. Banks and D.S. Jacobson. Department of Physiology, University of Cincinnati College of Medicine, Cincinnati, OH 45267.

We evaluated the mechanism by which ureteral occlusion (UO) causes inisipial renal vasodilation. Five adult dogs (19-23 kg) were anesthetized with pentobarbital. Renal arterial pressure (RAP) was measured with a femoral arterial catheter. Saline or the histamine H-1 receptor antagonist, chlorpheniramine (10 mg/ml) was infused into the renal artery via a 22 gauge catheter. These data suggest that UO causes intrarenal histamine release and a resultant vasodilation via H-1 receptors. Supported by NIH Grant HL24111.
DOES PROLACTIN REGULATE SODIUM TRANSPORT BY THE KIDNEY? Sidney Solomon, University of New Mexico, Albuquerque, New Mexico 87131.

Previous studies have indicated that prolactin is able to play a role in the regulation of renal sodium reabsorption. Most preparation of prolactin are contaminated by anti-


J.L. Cangiano and M. Martinez-Maldonado, Veterans Hospital and Medical Center, San Juan, Puerto Rico 00936.


Since the optimum pH for kallikrein and kininase I is alkaline, we studied whether increasing urinary pH in the presence or absence of kininase II inhibition affects intrarenal kinin formation. Urine was collected from both ureters of 30 anesthetized rats during control (cst) (0.15N NaCl infusion) and experimental (exp) periods of 40 min each. During exp periods, group 1 (time control) was infused with 0.15N NaCl, group 2 and 3 with 0.3M NaHCO3, and group 4 with 0.3M NaCl, all at a rate of 0.113 ml/min. Group 3 was pretreated with captopril (40 mg/kg). Urinary kinins (Ukin), kallikrein (Ukal), pH (pH), volume (V), and inulin (In) and furosemide (F) were measured during CST and EXP periods. Ukin was 146.2 and 146.4 (p<.001); 146.2 and 224.0 (p<.001); 146.2 and 224.0 (p<.001); and UV was 67410 and 62208 (p<.001) respectively. Ukal was 3.2909 and 6.1920 (p<.001); 3.2909 and 6.1920 (p<.001); 3.2909 and 6.1920 (p<.001); and UV was 67410 and 62208 (p<.001) respectively. We conclude that urinary alkalization increases intrarenal formation of kinins. (Supported by NHR ML03625)
Because many students view their educational environment primarily as one in which facts associated with each course are to be memorized and recalled, they often fail to recognize that common themes exist in physiology around which a unifying conceptual framework can be built. In developing a set of independent study materials to reinforce common themes in physiology, we have taken the approach illustrated below using the principle of conservation of mass (CM). Each exercise in the set deals with one concept and consists of 3 components: a microcomputer based simulation, a written procedure for the model, and a problem set. The CM model consists of a reservoir having several possible inlets and outlets, the number of which are defined by the student's choice of organ system and specific conditions. The student provides values for known volume times and mass concentrations and specifies whether steady state or transient data are desired. The model returns numerical data and a visual aid describing the quantity of mass entering, contained in, and leaving the reservoir. The written procedure describes, in the context of the model, applications of the concept to several physiological systems (e.g., pulmonary, cardiovascular), and includes sample input values for each case. The problem set consists of latent image materials arranged in a format that presents a problem and allows the student to selectively view the correct numerical answer, additional information, or the complete solution to the problem. The problems illustrate and reinforce the CM concept as it relates to various organ systems.

(Supported in part by AFOSR Contract F49620-78-C-0058)
Early biochemical studies examining adaptation in the central nervous system concentrated on presynaptic events. This work demonstrated that modifications in membrane transport systems, transmitter synthesis, metabolism and release are important in the maintenance of homeostasis. Because of technological advances it is now possible to examine changes in neuronal activity brought about by alterations in postsynaptic elements. Particular emphasis has been placed on characterizing membrane receptors for neurotransmitters. These efforts have led to a number of significant advances in the understanding of receptor-mediated phenomena in general, and synaptic transmission in particular. The present communication is designed to highlight and summarize some of the more fundamental concepts relating to receptor regulation that have resulted from these studies.

Receptor Components

Neurotransmitter receptor proteins are synthesized in the neuron, transported in small vesicles and inserted into the plasma membrane. Eventually the receptors are returned to the cytosol by endocytosis and destroyed by lysosomal enzymes. A common endpoint for neurotransmitter receptor function is a change in membrane permeability to ions. The basic units of a receptor are the transmitter recognition site and an ion channel. It is unclear whether the recognition site and ion channel are parts of the same molecule, or are separate constituents of a supramolecular complex. Evidence suggests that ion channels may be associated with more than one type of recognition site. There are at least two ways in which recognition site activation leads to channel opening. One is through a direct coupling between the recognition site and the ion channel, and the other by way of a cyclic nucleotide system (Fig. 1).

Recognition Site Regulation

Radioligand binding assays have provided a great deal of information about the molecular characteristics of receptor recognition sites. The basic principle of these assays is that the amount of radioligand bound to plasma membrane fragments at equilibrium is a function of recognition site number and affinity. Several criteria must be fulfilled before a binding assay may be considered valid for a particular recognition site. Paramount among these are saturability and specificity. By exposing membranes to increasing concentrations of ligand it should be possible to demonstrate that the binding plateaus (saturates) at a biologically
relevant concentration (Fig. 2A). Scatchard analysis of saturation data reveals the equilibrium binding dissociation constant \( (K_d) \) of the receptor for the ligand, and the binding site concentration \( (B_{max}) \). In the Scatchard plot shown there appear to be two binding compounds, a relatively high affinity site having a \( K_d \) of 1 nM and a \( B_{max} \) of 1 pmole/mg protein, and a lower affinity component with a \( K_d \) of 20 nM and a \( B_{max} \) of 5 pmole/mg protein (Fig. 2B).

Further proof that the ligand is attaching to the relevant site is provided by defining the specificity of the ligand-membrane interaction. Binding should be greatest in those organs, tissues, and subcellular fractions known to have the greatest density of receptors for the radioligand. Furthermore, only physiologically active receptor agonists and antagonists should inhibit ligand attachment, and relative potencies or inhibitors should be similar to relative potencies in physiological tests. Binding assays have now been developed for virtually all neurotransmitter candidates.

Ligand binding assays have revealed that the recognition site can be regulated either directly or indirectly. For example, it has been demonstrated that recognition site number is a function of receptor activity. An increase or decrease in synaptic activity will eventually lead to a decrease or increase, respectively, in recognition site number. Likewise receptor number can be modified by chronic administration of direct-acting recognition site agonists or antagonists. These alterations are viewed as an adaptive response to compensate for the relative excess or deficiency of neurotransmitter.

Recognition site affinity can be altered by inorganic ions, guanine nucleotides and protein modulators. These alterations occur almost instantaneously, providing the receptor with the capacity to make rapid adjustments in response to a change in demand.

Recognition site number or affinity may also be altered by activation of a separate receptor system. Thus, GABA receptor activation increases the affinity of the benzodiazepine binding site, and benzodiazepines modify the number and affinity of GABA receptors. This finding suggests that receptors can influence membrane sensitivity to other neurotransmitter substances.

**Receptor Coupling**

Modifications in recognition site-coupled components can also alter receptor responses. In regard to the \( \beta \)-adrenergic system, it has been proposed that norepinephrine (NE) activation of the recognition site \( (R) \) causes a conformational change that favors the attachment of a regulatory protein \( (G/F) \) to the recognition site (Fig. 1). Binding of GTP to \( G/F \) activates the enzyme adenylate cyclase \( (AC) \) and catalyzes the formation of cyclic AMP from ATP. The cyclic AMP activates protein kinases, one of which may be a constituent of the ion channel. This results in channel opening and an alteration in the polarity of the cell. The cyclic AMP is subsequently converted to AMP by the enzyme phosphodiesterase \( (PDE) \). Receptor activity is diminished by a sequential change in the affinities of the various receptor components. Thus, GTP is hydrolyzed to GDP, returning the \( G/F-AC \) complex to an inactive state and lowering the affinity of the recognition site for neurotransmitter. The transmitter is released and the \( R-G/F-AC \) complex separates. Such a receptor system can be modified in a variety of ways. These include alterations in the coupling between the components due to a change in the \( G/F \) or receptor recognition sites, or modifications in the amount, or activity, of AC or PDE. In the latter two cases receptor function would be altered even though a normal complex is formed.

Less is known about the coupling mechanism in systems where the recognition site is directly linked to the ion channel. However, it appears that perturbation of the channel can influence the affinity of the recognition site, suggesting that there is a reciprocal influence the affinity of the recognition site, and that such changes need not be reflected by a modification in the recognition site. Conversely, alterations in the recognition site do not necessarily result in a modification in receptor function since there may be compensatory changes that occur in the recognition site-coupled components. These possibilities illustrate the importance of directly relating biochemical changes to functional alterations before drawing conclusions about biological consequences.
Conclusions

Neurotransmitter receptor sites are composed of a variety of constituents, including the recognition site, ion channel and, in some cases, a cyclic nucleotide system. A number of factors are capable of modifying the biochemical properties of these various components. Certain modifications, such as a change in receptor number, may take days or weeks to become apparent, whereas others occur quite rapidly. This makes it possible for the cell to adapt immediately to a change in demand and to make long-term adjustments that may be necessary for functioning. Thus, neurotransmitter receptors are dynamic entities that play an ongoing role in maintaining homeostasis in the central nervous system.

Selected Readings

STRUCTURAL AND FUNCTIONAL ASPECTS OF THE RECEPTORS FOR INSULIN AND THE INSULIN-LIKE GROWTH FACTORS

Michael P. Czech

University of Massachusetts Medical School

Receptor Subunit Structures

The event that initiates the cellular actions of insulin is its recognition and binding by specific receptors in the target cells. The insulin receptor is also the vehicle for internalization and degradation of receptor-bound ligand. Receptors for insulin are present in almost every cell type in chordates and the general structure of these receptors has been preserved for at least 500 million years of evolution (1). Relatively high amounts of these receptors are present in human placenta, rat liver and rat adipocytes, and in the cultured cell lines 3T3-L1 adipocytes and IM-9 human lymphoblasts and for this reason these tissues and cell lines have been extensively used in biological and structural studies of the insulin receptor. Like many other types of hormone receptors, insulin receptors exhibit a $K_d$ for insulin in the low nanomolar range. A complication of the binding of insulin to its receptor is that the kinetics of this process do not reflect a simple interaction with one single class of binding sites, but rather a more complex type of interaction. This atypical behavior has been attributed to either "negative cooperativity" among insulin binding sites (2), interaction of insulin with a heterogenous population of receptors (3), or conformational and kinetic changes that occur in the receptor upon insulin binding (4), and in many cases it probably reflects the summation of various of these, and perhaps other factors. The insulin-like growth factors I and II (IGF-I and IGF-II) are peptide hormones with extensive amino acid sequence with insulin (5,6). The biological actions of insulin, IGF-I and IGF-II include activation of cellular metabolism and macromolecule synthesis (7,8). They also exhibit mitogenic activity on selected cell types (7,8). These actions are thought to be initiated by the interaction of the growth factors with specific cell surface receptors. The molecular basis of the events immediately triggered by the interaction of these hormones with their respective receptors is as yet unknown, and represents a major question in the area of cellular physiology. Critical clues to address this question have been recently provided by the rapid progress in identification and molecular characterization of receptors for insulin and these factors. Our laboratory has developed an affinity-labeling methodology using chemical crosslinkers that allow the identification of hormone receptor components on cell surfaces and membranes (9). Using this methodology, it was possible to establish a model for the structure of the insulin receptor (10). We proposed that the insulin receptor consists of the symmetrical heterotetrameric structure (2-$\alpha$-$\beta$-$\gamma$-$\delta$) in which the $\alpha$ (Mr=125,000) insulin receptor subunits and the $\beta$ (Mr=90,000) insulin receptor subunits are all linked by disulfide bonds (10,11). This model was simultaneously formulated by Jacobs and Quatrecasas (12) on basis of their work on insulin receptor purification by affinity chromatography (12,13). In addition to this predominant insulin receptor structure, free $\alpha$ and $\beta$ insulin receptor subunits, partially reduced ($\alpha\beta$) and ($\alpha\beta_2$) receptor fragments, and receptor complexes containing biosynthetic precursors of the $\alpha$ and $\beta$ subunits have been identified in various cell types by receptor affinity-labeling (14) and immunoprecipitation with anti-insulin receptor antibodies (15). An intriguing possibility based on the multiple chemical and biological similarities between IGF-I, IGF-II and insulin is whether the respective receptors for these hormones also share structural and biological properties. Using the affinity labeling methodology mentioned above we (16,17) and others (18,19) recently crosslinked many types of intact cells and membranes from human and rodent tissue to cell- or membrane-bound IGF-I-IGF-I and IGF-II-IGF-IT. These studies revealed the existence of two distinct types (type I and type II) of the high-affinity receptors for IGF-I and IGF-II (17). The type I IGF receptor is a disulfide-linked, multisubunit complex strikingly similar to the insulin receptor in molecular size and subunit structure. Thus, the type I receptor consists of Mr130,000-140,000 $\alpha$ subunits and Mr97,000 $\beta$ subunits, all linked in an ($\alpha\beta_2$) configuration like the insulin receptor (17). The $\beta$ subunits in the type I IGF-I receptor contain a site in $\beta$ the middle of their amino acid sequence very susceptible to cleavage by elastase-like enzymes, in analogy to a similar site in the subunit of the insulin receptor (17,20). However, the type I IGF receptor exhibits a higher affinity for IGF-I than for IGF-II, and a low affinity for insulin (17). We refer to this receptor type as IGF-I receptor. The type II IGF receptor consists of a single peptide chain (Mr=250,000-270,000) on dodecyl sulfate-polyacrylamide gels that is not disulfide linked.
to any other membrane component. This receptor type has been affinity-labeled with either "I-IGF-I, "I-IGF-II (17, 18) or "I-

multiplication stimulating activity (rat IGF-II) (16). The type II IGF receptor is also termed IGF-II receptor because it exhibits a higher affinity for this ligand than for IGF-I (17).

These studies have led to the conclusion, schematically shown in Fig. 1, that three receptor structures account for all of the binding and biological signalling by insulin, IGF-I and IGF-II. Peptide mapping of the receptors for insulin and IGF-I indicate extensive homology, but further work will be required to determine the presence or extent of actual protein sequence homology.

Figure 1. Schematic representation of proposed structures and some interrelationships among the receptors for insulin, IGF-I and IGF-II. The ligand with highest affinity for each of the three receptor types is shown with a vertical arrow, and the cross-reactivities with diagonal arrows. Other subunit forms or states of the receptors shown also appear to exist. The receptors for insulin and IGF-I are both capable of activating hexose transport and the rapid enzyme changes exemplified by the box at the left. The IGF-II receptor does not have this capability.

IGF Receptor Purification

While current methods to purify the insulin receptor are available, purification methods for the IGF-I receptor are just now being developed. Recently, we have developed methodology to fully purify large quantities of the IGF-II receptor (21). The membrane receptor for insulin-like growth factor II (IGF-II) has been purified to near homogeneity from rat placenta membranes and in purified form using 125"I-IGF-II and the crosslinking agent disuccinimidyl suberate resulted in covalent labeling of only the Mr=250,000 band. Such labeling was abolished by unlabeled IGF-II but was unaffected by insulin, consistent with the previously reported specificity of IGF-II receptor (17). These results establish a one-step affinity method for the purification of the type II IGF receptor that is rapid and highly efficient.

Insulin Action on the IGF-II Receptor

The binding of IGF-II to its own receptor in rat adipocytes and hepatoma cells has been reported to be markedly stimulated by physiological concentrations of insulin, presumably acting through the insulin receptor (22, 23). Incubation of intact rat adipocytes with physiological concentrations of insulin stimulates binding of insulin-like growth factor II (IGF-II) to its receptor by 3 to 10 fold. The effect is temperature and dose dependent, with 0.1 nM insulin giving half-maximal stimulation. Scatchard analysis of IGF-II binding to intact adipocytes indicates that this effect is due to an apparent increase in receptor affinity, from Kd=63 mM in the absence of insulin to Kd=5.8 mM in the presence of 10 nM insulin, with no apparent change in the number of cell surface binding sites (220,000 per cell).

Scatchard analysis of 125"I-IGF-II binding to isolated membrane fractions demonstrated that all IGF-II receptors in plasma membranes and low density microsomes from control cells are converted during homogenization to the high affinity form (Kd=2-6 nM) seen in insulin-treated intact adipocytes. No significant difference in affinity was observed between low density microsomes from control or insulin-treated cells. However, in apparent contrast to the results obtained in intact adipocytes, the number of binding sites is increased in the plasma membrane fraction from insulin-treated cells by an average of 60%, while the number of receptors is decreased by 40% in low density microsomes from insulin-treated cells compared to control cells. These results were confirmed by direct visualization of the Mr=270,000 IGF-II receptor band on dodecyl sulfate gels following affinity labeling with 125"I-IGF-II and the crosslinker disuccinimidyl suberate. Scatchard analysis of the total cellular membranes showed no difference in the total number of binding sites between control and insulin-treated cells.

These results demonstrate that insulin has two effects on the IGF-II receptor in adipocytes: (1) it rapidly increases the apparent affinity of the receptor in the intact
cell without changing the apparent number of receptors on the cell surface; and (2) it induces a redistribution of the high affinity IGF-I receptor between plasma membranes and low density microsomes upon homogenization of cells and preparation of membranes. The latter effect closely parallels the insulin-induced membrane redistribution of the glucose transporter that occurs in the rat adipocyte by an unknown mechanism.

The Insulin Receptor as a Protein Kinase

A recent discovery by Kasuga and co-worker (24,25) showed that insulin stimulated the incorporation of 32P into the β subunit of its own receptor in cultured human lymphocytes and rat hepatoma cells. Subsequent studies have shown that insulin also increased the phosphorylation of the insulin receptor in rat adipocytes (26), human placenta (27-29), 3T3-L1 adipocytes (27) and rat adipocytes (30). In cell free systems, the interaction of insulin with its receptor in the presence of γ-32P-labeled ATP also resulted in increased phosphorylation of the insulin receptor (26-35). The increased phosphorylation of the insulin receptor in insulin-treated cells was predominately due to an increase in the level of phosphoserine with the simultaneous appearance of phosphotyrosine (5), whereas the increase by insulin added to detergent extracts of membranes or cells was primarily due to phosphotyrosine (27,29,31,33). Petruzelli and co-workers (27) demonstrated that insulin activated a tyrosine-specific protein kinase in Triton X-100 extracts of 3T3-L1 adipocytes and human placenta. The insulin-activated tyrosine specific kinase was capable of phosphorylating added substrates such as histone and casein. The insulin-stimulated tyrosine specific kinase co-purified with the insulin receptor until the final elution from insulin-agarose with urea at pH 6. It is not clear from these studies whether the loss of the kinase activity was due to the denaturing effect of the harsh conditions used to elute the insulin receptor or to the loss of a distinct kinase that does not absorb to the insulin-agarose matrix. Thus a critical question is whether the kinase activity is intrinsic to the insulin receptor structure in a manner analogous to the EGF receptor (36) or is associated with a distinct protein.

This hypothesis that the insulin receptor complex contains intrinsic protein kinase activity was tested by assaying in our laboratory the receptor, specifically immobilized on insulin-agarose, for enzyme activity. Human placental membranes solubilized in Triton X-100 were absorbed with wheat germ agglutinin-agarose and eluted with N-acetylgucosamine. The eluent was absorbed with wheat germ agglutinin-agarose which blocks receptor absorption to the immobilized insulin. After absorption the insulin-agarose preparations were incubated at 24°C with [γ-32P] ATP and type II as histone followed by boiling in sodium dodecyl sulfate and analysis on polyacrylamide gels. Five endogenous proteins of Mr=180,000, 120,000, 93,000, 53,000 and 45,000 as well as the added histone incorporated 32P to a much greater extent in the reaction mixture containing insulin agarose that had absorbed membrane extract in the absence of free insulin. The Mr=93,000 protein corresponds to the β subunit of the insulin receptor, while the other endogenous proteins are contaminants absorbed non-specifically to the insulin-agarose. This conclusion was documented by: (1) inhibition of absorption of the β subunit was specific for insulin, while desoctapeptide insulin only partially inhibited and cytochrome c was without effect, (2) little or no β subunit was absorbed when the experiment was performed with boiled insulin agarose, (3) absorption of the extracts with boiled insulin-agarose prior to absorption with insulin-agarose resulted in a greatly reduced background of absorbed Coomassie blue stained bands, while the β subunit was the major labeled protein absorbed under these conditions. The receptor-mediated increase in phosphorylation of the Mr=180,000 band, the β subunit of the insulin receptor and histone was due to the increase in phosphotyrosine content. We conclude that the insulin receptor itself or a protein that remains bound to the receptor in Triton X-100 solution contains intrinsic protein kinase activity.

Experiments in progress in our laboratory and others are designed to test whether the IGF receptors may also be associated with protein kinase activity. The key question related to the insulin receptor kinase activity is its possible relevance to biological signalling or other receptor functions. This question is under intensive investigation.

REFERENCES

LIPOPROTEIN RECEPTORS AND THEIR ROLE IN CHOLESTEROL METABOLISM

Robert W. Mahley

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I. Plasma Lipoproteins

Plasma lipoproteins transport triglycerides, cholesterol, and phospholipids to and from various tissues of the body. The major classes of lipoproteins, along with their functions and properties, are described in Table 1. Much attention has been focused on the protein constituents of lipoproteins, referred to as apoproteins, because of their central role in regulating the metabolism of lipoproteins. There are nearly a dozen different apoproteins. The major ones are shown in Fig. 1. Two of these proteins, apoproteins B and E, mediate the specific interaction of lipoproteins with various lipoprotein receptors on cells.

II. Lipoprotein Receptors

There are several different lipoprotein receptors on cells that have thus far been described. The most extensively characterized receptor is the LDL (apo-B,E) receptor, which was initially described by Goldstein and Brown (1,2). Their classic work on the subject defined familial hypercholesterolemia as a condition in which LDL receptors are defective or absent, and highlighted the importance of specific cell surface receptors in the regulation of lipoprotein metabolism. These receptors are expressed in several tissues, both hepatic and extrahepatic.

A second major lipoprotein receptor appears to be present only in the liver. This receptor, referred to as the apo-E or chylomicron remnant receptor, has been shown to mediate the uptake of cholesterol-rich chylomicron remnants and certain other apo-E-containing lipoproteins, but not the apo-B-containing LDL (2,3,4). The liver is the organ of paramount importance in regulating total body cholesterol homeostasis. Cholesterol is primarily eliminated from the body via the liver through the bile.

Lipoprotein receptors are also present on macrophages (5,6,7). It is now apparent that macrophages have receptors, or high affinity binding sites, for two different types of lipoproteins: 1) cholesterol-rich β-VLDL of patients with type III hyperlipoproteinemia and β-VLDL (chylomicron remnants) induced by diets high in fat and cholesterol, and 2) negatively charged LDL that can be generated by a chemical modification of its apoprotein constituent. The macrophage receptors may be of particular importance, in that macrophages are one of the progenitors of arterial wall foam cells that occur in atherosclerotic lesions.

A. LDL (Apo-B,E) Receptors

The LDL (apo-B,E) receptor has been described in several reviews (1,2,8). The general properties of apo-B,E receptors are compiled in Tables 2 and 3. In addition, Fig. 2 shows...
how lipoproteins binding to these receptors in coated pits are internalized and degraded in the lysosomes. Three intracellular processes are initiated by this internalization process: 1) suppression of HMG CoA reductase, the rate-limiting step in cholesterol biosynthesis, 2) stimulation of ACAT for cholesterol esterification and intracellular storage of cholesterol and 3) the down-regulation of the expression of the apo-B,E receptors.

Initial studies demonstrated that only LDL containing apo-B interact with these receptors. However, it is now known that apo-E containing lipoproteins, such as HDL-with apo-E, also interact with apo-B,E receptors (8). The HDL-without apo-E do not bind to these apo-B,E receptors. It is now understood that apo-B and apo-E are the determinants responsible for the receptor interaction (hence, the receptor is referred to as the apo-B,E receptor).

The importance of these apoproteins in the interaction between lipoproteins and apo-B,E receptors was established by selective chemical modification of specific amino acid residues. The chemical modification of a limited number of arginyl residues by Nω-cyclohexanemione, and of lysyl residues by acetoacetylation, reductive methylation, and carbamylation, not only established the importance of the apoproteins, but also demonstrated the significance of these particular amino acid residues in the recognition process. The modification of relatively few arginyl or lysyl residues totally prevents LDL or HDL-with apo-E from binding to cell surface receptors on fibroblasts (8).

The interaction of apo-B- and apo-E-containing lipoproteins with apo-B,E receptors is identical except for one important property. It has been established that HDL-with apo-E (apo-E HDL) bind to apo-B,E receptors of fibroblasts with a much higher affinity (20 to 25 times higher) than that observed for the binding of LDL. The equilibrium constant (Kd ≈ 10^9 M) for HDL and LDL binding are ≈ 0.1 M and ≈ 2.8 × 10^6 M, respectively. In addition, 4 times more LDL particles are required to saturate all available apo-B,E receptor sites on fibroblasts. In a typical study, it requires 90,000 to 100,000 LDL particles to saturate the receptors, as compared to 25,000 HDL particles (a 4:1 ratio). The LDL and HDL are very similar in chemical composition and particle size. Based on these and other observations, it has been proposed that the apo-B,E receptor possesses multiple binding sites (shown schematically in Fig. 3). This model is compatible with the higher affinity of HDL binding and the decreased number of HDL particles necessary to saturate all the binding sites. The simplest model would predict that one HDL particle binds to four binding sites and that each LDL particle binds to a single site (8).

The multiple binding site model proposed for apo-B,E receptors has been backed up by studies using the radiation inactivation technique (8,9). These studies have demonstrated that the receptor complex binding either one LDL particle or 4 HDL particles is a single binding unit with an average functional molecular weight of ≈ 110,000 daltons. The purified LDL (apo-B,E) receptor has been shown to have an apparent molecular weight of 164,000. In a series of eloquent studies, it was demonstrated that the apo-B,E receptor is actually synthesized as a precursor protein molecule of 110,000 to 120,000 daltons and that it possesses lipoprotein binding activity (10,11,12). Subsequently, the receptor molecule is processed (apparently by posttranslational glycosylation) into a mature form with a molecular weight of ≈ 160,000 daltons. The functional molecular weight determined by radiation inactivation agrees quite closely with the molecular weight of the precursor form of the receptor.

Detailed analyses of the structure of the 34,000 dalton apo-E molecule, and of several mutant forms of apo-E that have been shown to be defective in receptor binding, have resulted in the identification of the binding domain for this ligand (8,13,14). As shown in Fig. 4, the binding domain is the region near the center of the molecule, which is enriched in lysyl and arginyl residues. Naturally occurring mutants, resulting from single amino acid substitutions involving lysyl and arginyl residues occur at residues 142, 145, 146, and 158. These mutants are variably defective in receptor binding activity and have been associated with type III hyperlipoproteinemia. In addition, studies using chemically and enzymatically cleaved

Figure 3. Schematic diagram showing hypothetical structure of the apo-B,E receptor with multiple binding sites. The M, 100,000 to 110,000 M, receptor unit inserted in the cell membrane is capable of binding either one apo-E HDL particle, with its four binding sites, or four individual LDL particles (from Ref. 9).
The liver possesses at least two different high affinity receptors, the apo-B,E receptor and the apo-E receptor (2,3,4). The LDL (apo-B,E) receptor in the liver appears to be very similar to the apo-B,E receptor in extrahepatic tissues, i.e., they are both capable of interacting with apo-B-and apo-E-containing lipoproteins. However, the second hepatic receptor, the apo-E receptor, is unique to the liver and interacts with apo-E-containing HDL and chylomicron remnants but not with LDL. The ligand mediating the interaction between lipoproteins and this receptor is apo-E. The apo-E receptor has been described in the livers of dogs, swine, baboons, and man (t3,4,8). (For summary see Table 3.)

Regulation of the hepatic apo-B,E and apo-E receptors appears to be under independent control (8,15). The apo-B,E receptors are prominent in the livers of immature, growing animals, but are expressed at low levels in adults. Furthermore, the apo-B,E receptors are markedly - and in some cases very rapidly - down-regulated. Cholesterol feeding in animals, or the infusion of lymph lipoproteins or bile salts, suppress the expression of this receptor to almost undetectable levels. However, treatment of animals with cholesteryamine (a bile-acid binding resin) or estrogen results in a marked induction of the expression of hepatic apo-B,E receptors. Under all these conditions, which markedly modulate the expression of the apo-B,E receptors, the expression of the apo-E receptors remains at a relatively constant level.

B. Hepatic Lipoprotein Receptors (Apo-B,E Receptors and Apo-E Receptors)

The liver possesses at least two different high affinity receptors, the apo-B,E receptor and the apo-E receptor (2,3,4). The LDL (apo-B,E) receptor in the liver appears to be very similar to the apo-B,E receptor in extrahepatic tissues, i.e., they are both capable of interacting with apo-B-and apo-E-containing lipoproteins. However, the second hepatic receptor, the apo-E receptor, is unique to the liver and interacts with apo-E-containing HDL and chylomicron remnants but not with LDL. The ligand mediating the interaction between lipoproteins and this receptor is apo-E. The apo-E receptor has been described in the livers of dogs, swine, baboons, and man (3,4,8). (For summary see Table 3.)

Regulation of the hepatic apo-B,E and apo-E receptors appears to be under independent control (8,15). The apo-B,E receptors are prominent in the livers of immature, growing animals, but are expressed at low levels in adults. Furthermore, the apo-B,E receptors are markedly - and in some cases very rapidly - down-regulated. Cholesterol feeding in animals, or the infusion of lymph lipoproteins or bile salts, suppress the expression of this receptor to almost undetectable levels. However, treatment of animals with cholesteryamine (a bile-acid binding resin) or estrogen results in a marked induction of the expression of hepatic apo-B,E receptors. Under all these conditions, which markedly modulate the expression of the apo-B,E receptors, the expression of the apo-E receptors remains at a relatively constant level.

This observation is compatible with its proposed role in lipoprotein metabolism.

It appears that the apo-E receptor functions to clear chylomicron remnants from the plasma (8). In addition, the apo-E receptor (also referred to as the chylomicron remnant receptor) seems to be genetically distinct from the apo-B,E receptor. Patients with familial hypercholesterolemia, who lack apo-B,E receptors or have defective receptors, do not have difficulty clearing chylomicron remnants from their plasma. This reflects the apparent normal activity of the apo-E receptor in these subjects. Chylomicron remnants (β-VLDL) which possess an abnormal form of apo-E, accumulate in the plasma of patients with type III hyperlipoproteinemia. This accumulation reflects the defective receptor binding activity of the abnormal apo-E in these subjects.

C. Macrophage Receptors

Macrophages are capable of taking up two distinctly different types of lipoproteins by high affinity processes, including β-VLDL and chemically modified LDL (8). (For summary see Table 3.) The only naturally occurring plasma lipoprotein that these cells take up are β-VLDL. These lipoproteins occur in the plasma of patients with type III hyperlipoproteinemia (a genetic disorder characterized by hypercholesterolemia and accelerated vascular disease) and in animals fed diets high in fat and cholesterol. The β-VLDL occurring under these conditions are at least partly derived from cholesterol-enriched chylomicron remnants. The β-VLDL receptor on macrophages is distinct from other lipoprotein receptors (8). Unlike the apo-B,E receptor, it is poorly regulated, and internalization of β-VLDL results in excessive cholesteryl ester uptake and accumulation. The cholesteryl ester content of macrophages can increase 100- to 200-fold following incubation with β-VLDL from cholesterol-fed dogs, rats, rabbits, or monkeys. The β-VLDL from type III hyperlipoproteinemic subjects also cause excessive cholesteryl accumulation in macrophages. The uptake is mediated by the β-VLDL receptor.

Chemical modification of LDL by a variety of procedures, including acetylation, acetoxcetosylation, and malondialdehyde treatment, causes these lipoproteins to be taken up by macrophages via a high affinity process (5,6,7). The high affinity binding sites are clearly distinct from the β-VLDL receptors, apo-B,E receptors, or apo-E receptors described above. The uptake is unregulated and results in massive intracellular cholesteryl ester accumulation.

The uptake of β-VLDL and chemically modified LDL is of potential physiological significance in the development of atherosclerosis. Macrophages are one of the cell types within the arterial wall that accumulate cholesterol. The observation that
diet-induced β-VLDL can cause excessive cholesteryl ester accumulation in these cells may represent a direct link between diets high in fat and cholesterol and accelerated atherogenesis. Furthermore, the association of β-VLDL in the plasma of type III patients with accelerated atherosclerosis may reflect the propensity of these lipoproteins to deliver cholesterol to macrophages. In addition, it has been postulated that LDL may become chemically modified as they circulate in the plasma or perfuse the extracellular space of various tissues and that these modifications allow their uptake by macrophages, including those of the arterial wall. Foam cells within atherosclerotic lesions have been shown to possess receptors for β-VLDL and chemically modified LDL. 

Selected References and Review Articles


**TABLE 1**

**HUMAN PLASMA LIPOPROTEINS**

<table>
<thead>
<tr>
<th>Origin</th>
<th>Major Function(s)</th>
<th>Density of Electrophoretic Particle</th>
<th>Mobility</th>
<th>Major Lipids</th>
<th>Major Proteins</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chylomicron Remnants</td>
<td>Derived from chylomicron remnants following lipolysis</td>
<td></td>
<td>d&lt;1.006</td>
<td>Origin to</td>
<td>&gt;1000Å</td>
</tr>
<tr>
<td>Very low density lipoproteins (VLDL)</td>
<td>Liver</td>
<td>Redistribution of triglyceride from liver to various tissues utilizing fatty acids.</td>
<td>d&lt;1.006</td>
<td>Pre-B</td>
<td>300-900Å</td>
</tr>
<tr>
<td>Low density lipoproteins (LDL)</td>
<td>Derived from VLDL following lipolysis</td>
<td>Provide cholesterol to various tissues for:</td>
<td>d&lt;1.006</td>
<td>Pre-B</td>
<td>~200Å</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1. membrane biosynthesis</td>
<td>1.063</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. steroid hormone production</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Uptake mediated via apo-B,E receptors.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
TABLE I (cont)
HUMAN PLASMA LIPOPROTEINS

<table>
<thead>
<tr>
<th>Origin</th>
<th>Major Function(s)</th>
<th>Density of Electrophoretic Particle</th>
<th>Flotation</th>
<th>Mobility</th>
<th>Size</th>
<th>Major Lipids</th>
<th>Major Proteins</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. HDL- without apo-E</td>
<td>Liver, intestine ?</td>
<td>Reverse cholesterol transport (acquisition of chol. from various tissues)</td>
<td>d=1.063-1.21</td>
<td>a, a1</td>
<td>80-100A</td>
<td>Phospholipid A-I, A-II, C</td>
<td></td>
</tr>
<tr>
<td>II. HDL-with apo-E</td>
<td>Apparently derived from HDL-without apo-E by acquisition of cholesterol &amp; apo-E receptors.</td>
<td>Redistribution of cholesterol to hepatic and extrahepatic tissues mediated via apo-B,E and apo-E receptors.</td>
<td>d=1.063-1.21</td>
<td>a1,a2</td>
<td>100A</td>
<td>Phospholipids, l, A-I, A-II, C</td>
<td></td>
</tr>
</tbody>
</table>

TABLE 2
PROPERTIES OF THE LDL (APO-B,E) RECEPTORS

Localizatation: Fibroblasts, smooth muscle cells, leukocytes, adrenal cortex, testes, ovaries, liver

Protein determinants for binding: Apo-B, apo-E

Binding specificity: LDL, HDL with apo-E, including HDLc, Chylomicron remnants, VLDL (especially hypertriglyceridemic VLDL), Lp(a)

Binding affinity (Kd): LDL = 2.18 x 10^-7; HDL = 0.1 x 10^-7

Receptors per cell (fibroblasts): 50,000 to 100,000

Entry of LDL into cell (fibroblasts): t1/2 < 5 minutes

Turnover of receptors (fibroblasts): t1/2 < 20 hours

Molecular weight of receptors: Isolated and purified (adrenal) ~ 164,000 daltons, by radiation inactivation (fibroblasts) ~ 106,000 daltons

Enzymatic sensitivity: Pronase, trypsin, pepsin

Binding characteristics: a) Requires divalent cations b) Abolished by chemical modification of lysine and arginine residues of apo-B and apo-E
## TABLE 3

**SUMMARY OF LIPOPROTEIN RECEPTORS**

<table>
<thead>
<tr>
<th>Receptors</th>
<th>Cells or Tissues</th>
<th>Lipoproteins Bound</th>
<th>Ligands Involved</th>
<th>Receptor Regulation</th>
<th>Functional Roles</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL (apo-B,E)</td>
<td>Fibroblasts</td>
<td>LDL</td>
<td>Apo-B</td>
<td>Regulated by delivery</td>
<td>Regulation of LDL levels.</td>
</tr>
<tr>
<td>Liver</td>
<td>VLDL</td>
<td>Chylomicron remnants</td>
<td>Cholesterol utilized for membrane or hormone production.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adrenal cortex</td>
<td>Uterus</td>
<td>Lp(a)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ovaries</td>
<td>Testes</td>
<td>B-VLDL (cholesterol)</td>
<td>Uptake of chylomicron remnants and cholesterol-loaded HDL with apo-E.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adipocytes</td>
<td>Lymphocytes</td>
<td>Macrophage-monocytes</td>
<td>Delivery of cholesterol to the liver for excretion.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Apo-E

<table>
<thead>
<tr>
<th>Liver</th>
<th>Chylomicron remnants</th>
<th>Apo-E</th>
<th>Not subject to marked down-regulation</th>
<th>Uptake of chylomicron remnants and cholesterol-loaded HDL with apo-E.</th>
</tr>
</thead>
</table>

### B-VLDL

<table>
<thead>
<tr>
<th>Macrophage</th>
<th>B-VLDL</th>
<th>Poorly regulated</th>
<th>Potential role in foam cell production in atherogenesis.</th>
</tr>
</thead>
<tbody>
<tr>
<td>(from Type III subjects and induced by cholesterol)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Chemically-modified LDL

<table>
<thead>
<tr>
<th>Macrophage</th>
<th>Modified LDL</th>
<th>Charge-modified apo-B</th>
<th>Not regulated</th>
<th>Potential role in foam cell production in atherogenesis.</th>
</tr>
</thead>
</table>
The calcium antagonists, verapamil (V), nifedipine (N), and diltiazem (D), or slow channel inhibitors, are extremely interesting and important new therapeutic agents for the treatment of cardiovascular diseases. The diverse chemical structures of the calcium antagonists do not permit the assignment of a specific receptor or a structure-activity relationship. D, N, and V shorten the Action Potential Duration 50 (APD 50), but V also lengthens the APD 50. In the doses used to dilate the coronaries, D and V also lengthen the APD 50. In the doses used to dilate the coronaries, D and V prolong A-H interval, but N has no effect. All three produce negative inotropy on isolated ventricular, atrial and Purkinje tissue, with a potency N>V>D. D has a much greater effect on coronaries (particularly collaterals) than it does on the peripheral vascular system or veins, while both N and V are very potent peripheral vasodilators. In conscious animals, equipotent doses of D, N and V that lower blood pressure by about 15-20 mmHg, result in increase in LV dp/dt by N, decrease by V and no change by D. D markedly protects ischemic myocardium by dilating coronaries and preventing calcium-induced damage to the gap junctions and to mitochondria. The calcium antagonists protect the heart and relieve angina by affecting the "supply" side to a greater extent than they affect "demand". [3H]-nitrendipine (NTD) and nimodipine (NMD) bind specifically to cell membranes and perhaps junctional SR. Kinetics and pharmacologic correlates will be discussed.

HOW DO THE CALCIUM ANTAGONISTS WORK? IS THERE A SPECIFIC SINGLE RECEPTOR AND/OR CHANNEL OR ARE THERE MULTIPLE SITES?

[3H]-NITRENIDIPINE OR NIMODIPINE

"RECEPTOR"

CELL MEMBRANE

"CALCIUM CHANNEL"
Table:

<table>
<thead>
<tr>
<th>Tissue</th>
<th>[3H]Ligand</th>
<th>Temperature (°C)</th>
<th>N</th>
<th>K_d (nM)</th>
<th>B_max (fmol/mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pig coronary arteries</td>
<td>Nitrendipine</td>
<td>37</td>
<td>3</td>
<td>1.6 ± 0.5</td>
<td>35 ± 2</td>
</tr>
<tr>
<td></td>
<td>Dihydralprenolol</td>
<td>30</td>
<td>3</td>
<td>0.7 ± 0.3</td>
<td>40 ± 8</td>
</tr>
<tr>
<td></td>
<td>Quinuclidinyl benzoate</td>
<td>37</td>
<td>2</td>
<td>1.4 ± 0.9</td>
<td>80 ± 7</td>
</tr>
<tr>
<td>Dog ventricular muscle</td>
<td>Nitrendipine</td>
<td>30</td>
<td>3</td>
<td>0.11 ± 0.01</td>
<td>230 ± 10</td>
</tr>
<tr>
<td></td>
<td>Dihydralprenolol</td>
<td>30</td>
<td>3</td>
<td>6.5 ± 0.9</td>
<td>2,700 ± 640</td>
</tr>
<tr>
<td></td>
<td>Quinuclidinyl benzoate</td>
<td>37</td>
<td>1</td>
<td>0.15</td>
<td>21,000</td>
</tr>
<tr>
<td></td>
<td>Ouabain</td>
<td>37</td>
<td>3</td>
<td>32 ± 6</td>
<td>370,000 ± 34000</td>
</tr>
</tbody>
</table>

**DISPLACEMENT OF [3H] -NITRENIDINE BINDING TO PIG CORONARY ARTERIES**

**LABEL CONCENTRATION: 0.3 nM**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Concentration</th>
<th>% Binding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitrendipine</td>
<td>10^-9 M</td>
<td>31</td>
</tr>
<tr>
<td>Nitrendipine</td>
<td>10^-8 M</td>
<td>43</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>10^-7 M</td>
<td>118*</td>
</tr>
<tr>
<td></td>
<td>10^-6 M</td>
<td>152*</td>
</tr>
<tr>
<td>Verapamil</td>
<td>10^-7 M</td>
<td>64</td>
</tr>
<tr>
<td></td>
<td>10^-6 M</td>
<td>37</td>
</tr>
<tr>
<td>D600</td>
<td>10^-7 M</td>
<td>51</td>
</tr>
<tr>
<td></td>
<td>10^-6 M</td>
<td>52</td>
</tr>
</tbody>
</table>

*STIMULATION
Stimulation by diltiazem of $[^3\text{H}]$nimodipine binding to cardiac membranes. The lower panel shows a typical experiment (triplicate determinations); the specific binding was analyzed according to Scatchard (Inset).

Upper panel: effect of diltiazem expressed as percentage of control specific binding in 4 to 13 different preparations ($\pm$ S.E.M.).

**Figure 1**

Effect of d-cis-diltiazem (O) and l-cis-diltiazem (a) on $[^3\text{H}]$nitrendipine binding to microsomes from pig coronary arteries.

**Figure 2**

$[^3\text{H}]$nimodipine specific binding to isolated myocytes (washed cells). The data represent means ($\pm$ S.E.M.) from experiments with 4 different myocytes preparations (1-2 x $10^6$ cells per ml). Same conditions as described in the legends to Fig. 2. Inset: Scatchard plot.

**Figure 3**

Drug-induced relaxation of depolarized pig coronary arteries. Cumulative doses of nitrendipine (O), d-cis-diltiazem (O) or l-cis-diltiazem were (O) added to the incubation medium after maximum tension development in response to 35 mM KCl. The data represent the tissue response in percent of initial maximum active tension. Decay of the maximum active tension was observed in simultaneously paired control tissue rings exposed to carrier solution alone. Appropriate corrections were made. Each point represents 4-12 coronary rings ($\pm$ S.E.M.). In separate experiments, single doses of nitrendipine produced the same response at equilibrium as cumulative doses.

**Figure 4**

\begin{align*}
\text{RAT HEART MYOCYTES} \\
[^3\text{H}]\text{NIMODIPINE} : 10^6 \\text{sites per cell} \\
[^3\text{H}]\text{DHA} : 0.2 \times 10^6 \\text{sites per cell} \\
[^3\text{H}]\text{QNB} : 0.9 \times 10^6 \\text{sites per cell}
\end{align*}
PACED RAT HEART (Langendorff)

Coronary Flow
(ml/min)

17
15
13
11

\( \frac{dP}{dt} \)

(mm Hg/s)

Nimodipine

4x10^{-8} M

0 10 20 30
Time (min.)

Figure 5

NORMAL VENTRICULAR ACTION POTENTIAL
MONOPHASIC AND IONIC CHARACTERISTICS
AND ACTION OF Ca CHANNEL BLOCKERS

Figure 6

POSSIBLE EFFECTS OF DILTIAZEM ON MYOCARDIAL ISCHEMEA

Figure 7

Figure 8
DILTIAZEM MAY LIMIT AMOUNTS OF CALCIUM ENTERING THE DISEASED HEART

Figure 9

HOW MIGHT DILTIAZEM PROTECT?

- Ca²⁺ Antagonist
  - + Ca²⁺ Myocyte
    - + Ca²⁺ Mitochondria
      - + Mitochondria Protected
        + Myocardium Protected
  - + Ca²⁺ Vascular Smooth Muscle
    - (Vasodilation)
      - + Blood Flow, O₂ Supply

Ca²⁺ REGULATION IN VASCULAR SMOOTH MUSCLE

Figure 10
Cardiac Muscle

Figure 11
Proceedings of the
Symposium
Teaching Cardiovascular Physiology
Outside the Lecture Hall

The 33rd Annual Fall Meeting of the
American Physiological Society
with
The Latin American Association of
Physiological Sciences

October 12, 1982
San Diego, California

Edited by
Joel A. Michael
Allen A. Rovick
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Teaching Cardiovascular Physiology Outside the Lecture Hall

Introduction

The easiest and least expensive way to teach physiology (or most other disciplines) is to hire a small number of lecturers, fill a hall with students, and let each lecturer "do his thing". If the lecturers are skilled their presentations will be logically organized, well illustrated and interestingly presented. Lectures are an efficient method of teaching basic physiology. In fact, this is how most of physiology is now taught.

However, the plethora of alternative techniques that have been developed, each of which takes the student and the faculty out of the lecture hall, clearly indicates that teachers think that something more is needed to properly educate students in physiology. Each of the non-lecture approaches is thought to do something that lectures don't do as well; something that is achieved by having students actively manipulate the facts, concepts and the anatomical substance that compose physiological systems; something that requires students to apply the ideas, components and relationships of physiology to solve problems. Alternative educational experiences help students to learn to solve qualitative problems (i.e. involving cause and effect relationships) as well as quantitative (numerical) problems.

In lectures it is difficult to convey many important features of physiological systems with verbal descriptions, conjured up thought experiments or mental images. Phenomena such as biological variation, sources of error, the stability and the mortality of living systems and the beauty that's revealed by the interaction of the components of a physiological system are examples of topics that "suffer" from presentation in a simple lecture format. Further, in the lecture hall, such topics are usually discussed piecemeal. Using other approaches, they may be experienced and directly appreciated and thus may be understood as a unified whole.

Students often have no difficulty in repeating the facts or relationships that they have heard in a lecture or read in a textbook. But, if faced with the need to explain the cause(s) of a particular state of an organism, they may not even know where or how to begin such an analysis. Exposure to similar challenges helps to develop in them the problem-solving "sense" that is needed.

Non-lecture exercises slow the frenetic pace that lecture series often assume. They give students time to think, to learn and to ask questions, while they give faculty time to explain and to guide. They reduce the student/teacher ratio and help to re-humanize the instructional process while guaranteeing that an essential ingredient in students' education, learning to use physiology, is not missing.

Alternative teaching techniques come in many guises. Each provides its own characteristic and often unique educational benefits. None alone supplements all of the weaknesses of lectures or, for that matter, is without deficiencies of its own. However, each makes a contribution toward the objective of a complete education in physiology.

We hope that the pluses and minuses of a number of non-lecture approaches will become clear in this volume. The techniques discussed are not the only ones now in use. The back issues of the Physiology Teacher contain many additional approaches. The papers assembled here deal with variations on traditional non-lecture teaching formats as well as some that are not so old.

The symposium was divided into three parts. First, there was a group of papers on laboratories. This started with a review of the results of the third national survey of laboratory teaching activities of departments of physiology in US medical schools (C. Rothe, published separately in The Physiologist 26, No. 3, 1983). This was followed by three novel approaches to "wet" labs. In the second part there were three papers on techniques for small group or individual instruction using clinical or pathophysiological problems. Finally, there was a group of papers on computer-based educational methods.

The papers are derived from a symposium that was held on October 12, 1982 at the combined Fall meeting of the American Physiological Society and the Latin American Physiological Society in San Diego, California. We organized the symposium at the suggestion of Arthur Vander, then Chairman of the Education Committee of APS and we chaired it along with W.T. Beraldo of Brazil.

Our sincere thanks to Glenda Keaton, who prepared all of the manuscripts and who typed endless versions of our papers.

Joel Michael
Allen Rovick
A MECHANICAL MODEL OF THE CARDIOVASCULAR SYSTEM
FOR EFFECTIVE TEACHING

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A circulation model effectively teaches interrelationships. Live animal studies provide a better realization of the beauty and complexity of living systems than do models, but animals are becoming more and more expensive to purchase and to use in the laboratory. Computer simulation is more precise than either, but such models do not seem as real for the student as a physical model.

The model is shown in Fig. 1. Except for the annual replacement of the rubber tubing, little maintenance has been required. The students are warned to keep their fingers from being caught under the cam.

Figure 1. Model of cardiovascular system. (From Rothe, C.F., J. Appl. Physiol. 17: 156-158, 1962).

Figure 2. Cross-sectional diagram of ventricle showing diaphragm, valves and ventricular volume indicator. (From Rothe, C.F., J. Appl. Physiol. 17: 156-158, 1962).

Aortic distensibility, simulated with a piece of 1/4 inch diameter thin-wall rubber tubing inside a piece of 3/8 inch diameter tubing, provides the student a tactile example of arterial pulsations. By switching to a piece of semi-rigid vinyl tubing, stiffening of the arterial bed reduces the mean flow and arterial pressure, because the ventricle is outflow-pressure dependent. The systolic arterial pressure does not increase appreciably, but the pulse pressure increases. No reflex or intrinsic compensatory mechanisms are represented in the model.

Ventricular volume changes are indicated by a plunger attached to a disk that rests on top of the ventricular diaphragm (Fig. 2). The plunger moves along a millimeter scale and the student estimates the minimum and maximum values ("end systolic" and "end diastolic" volumes). Zero is set by a rubber O-ring at the highest point (minimum end systolic volume) with the cam follower manually depressed far enough so that the cam tips just touch the cam follower. A movement of 1 mm is equivalent to about 1.5 ml of stroke volume. (The alternative method for calculating stroke volume is cardiac output divided by heart rate. Discrepancies provide the basis for some subsequent laboratory discussion.)
Valvular lesions may be studied because the valves, constructed from disks of stainless steel, can be held open to simulate insufficiency or held closed to simulate stenosis (Fig. 2).

**Laboratory Exercise**

Groups of 2-4 students spend about three hours with the model. A day or so later in laboratory conferences, groups of about 20 students spend another two hours discussing their data under the guidance of a faculty member.

We ask the student first to make qualitative observations of arterial pulsation, venous collapse, motion of valves and ventricular filling. By gently lifting up the plunger from the end of the "ventricle" opposite to the cam follower, the students observe how easily cardiac tamponade impedes filling and so cardiac output. The students then systematically vary the vigor of contraction, a peripheral resistance needle-valve, heart rate, and venous filling pressure. Flow, arterial pressure (mean, systolic and diastolic) and atrial filling pressure measurements provide the basis for calculation and understanding. Data manipulation involves plotting mean flow and the arterial pressures as functions of heart vigor, peripheral resistance, heart rate and venous filling pressure.

The students are expected to discover that with either inlet or outlet valve insufficiency, the actual stroke volume is large compared to the stroke volume calculated from flow and heart rate. They also should note that aortic valve problems are associated with a large heart (large end diastolic volumes), whereas with mitral (filling valve) problems, the heart tends to be small (small end systolic volume).

The effects of cardiac tamponade, arteriosclerosis, heart failure and hemorrhage are mimicked. The students are asked to consider possible reflex compensation or therapeutic interventions. They try various forms of compensation and then discuss limitations of the attempted compensation, as well as the reality of the model.

Medical and graduate students are also asked to interrelate the influence of venous pressure and heart rate on cardiac output. Data are plotted for the 3 heart rates, with venous pressure as the independent variable and flow as the dependent variable. They "discover" that with bradycardia, flow tends to plateau, and further increases in filling pressure have little influence because end diastolic volume is limited. With high heart rates, an increase in venous pressure has a marked influence on flow. At normal venous pressures, flow is greater at the normal heart rate than with either bradycardia (too few strokes per minute) or tachycardia (limitation due to filling time). On another graph, flow versus heart rate is plotted using the data from 3 different venous pressures. With high venous filling pressures, flow tends to be proportional to heart rate. At low filling pressure, heart rate, beyond a minimum, has little influence on flow.

The model described has been used by 3,000 medical, 2,000 dental, and several hundred graduate students at Indianapolis over the past twenty years. (It was described in J. Appl. Physiol. 17: 156-158, 1962). When asked to evaluate their teaching laboratory experiences, our students usually consider the exercise with the circulation model to have been the most effective. Copies have been constructed for use in over 30 other institutions throughout the world. Additional copies can be fabricated at reasonable cost in our machine shops.

In summary: Physical models provide an effective teaching tool with distinct advantages compared to lectures, reading, animal experiments, or computer-based aids. However, because they are only models, students must be warned of their limitations.
A SEPARATE COURSE FOR EXPERIMENTS IN CARDIOVASCULAR PHYSIOLOGY

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For the past decade, students at University of Texas Medical Branch, in Galveston, have enjoyed the benefits of several interdisciplinary courses in addition to the traditional basic science courses. The interdisciplinary courses were introduced by the Faculty of Medicine as part of an overall curricular revision. The objective of the interdisciplinary courses is to draw the various basic science courses together while reducing the student's total contact hours. The Integrated Functional Laboratory, together with endocrinology and neuroscience comprise the interdisciplinary courses.

Curricular Organization: The organization of the various courses in the curriculum is illustrated in Figure 1. The curriculum is built on a structure of four, 16 week blocks or terms. The Integrated Functional Laboratory is taught during the second and fourth terms. During the second term the course runs simultaneously with medical physiology which contains lectures on cardiovascular physiology and with the neuroscience course, in which the anatomy and the physiology of the autonomic nervous system were presented.

The second half of the Integrated Functional Laboratory is taught simultaneously with pharmacology and the second-half of pathology. Both of these courses contain a great deal of information related to the function of the cardiovascular system. In addition, in the interim term (term three) students take the first-half of pathology and endocrinology and are introduced to the hormonal influences on the cardiovascular system as well as the factors in the immune system which affect cardiovascular function and other cardiovascular pathology. It is advantageous to teach some cardiovascular physiology at the end of the basic science years since it offers the unique opportunity to integrate and reinforce the students' knowledge through review and problem solving experiences.

Course Organization: The course is organized by an interdisciplinary committee appointed by the Dean of Medicine and chaired by the director of the interdisciplinary laboratories. The committee solicits and evaluates experiments for use in the laboratory, determining placement of experiments in sequence in the overall arrangement of the course and oversees the grading of the students. The day to day operation is handled by the director and his staff.

The laboratory is usually taught to well over 200 students as there are 203 Medical Students and Graduate Students also take the course. For laboratory, the class is divided into two sections, with half of the class taking laboratory on one day and half on another. Each of these sections is then divided into six groups. Each of these groups would eventually then do the same experience, be in the same room, and have the same instructor. (An explanatory note is necessary. Associated with each experiment is a conference period in which the experimental results are discussed. We have adopted the term "experience" to pertain to the combination of experiment and conference.) Each of the groups of sixteen to eighteen students is divided into four teams of four or five students. Each team would thus operate with the same animal model or other laboratory experience. Each member of these teams is designated as team leader on a rotating basis.

The manner in which the experiments are taught is somewhat different in our course compared to traditional laboratory courses. Rather than have the entire class do the same experiment during a given laboratory period we usually have six experiences being taught simultaneously. Each group of students then rotates from experience to experience on a weekly basis. At the end of six weeks all the students have completed all of the experiments. At this time six new experiments are then instituted and the rotations begin once more.

Figure 1. The Basic Science Years. This is a diagrammatic representation of the various courses taught during the basic science portion of the curriculum at the University of Texas Medical Branch. The Integrated Functional Laboratory (IFL) is taught during the second and fourth term blocks. We begin teaching the sophomore class in October and the freshman class in January. There is an overlap of several weeks. We end the year in April when we teach the last classes to the freshmen.

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BASIC SCIENCE YEARS

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The teaching of the laboratory in this way allows us to make better use of faculty expertise and equipment. If we have only one person sufficiently knowledgeable in a given area to conduct laboratories on that topic he may teach all 12 laboratory experiences over 6 weeks. With two authorities, each would conduct six experiments which could either run serially over six weeks or could be run simultaneously so that all students rotated through the experiment in only three weeks. The same principle applies to equipment. Where adequate quantities of equipment are available, experiments may be "double-up". There are 24 laboratory exercises: 12 experiments in term two and 12 in term four. The term two experiments are listed in Figure 2; the cardiovascular experiments performed in this term are underlined.

TERM II EXPERIMENTS

Compound action potential
Spinal cord reflex
Erythrocyte glucose-6 phosphate dehydrogenase deficiency
Hepatic necrosis and biliary obstruction
Cardiac muscle
Events in the Cardiac cycle
Intestinal secretion and absorption
Hemorrhagic shock
Human pulmonary function
Acid base balance
Genetic counseling
Neuromuscular transmission

Figure 2. The Term II Experiments. We teach twelve laboratories in each term. During this term there are three cardiovascular laboratories. The titles are underlined; note also that the cardiovascular labs are taught at the same time as the laboratory on Acid Base Function.

** Term Two Experiments: ** One of the first experiments the freshman take is entitled The Events of the Cardiac Cycle. The objectives of this experiment are to acquaint the students with the equipment, working with living preparations and to illustrate cardiac principles presented in the physiology course. The experiment is performed using dogs which have been anesthetized with pentobarbital. Their left ventricles are catheterized via the common carotid artery. This trace is displayed on a cathode ray oscilloscope of a VR-6 recorder (Electronics for Medicine). The aortic pressure is likewise obtained from the aorta via the femoral artery and displayed on the screen along with lead II of the electrocardiogram and heart sounds. The students thus look at the time relationship between these events. They manipulate these pressures by giving drugs which affect the afterload. They also manipulate the electrical activity of the heart, first by giving large doses of epinephrine and then by opening the thoracic cavity and pericardium and creating atrial fibrillation with a stimulating electrode. Ideally, students should anesthetize the animals and perform the surgical procedures. But because the students' time is limited we have hired technicians to prepare the animals. Since this is part-time work we have attracted a remarkably well qualified staff including one dentist and several registered nurses who do not want full time employment.

The influence of the respiratory system on the cardiovascular system is also examined in the cardiac cycle experiment, and the right and left vagi are stimulated to show the effect that these nerves have on the cardiac cycle. At the end of the experiment the students fibrillate the ventricles and subsequently defibrillate them using a clinical defibrillator. One of the major benefits of this experiment is a subtle one: students see--many for the first time--living tissue "in action". They are impressed with how it differs from cadaver tissue and with the "feel" of the heart in normal systole and in fibrillation.

Running simultaneously with the cardiac cycle experiment is a second experiment on contractility of the cardiac muscle. This gives the students a look at the isolated right ventricular strip of a rat. This preparation has previously been described in the PHYSIOLOGIST by another group (2). In this experiment the students look at the Frank-Starling relationship and then modify contractility by changing the ionic content of the bath solution as well as administering positive and negative inotropic drugs.

The last cardiovascular experiment to be performed in this term is somewhat more sophisticated than the other two and consequently has been placed at the end of the term. This allows the students to have learned to operate the polygraph and other equipment and to have overcome what fear they may have had of working with a live animal, before conducting the more involved experiment. This experiment is done on unanesthetized sheep which have previously been prepared for chronic study. The animals are used continuously in the laboratory, not only in this particular experiment, but in two others which are taught in term four. This is possible because term two immediately follows term four. In fact, there is a three week overlap of the two terms. The preparation of the sheep involves placement of a Swan-Ganz thermocirulation catheter into the pulmonary artery via the femoral vein. An arterial catheter is placed in the descending aorta via a femoral artery. A two mm i.d. polyethylene catheter is placed in the inferior vena cava via the opposite femoral vein. The catheters are filled with 1,000 units of heparin and they are flushed and re-heparinized on a weekly basis. On the day of the experiment the animals are brought to the student laboratories in mobile metabolic cages. They are connected aseptically to intensive care monitors (Electronics for Medicine, OM-9 recorder); the aortic, pulmonary artery and left atrial pressures are displayed. The cardiac output is de-
determined by the thermodilution technique using an Edwards Computer. Blood gases are determined by an Instrumentation Laboratories Blood Gas Analyzer. Once the baseline data have been obtained the students begin removing blood from the animal into sterile plastic bags. This blood is heparinized for reinfusion. As the animal reaches a new steady state following the withdrawal of the blood, variables are again measured. This sequence is repeated three times and then the animals are reinfused and a final set of data is obtained. The conference is utilized to look at the data which have been obtained during the experiment and are plotted on transparencies. These data are also discussed in conjunction with a syllabus on hypovolemia.

Between term two and term three in our curriculum, the students have an eight week free elective which approximately ten percent of them use to pursue research activity. In the autumn the students enter into their term four classes and we begin the second half of the Integrated Functional Laboratory.

TERM IV EXPERIMENTS

Temperature regulation
The effects of drugs on respiration
The effects of exercise on cardiovascular reflexes
Endotoxic shock
Immunology
Renal drugs
Glucose tolerance test
Anesthesiology
Effects of drugs on cardiovascular reflexes
Studies on the contractile state of the myocardium
Uterine responsiveness to hormones
Renal excretion of salicylates

Figure 3. The Term IV Experiments. Of the twelve experiments taught during this term, four are cardiovascular experiences. These are underlined in the figure. There are also several experiments that are related to cardiovascular physiology: notably the experiment on the uterus which includes a general discussion of smooth muscle, the experiment in anesthesiology where the students see anesthesia induced and there is a discussion of the relationship between uptake and distribution of anesthetic agents and cardiac output, and renal drugs in which a discussion of the relationship of the diuretic agents in hypertension are presented.

Term Four Experiments: The term four experiments are listed in Figure 3. As can be seen, during this term there are four cardiovascular experiments. In the first six weeks we teach an experiment on the effects of exercise on cardiovascular function and another on endotoxic shock. The first experiment uses the student as a subject. EKG electrodes, for the standard leads, as well as stress leads are connected to a VR-6 recorder. Their EKGs and blood pressure are monitored in the resting, supine state. The students then do standard exercises either on a treadmill or bicycle ergometer. The recovery process is observed and analyzed.

The endotoxic shock experiment is performed in instrumented sheep as described above. In this instance the sheep are injected with a dosage of 0.5 µg/kg of endotoxin and its cardiovascular and pulmonary-responses are monitored, again using the OM 9 Recorder and Edwards Cardiac Output Computer apparatus. While the endotoxin is taking effect a dialogue is carried out between the instructor and the students involving problem solving types of exercises. A syllabus on gramnegative sepsis is included in the packet for this experience.

The second-half of the term contains two cardiovascular experiences. One of these deals with cardiovascular reflexes. Here the subject is an anesthetized dog. These animals have a strain-gauge arch sewn onto their right ventricles, the femoral artery is cannulated for recording arterial pressure. The common carotid arteries are isolated and the vagal nerves are exposed and prepared for both central and peripheral stimulation. Students inject various sympathomimetic drugs and their antagonists and determine how all these affect the baroreceptor reflexes by occluding the carotid arteries. The last cardiovascular experiment that is performed is entitled The Effects of Drug on Myocardial Contractility. The left ventricles of dogs are cannulated via the carotid arteries. The signal from the catheter tip manometer recording the left intra-ventricular pressure is amplified and then fed into an electrical circuit which develops an index of contractility known as the peak (dP/dt)/P students monitor this index while they change afterload by injecting an α-adrenergic agonist. They change preload through volume loading; and they modify myocardial contractility with catecholamines, cardiac glycosides, and β-adrenergic antagonists.

Student Evaluations: Each of these experiments is evaluated by the students at the end of each laboratory experience. The evaluation is on a scale from 0 to 12; 12 being excellent. A table of the ratings of individual experiments appears in Figure 4. The Medical Students' overall evaluation of these cardiovascular experiments has been between 9 and 10. This is slightly higher than the overall evaluation of the cardiovascular lecture series in physiology. In addition, the laboratory staff as well as the Integrated Functional Laboratory Committee, periodically evaluates the experiments. Since we collect student evaluations on a weekly basis we can monitor all experiments during the six weeks they are taught and reorganize, re-staff, or re-equip any experiment in which a problem is identified. We monitor the
student's comments and attempt to make improvements suggested by the comments. For instance, an instructor who has failed to make clear one of the objectives for the experience can quickly identify this problem from the student evaluation. Or if there is continued comment that an instructor is difficult to understand or that there has been a continuous failure of item of equipment during lab period, this can be rapidly corrected. The Integrated Functional Laboratory Committee, based upon input from several sources including the students, periodically reviews the experiences as well as reviewing proposed experiments which have been submitted by the faculty. In addition, many innovative changes in experiments are the result of developments in technology. Through the years, as a result of this particular fine tuning, the experiments have become progressively more perfect. On the average, we make one major modification of an experiment a year. Most recently, this has involved the utilization of computer technology as a part of our experimental experience. To date our experience with this innovation is not sufficient to include here.

REFERENCES


Figure 4

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CV_1: Studies of the contractile State of the Myocardium; CV_2: Events of the Cardiac Cycle; CV_3: Hemorrhagic Shock; CV_4: Effects of Exercise on Cardiac Function; CV_5: Cardiac Muscle; IF_2: Endotoxin Shock; IF_3 Effects of Drugs on Cardiovascular Reflexes

Figure 4. Student Evaluations. This figure is a copy of our student evaluation form. These are handed out to the students and they are asked to evaluate each experience as they do it. These are usually given them to be filled out at the very end of the experience and they then turn them in within a few minutes of the ending of their laboratory period. These forms can be rapidly processed into a computer and weekly printouts are given to each instructor which evaluate his daily performance. The evaluation comments are also available to the instructor. We have summarized the evaluations which the students gave to the various experiments during the 1981-82 school year.
INTRODUCTION

It has been noted that there has been a general downward trend in the use of "wet" labs as a teaching tool in medical education (3). There are undoubtedly many factors that have contributed to this phenomenon; e.g., the need to streamline courses due to an ever increasing knowledge base vis-a-vis reduced teaching time. However, as Eichna (1) has pointed out, medical education should be, but for the most part is not, a thinking, problem solving process. In a basic science discipline, such as physiology, the optimal setting for problem solving is the laboratory. Unfortunately, the aforementioned reduction in teaching labs has resulted in remaining laboratory experiences being mainly "cookbook" exercises in which students follow prescribed procedures, the outcomes of which are usually known in advance. Although such laboratory exercises do provide valuable experiences such as working with live tissues and directly observing temporal phenomena (e.g., the action potential), the traditional cookbook labs do not provide students with the opportunity to work through all aspects of a laboratory problem, e.g., design and performance. We feel that this is a definite deficiency in medical education since physicians are constantly faced with the task of evaluating research information in professional journals, etc. If a physician's only experience with medical science laboratories is with "tried and true" exercises, then he or she has no substantial knowledge base with which to evaluate the research of others.

The purposes of the selective laboratory described herein were to 1) enable students to gain experience in all aspects of medical science experimentation (e.g., design, performance, evaluation, and presentation); and 2) provide them with an opportunity for creativity and individual expression. This was approached by providing one selective laboratory experience in addition to six regular wet labs given within the framework of a one semester 7 credit hour course in medical physiology. At the University of Kentucky, physiology is given during the first year of medical school to a class of about 110 students. This manuscript is based on the results from our 1981 and 1982 courses.
be, divide them up into teams for the actual performance of the experiments. The number of students working as a team depended on available space and equipment. For most of the experiments, students worked in teams of two or three, but for the more complex topics requiring extensive animal preparation and/or sophisticated equipment, the students worked in teams of four.

Table 1
Selective Lab Topic List

1) Aerobic Conditioning
   Faculty: Drs. Richardson and Kearney
   Limit: 10 students

2) Cardiac Contractility
   Faculty: Dr. Randall
   Limit: 8 students

3) EEG and Evoked Potentials
   Faculty: Drs. Frazier and Lastimosa
   Limit: 20 students

4) Ionic Mechanisms of Nerve
   Faculty: Dr. Peretz
   Limit: 16 students

5) Muscle Blood Flow in Humans
   Faculty: Dr. Richardson
   Limit: 8 students

6) Regulation of Heart Rate
   Faculty: Dr. Randall
   Limit: 8 students

7) Renal Diuresis
   Faculty: Dr. Ott
   Limit: 20 students

8) Pulmonary Mechanics
   Faculty: Drs. Lee and Zechman
   Limit: 20 students

If a student or group of students wished to generate their own topic or problem independent of the list, they were free to do so within the limits of our facilities and provided they could recruit a faculty sponsor. The results of one such experience led to a presentation by one of the student groups at a national meeting (2).

Subsequent to the initial contact between students selecting a particular topic and the associated faculty person, that faculty member met with the students individually and/or as a group to assist them in the design, performance and analysis of their experiments (Fig. 2). The degree of faculty assistance in each of these areas, as well as the total time the students spent on their selective lab, depended upon the nature of the experiments. For example, the topic dealing with aerobic exercise conditioning was spread out over a six week period, whereas the topic concerned with ionic mechanisms of nerve was concentrated over a two week interval.

The number of times a given student team actually performed an experiment depended upon the nature of the experiments. Those requiring modest equipment and preparation (e.g., renal diuresis, human muscle blood flow) were performed several times, whereas, those requiring extensive preparation (e.g., cardiac contractility) were usually performed only once. The location of the laboratories used also depended upon the nature of the experiments. Some experiments (e.g., ionic mechanisms of nerve, aerobic conditioning,

Table 2
Samples of Selective Lab Descriptions

Topic 2 - Cardiac Contractility

The objective of this study will be to measure the effects of the following on regional cardiac contractility in the anesthetized dog: 1) increases in sympathetic activity; 2) changes in preload and afterload of the heart; 3) hypoxia; and 4) curvilinear occlusion.

Equipment available will include ventricular force transducers, catheters and pressure transducers for the measurement of intraventricular and systemic pressures, nerve stimulators, and sympathetic agonistic and antagonistic drugs.

Topic 5 - Muscle Blood Flow in Humans

The objective of this study will be to examine relative values of "active" and "reactive" hyperemia in the skeletal muscle circulation of humans.

For these experiments forearm blood flow will be measured by placing a Doppler ultrasonic flow probe over the brachial artery. Active hyperemia will be induced by static and by rhythmic hand grip contractions. Reactive hyperemia will be induced by occluding brachial arterial blood flow via a pneumatic cuff.

Possible questions to answer:
1) How does reactive hyperemia following a period of ischemia compare with active hyperemia following an equal period of static muscle contraction at different levels of muscle force?
2) Are active and reactive hyperemia additive?
3) How does active hyperemia following a period of static exercise compare with that following a period of rhythmic exercise at different contraction frequencies?
4) Etc., etc., etc. (Students doing these experiments should think of some more questions).

Equipment will include: a Doppler flow meter, pressure cuffs, ECG equipment, and a hand dynamometer for rhythmic and static hand grip exercise.
human muscle blood flow) were performed in the faculty member's research laboratory using his/her own equipment; whereas other experiments (e.g., pulmonary mechanics) used the regular teaching labs and equipment.

At the conclusion of their selective laboratory experience, each student independently prepared a written report in journal format. These reports were graded subjectively by the faculty responsible for the particular topic and given a score ranging 1 to 30. This constituted a maximal 10 percent of the total points used in determining a student's final grade. The other 270 possible points were derived from objective multiple choice tests on lecture material.

RESULTS AND DISCUSSION

Both quantitative and qualitative types of analysis were used to evaluate the selective laboratory experience. Quantitative analysis involved statistical comparisons of points earned on the selective lab write-up with points earned for the total course (exams plus lab). Qualitative analysis was achieved via a questionnaire given to the students in which they evaluated the selective lab vis-à-vis the regular wet labs and the lecture portion of the course.

Quantitative Evaluation: Figure 3 presents class means for percentage scores (number of points as a percentage of maximum possible) for the selective write up and for the total course. Both the 1981 and 1982 classes did slightly, but not significantly, better in the selective lab compared to the total course. Thus, for the class as a whole, the selective lab tended to help rather than hurt with regard to a final grade. Note also that both classes performed essentially the same in the selective lab and the total course. This demonstrates that selective lab grades, which are determined subjectively via written reports, are reproducible between classes that are academically matched in terms of objective matching graded exams.

The data presented in Figure 3 shows that in terms of a whole class, students performed about equally in the selective lab and in the total course. To determine if this was generally true for individual students, the correlation between selective lab and total course scores was determined. This information is presented in Figure 4 for the 1982 class. There is a general linear trend between selective lab and total course scores, but the regression coefficient ($r$) was low. The 1981 class was similar but with an $r$ value of 0.403. Therefore, performance of a student in the selective lab was not generally reflective of total course performance. In terms of an overall education, this is probably more beneficial than detrimental since it points out that a student who does not do well in objective grading may still have the ability and motivation to learn through laboratory experimentation and the communication skills necessary to express what he or she has learned. In this regard, 35 percent of the students from both classes combined, scored better than 10 percentage points higher in their selective lab write-ups compared to total course scores, while only 6 percent of the students had selective lab scores 10 percentage points or more lower than their total course scores.

Fig. 4. Relationship between selective lab and total course scores, as percentage of maximum possible points, for the 1982 class. $r$ = linear regression coefficient.

Qualitative Evaluation: At the end of the semester the students were given a questionnaire in which they were to rate a variety of aspects of the physiology course (e.g., quality of the instructors, the examinations, the labs, etc.) as good, fair, or poor. Figure 5 gives the combined...
1981 and 1982 class ratings of the selective labs, the traditional (cookbook) labs and the course as a whole. Neither the selective lab nor the traditional labs received high ratings compared to the total course. However, the higher ratings of the selective lab, compared to the traditional labs, clearly indicates that providing students with the opportunity for a complete and creative laboratory experience is a move in the direction of a more positive attitude towards wet labs in medical education.

Fig. 5 Qualitative evaluation of the selective lab, the traditional lab and the total course. The percent response refers to the 1981 and 1982 classes combined.

SUMMARY

In overall scope, the addition of at least one laboratory that enables students to experience all aspects of laboratory science adds several valuable dimensions, which compliment the traditional labs given within the framework of a classical physiology course. To provide such an experience, The Selective Lab procedure was developed and added to a one semester course in medical physiology. The following paragraphs summarize and compare some of the advantages and disadvantages of The Selective Lab vis-a-vis our experience with the 1981 and 1982 classes.

The major advantages of the selective lab were: 1) the opportunity for individual expression in an otherwise objective, impersonal course presentation; 2) higher motivation on the part of the students by allowing them some degree of personal preference in the labs they select; 3) the opportunity for the students to experience all phases of experimental science, and to delve deeper into a given topic than would be possible in a cookbook lab format; and 4) the opportunity to be graded on a subjective basis.

The disadvantages were: 1) a decrease in topic breadth, (with the present limits of equipment, space, faculty personnel, and time, all possible topics simply cannot be covered), and 2) logistics. The need to accommodate 110 students with a limited number of selective labs does create problems with regard to sharing equipment, working in teams rather than individually, and finding the time to perform complex experiments.

On balance, both the students and the faculty felt that The Selective Lab was a positive experience.

ACKNOWLEDGEMENTS

The author would like to thank the Division of Educational Development for their assistance in evaluating The Selective Lab.

REFERENCES


The Clinical Reasoning Process

Research into the actual behavior of physicians has revealed certain fundamental steps in the process of clinical reasoning (1-6). There is no a priori reason to suppose that the process of clinical reasoning in medical problem-solving is any different than the reasoning process invoked by any experts when confronting a problem in their respective disciplines (7).

In summary the process contains the following steps illustrated here within the framework of clinical problem solving (see figure 1): The physician or the student confronts the patient, perceives cues from the environment and the subject, and assembles an initial mental formulation of the problem. Very rapidly multiple hypotheses are generated as possible explanations of the problem. An inquiry strategy is engaged which involves, among other things, the use of clinical skills to acquire data which may be used to refine the initial problem formulation. The refined problem formulation is then compared to the hypotheses generated. These hypotheses are retained, discarded, or enlarged. Further inquiry is pursued until a particular hypothesis attains sufficient confidence to form the basis of management decisions.

Self-Directed Learning

At any stage in the reasoning process progress may be obstructed by lack of appropriate knowledge or skills. When progress or understanding is impeded, learning issues may be identified. A wide variety of learning resources may be brought to bear upon the problem in a context of immediate application (8). (see Figure 2): This self-directed learning may be summarized as follows: In the clinical reasoning process, at any stage in the cycle (see Figure 1), students may find progress obstructed by ignorance or lack of understanding and skills. When this occurs the student notes the obstruction as a learning issue and continues to confront the problem. When learning issues accumulate to the point where progress is frustrated the process is stopped. The student then designs a learning prescription, under faculty guidance, which considers both acute learning needs and objectives for the relevant phase of the curriculum. Learning resources are then consulted by the student to meet the dictates of the prescription. These resources may be any of a wide variety—tests: journals, faculty, slide tapes, etc. After relevant study the student then returns to the problem either at the point left off or to begin anew better equipped for the process.
Utility of the Physician's Knowledge

The practicing physician must have a copious store of recallable factual knowledge as well as a battery of clinical skills which can be relied upon in the context of medical problems. This is so because the professional consultation cannot, as a rule, be interrupted while the physician consults a textbook or a journal article or perhaps makes inquiries of colleagues or professors. In some cases, of course, these things must be done and it may be better for patient rapport if they are accomplished without the patient's acute knowledge. Naturally, in some instances, the patient will be better served in the certain knowledge that the physician is consulting other sources of expertise.

A large fraction of the essential knowledge which a physician must have in recallable form or effective practice is physiology. The most widespread and relentless form of health failure or disease is cardiovascular disease. For these reasons, a sound recallable background of cardiovascular physiology is essential to the effective physician. Recallable knowledge is not enough. It must also be recallable in the context of a problem to which it may be applied. For example, it is of no consequence to know the Reynolds number for blood if the implications of turbulent and laminar blood flow are not understood. The relationship and character of heart sounds within the cardiac cycle are of no value if the association between valve stenosis or regurgitation and hypertrophy of the myocardium is not recognized. The list of examples may be endless. The point is that the massive accumulation of facts and concepts out of context is either lost or not reliably useful (9, 10). Numerous investigations have now demonstrated that most of the material memorized by students for examinations is forgotten or not usefully recallable within a short time (11, 12). It is known that most students in clerkships cannot pass even the clinically relevant portions of their first year basic science exams if they are readministered (13). Fortunately, this turns out not to be a serious problem for the health of the nation because the physicians in training as clerks and residents or later in practice relearn the relevant information in the context of patient problems where it may be brought to bear upon other clinical problems to which practitioners are exposed. The tragedy lies in the time and resources wasted in the teaching by faculty and the memorizing by students of vast amounts of data which is either forgotten or not recallable within a practical context. The student would be better served learning how to acquire relevant knowledge in a context of the professional task environment. The faculty would better serve the academic community by devoting their time to their research and their particular fields of expertise. When faculty are consulted by students in pursuit of learning resources for the acquisition of knowledge relevant to a professional task situation, the student benefits greatly and the faculty suffer only a minor inconvenience. The faculty talents are accurately used and the student acquires useful current information. The student gains in education and learns early in the career the methods of self-education which must be relied upon for a lifetime of continuous education.

Sources of Problem-Based Learning Material

All of the foregoing may be well recognized but, where do we obtain patients for first year medical students to use in a professional task situation while they generate learning issues and gain practice in using faculty and other learning resources? As a rule, we don't. However, we can obtain such patients if we use simulations. A variety of patient simulations are available. The simulated patient is one (14). In this case a person is trained to simulate a patient problem so exactly that expert physicians cannot tell them from real patients (15). These simulations are expensive and most appropriate for clinical skills training; physical examination and interview skills—the benefits for the advancing student are obvious. Another simulation is the Problem-Based Learning Module—P.B.L.M. (16). In this simulation a real patient problem is recorded on paper in an easily accessible format. The P.B.L.M. permits inquiry. Any action, which was or could have been taken by the real physician, can be taken by the student. The patients' actual response is obtained. Actions can be taken in any order or disordered for that matter. Items from the interview, physical examinations, laboratory tests, specialist consultations are available from the simulation.

Problem Based Learning in Practice

Students encounter the problem (PBLM) in a group of six. This number may range from five to seven. Four is too few to ensure an adequate pool of background knowledge for first year students and eight is too many to maintain a uniformity of participation. There is a faculty tutor who ensures that the group adheres to the reasoning process. The tutor does not normally serve as a resource person although he or she may be specifically requested to do so. Supportive resources are not normally consulted in the course of a group meeting except for brief interruptions to consult a medical dictionary or a ready reference. The students engage the patient's actual response in the simulation. Any action, which was or could have been taken by the real physician, can be taken by the student. The patients' actual response is obtained. Actions can be taken in any order or disorder for that matter. Items from the interview, physical examinations, laboratory tests, specialist consultations are available from the simulation.
progress can be made because of the lack of knowledge, the group process is stopped. This usually occurs after about two hours. The students, with the help of the group and the tutor, design an educational prescription which takes into account each student's existing knowledge and skills (8). They may partition the topics and exchange investigated resources. At a later date, usually a few days, the group reconvenes and brings their newly acquired relevant knowledge to bear on the problem either beginning anew or continuing from where they left off. The student-directed learning is active. The relevance of the basic science learned is perceived directly, and vocabulary, skills and problem-solving abilities are enhanced simultaneously. The student learns in the professional task environment. The faculty tutor, once having gained Socratic tutorial skills, does not have to prepare for the session and when consulted in session or out, it is as an expert in a particular discipline area where no extra preparation is required.

Results of a Problem Based Learning Trial

Two classes of first year medical students were compared. One class, the control group, received the Cardiovascular section of a system based curriculum in a modular format. They were given written modules containing specific learning objectives, official sources of reference material for each objective and lectures or laboratory exercises on each topic. The problem based learning class in the following year received seven Problem Based Learning Module simulations of patients with cardiovascular disease. They received no written objective modules, no specified learning resources, but the same lectures and laboratory exercises. The two classes had similar backgrounds with Grade Point Averages from prior college work and Medical College Admission Test scores which were essentially comparable. The means for both estimators of success in medical school were slightly higher for the control group (see Table I).

Both classes were evaluated for subject matter content knowledge with the same objective multiple choice exam encompassing Anatomy, Behavioral Science, Biochemistry, Pharmacology and Physiology. There was no significant difference between the two classes in the scores obtained in any of the disciplines examined (see Table II). The correlations among scores (in the sense that the score in any one discipline may be a predictor of performance in another discipline) were significantly improved in the problem based learning class (see Table III).

Twelve weeks after the cardiovascular systems examination both classes were reevaluated using the identical subset of the original examination. Again, there was no significant difference between the scores obtained by the two classes. However, when the absolute level of the mean scores was considered the rate of decline of score was significantly less (twice as slow) than in the PBLM group (see Figure 3).

DISCUSSION

It is evident that there are deficiencies in the current widespread teacher-centered subject-based curricula popular in most medical schools. Student-centered problem-based learning has been proposed as an alternative.

In this limited trial, which was admittedly retrospective to the extent that it was not devised until the control class had progressed to the second year, some positive evidence in support of problem based learning has been accumulated. In the objective sense of discipline exams problem-based learning students perform just as well as traditional subject-based learning students. The observation that correlation among discipline exam scores is significantly enhanced could be interpreted as better integration of knowledge by problem based learning students. The rate of decline of scores after the course was less than half as fast in the problem based learning class suggesting that knowledge is better retained by this group.

Figure 3. Decline in test score over 12 weeks following initial exam. There were 72 students in each group. (●) represents the control group having an objectives based curriculum only while (○) represents the group having objectives based curriculum with P.B.L.M.’s. The rate of decline of score was 1.114%/Wk vs. 0.454%/Wk for the two groups respectively.

It should be mentioned that all was not "roses" with the problem based learning group. The level of apprehension among faculty and students was greater than usual. Some faculty were concerned that the four to six hours per week spent as tutorial group facilitators was an unwarranted extra burden on their time. Many
students were uncertain that they were learning enough of the appropriate material when they were not told exactly what to learn and where to read about it. The faculty concern can only be addressed by administrative recognition of tutorial facilitation efforts as valid teaching time. In this university that recognition has been extended. The student concern will be addressed only if future behavior vindicates the anxieties expressed during the course. For future classes who may have the experience of an entirely problem-based curriculum familiarity should considerably reduce anxiety.

In summary it cannot be overlooked that problem-based learning students learned at least as well as subject-based predecessors, forgot at less than half the rate, and indicated improved integration of knowledge among basic science disciplines.

Finally, it must be recognized that problem-based learning students had the additional benefit of gaining experience in patient problem solving, the repeated practice of discovering their own learning needs, and the opportunity to apply their knowledge in the professional task environment of their vocation.

### Table I

<table>
<thead>
<tr>
<th>Score Category</th>
<th>Objectives Based Curriculum Only</th>
<th>Objectives Based With P.B.L.M.'s</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade Point Average</td>
<td>3.474 ± 0.047 *</td>
<td>3.368 ± 0.048</td>
</tr>
<tr>
<td>M.C.A.T. Scores</td>
<td>9.465 ± 0.146 *</td>
<td>8.990 ± 0.190</td>
</tr>
<tr>
<td>FB</td>
<td>9.324 ± 0.193</td>
<td>9.060 ± 0.207</td>
</tr>
<tr>
<td>BI</td>
<td>9.408 ± 0.183 *</td>
<td>9.060 ± 0.207</td>
</tr>
<tr>
<td>PH</td>
<td>9.070 ± 0.202 *</td>
<td>8.971 ± 0.212</td>
</tr>
<tr>
<td>RD</td>
<td>8.845 ± 0.180</td>
<td>8.784 ± 0.174</td>
</tr>
<tr>
<td>OT</td>
<td>8.845 ± 0.182</td>
<td>8.784 ± 0.174</td>
</tr>
<tr>
<td>Mean M.C.A.T.</td>
<td>9.124 ± 0.036 *</td>
<td>8.747 ± 0.025</td>
</tr>
</tbody>
</table>

The values reported are class means and standard error of the mean. There were 72 students in each group with column one representing the class completing first year in 1981 and column two representing the class completing first year in 1982. (*) indicates a significant difference between means at the P<0.05 level. If there was any advantage derived from college preparation or aptitude for medical school implied by these estimators it was in favor of the control group.

### Table II

<table>
<thead>
<tr>
<th>Discipline</th>
<th>Objectives Based Curriculum Only</th>
<th>Objectives Based With P.B.L.M.'s</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anatomy</td>
<td>13.40 ± 1.88 / 17</td>
<td>14.83 ± 2.37 / 17</td>
</tr>
<tr>
<td>Pharmacology</td>
<td>10.97 ± 2.32 / 14</td>
<td>10.69 ± 2.76 / 14</td>
</tr>
<tr>
<td>Physiology</td>
<td>47.57 ± 5.40 / 56</td>
<td>40.63 ± 10.49 / 56</td>
</tr>
<tr>
<td>Biochemistry</td>
<td>5.42 ± 0.76 / 6</td>
<td>4.90 ± 1.24 / 6</td>
</tr>
<tr>
<td>Behavioral Science</td>
<td>5.40 ± 0.89 / 7</td>
<td>5.09 ± 1.44 / 7</td>
</tr>
<tr>
<td>Total (At End of Course)</td>
<td>83.03 ± 8.68 / 100</td>
<td>76.14 ± 15.23 / 100</td>
</tr>
</tbody>
</table>

In all disciplines except Physiology curriculum was derived from faculty prescribed objectives for both groups. In Physiology, curriculum was derived from student-generated learning issues associated with the solving of simulated patient problems (P.B.L.M.'s). The standard multiple choice (National Board Format) exam was the same for both classes and consisted of the number of questions indicated to the right of each discipline mean score in the two columns above. There were /2 students in each group and variability is expressed as standard deviation. There was no significant difference between any of the scores obtained by the two groups at the P<0.05 level.

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### TABLE III

**CORRELATION MATRIX FOR DISCIPLINE EXAM AND TOTAL SCORES**

<table>
<thead>
<tr>
<th></th>
<th>ANATOMY</th>
<th>ANATOMY</th>
<th>PHARMACOLOGY</th>
<th>PHYSIOLOGY</th>
<th>BIOCHEMISTRY</th>
<th>BEHAV. SCI.</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>PHARMACOLOGY</td>
<td>1.00</td>
<td>0.50</td>
<td>0.14</td>
<td>0.29</td>
<td>0.64</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PHYSIOLOGY</td>
<td>0.64*</td>
<td>1.00</td>
<td>0.57</td>
<td>0.10</td>
<td>0.31</td>
<td>0.72</td>
<td></td>
</tr>
<tr>
<td>BIOCHEMISTRY</td>
<td>0.62*</td>
<td>0.62</td>
<td>1.00</td>
<td>0.36</td>
<td>0.43</td>
<td>0.95</td>
<td></td>
</tr>
<tr>
<td>BEHAVIORAL SCIENCE</td>
<td>0.43*</td>
<td>0.34*</td>
<td>0.60*</td>
<td>1.00</td>
<td>0.26</td>
<td>0.30</td>
<td></td>
</tr>
<tr>
<td>TOTAL</td>
<td>0.50*</td>
<td>0.34*</td>
<td>0.61*</td>
<td>0.51</td>
<td>1.00</td>
<td>0.52</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.76*</td>
<td>0.66</td>
<td>0.97*</td>
<td>0.66*</td>
<td>0.68*</td>
<td>1.00</td>
<td></td>
</tr>
</tbody>
</table>

The upper right half of the matrix shows correlation coefficients relating test scores in each discipline and the total score to every other discipline and the total score for the class having only a faculty prescribed objectives based curriculum. The lower left half of the matrix shows the same data for the class having the same curriculum except for student-generated learning issues in Physiology and patient problem solving using P.B.L.M.'s. The *'s in the lower left half of the matrix indicate increased correlation associated with the use of P.B.L.M.'s and student-generated curriculum in Physiology.

### REFERENCES

8. Ibid. Chapter 6.
INTRODUCTION

Almost every medical student can properly state the Fick equation, tell you that the outputs of the right and left hearts are equal, or define the notion of cardiac reserve. However, if we ask this same student to calculate cardiac output using data from the cardiac catheterization laboratory...or discuss how a patient can have a pulmonary blood flow of 15 L/min with a systemic flow of 5 L/min...or explain how a patient might have normal pressures throughout his cardiovascular system but be unable to play a round of golf...we are likely to find that the student can not give us an answer without considerable coaching.

The lesson here is well known to most of us. An instructor in front of an audience in a lecture hall is a system well suited for the passive, one way transmission of "facts". It does a much poorer job of assisting students to become active thinkers about physiology. That is to say, it is not much good at encouraging integration of information or the development of problem solving skills. Nevertheless, lectures remain the dominant instructional mode in most of our physiology courses.

However, medical students, and ultimately physicians, need to be more than passive regurgitators of stored "knowledge". In fact, it is fair to say that:

MASTERY OF PHYSIOLOGY=ACQUISITION OF "FACTS"+THE ABILITY TO "SOLVE PROBLEMS" WITH THESE "FACTS".

Therefore, recognizing the limitations of the lecture hall in fostering problem solving, then we need to devise other teaching/learning formats that will encourage more active "thinking about" physiology.

In Table I are listed some of the processes that may be involved in "problem solving" in physiology. It equally well describes the thought processes that are involved in clinical diagnosis and patient management.

<table>
<thead>
<tr>
<th>TABLE I</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Problem-Solving Processes That May Be Involved in Physiology (or Medicine)</strong></td>
</tr>
<tr>
<td>1. &quot;Translation&quot;</td>
</tr>
<tr>
<td>2. Interpretation</td>
</tr>
<tr>
<td>3. Calculation</td>
</tr>
<tr>
<td>4. Integration</td>
</tr>
<tr>
<td>5. Analysis</td>
</tr>
<tr>
<td>6. Prediction</td>
</tr>
<tr>
<td>7. Hypothesis Generation</td>
</tr>
</tbody>
</table>

Laboratory exercises, whether they be "wet" labs in which the students prepare an experimental animal, or "dry" labs in which they only "exercise" a paper and pencil or a computer terminal, are one kind of experience in which we seek to develop the problem solving ability that is necessary for a truly complete mastery of physiology.

At Rush we use the lecture hall in the conventional way. We also schedule a variety of laboratories, one of which will be described later in this volume. However, we utilize a third kind of teaching exercise that we call the tutorial.

**THE SMALL GROUP TUTORIAL**

The tutorial is simply an instructor and a small number of students (ideally no more than 20) meeting together to consider a set of problems. These might be numerical problems to be solved by calculation. Or the problems may be the output of a system to be explained by describing the set of physiological interactions that generates it. The only requirement for these problems is that they not be answerable by simply memorizing numbers or facts.

One of our most successful tutorials utilizes data from three patients obtained in the cardiac catheterization laboratory at our hospital. And we must extend our thanks to Neil Ruggie, MD, the Director of the Cardiac Catheterization Laboratory, for providing us with case reports we have used. For each patient the data have been put together in a structured way that encourages the students to think through these problems in a series of logical steps. In this way they can be led to an explanation of how a cardiovascular system with relatively discrete pathology can produce the patient's condition.

A tutorial is most likely to help in the development of problem solving skills if student input to the discussion is maximal. This ought not be the occasion for still another lecture to be received passively by the students. The instructor's role is to guide the discussion, serve as a resource person, and see to it that as many of the students as possible take an active part in the exercise. This latter function usually requires that the instructor gently coerce participation from those reluctant to speak (perhaps because of a fear of being wrong "in public")
while not actively discouraging the more vocal.

One reason for the success of this exercise is the students' perception of the relevance of pathophysiology. To them stenosed valves or a-v shunts are "medicine" in a way that Na and Ca channels in the myocardium are not. (Never mind the clinical relevance of these channels, the issue is the students' perception of such phenomena.) While we should not try to "sell" every piece of physiology we want to teach by documenting its immediate and direct applicability to medicine, it is clear that the clinical flavor intrinsic to our pathophysiology problems encourages student involvement in a significant way.

Let us add that there is no reason to think that the appeal of pathophysiology problems is limited to medical students; everyone, undergraduate, graduate or medical students alike finds problems about "real people" fascinating.

THE STRUCTURED PATHOPHYSIOLOGY PROBLEM

The key to the success of this approach to teaching problem solving is the structuring of the problems and the discussion to channel the students' thinking without obviously suggesting the "right" answer. This may be achieved in a number of ways.

First, one must carefully select the problems to be used. Even the most "classical" case is likely to contain some data that is difficult to reconcile with the rest of the physiology at work. Judicious editing yields a case report that is understandable and clinically realistic while remaining "solvable" by first-year medical students. This does not mean that all ambiguities need to be removed; they can often be used to generate lines of discussion that are particularly instructive.

A second tactic that is helpful is to generate within the problem a required sequence of steps, i.e. a structure. As this will represent the major focus for the rest of this paper, we will briefly defer comment on this.

Finally, a plan for instructor "involvement" is developed, the Faculty Guide. This consists of a sequence of questions to be put to the students, or issues to be raised at certain points in the discussion. While these should not be taken as the only inputs to be provided by the instructors, they are a minimal set that ought to be discussed to derive adequate benefit from the material contained within each problem.

The Faculty Guide serves two additional purposes. It ensures some minimal level of uniformity in the discussions that occur in tutorial sessions held at different times or by different faculty. And it allows faculty other than the current lecturer (or the authors of the pathophysiology problems) to participate effectively in the tutorials.

Students encountering complex pathophysiology problems initially need considerable guidance. They are often completely baffled and need to learn how to approach such problems in a logical manner. This guidance is provided by structuring the material they are given. Information in the tutorial write-up is presented in a carefully determined sequence. Calculations are requested at appropriate places as are questions to be answered.

Table II illustrates the over-all format that we have adopted for structuring our cardiovascular pathophysiology problems. We begin with a brief case history in which the patient's signs and symptoms are presented. Next, the students are asked to examine some general descriptive data obtained during the cardiac catheterization procedure and to make some simple but important calculations. Then static pressure values from various locations are presented, followed by an example of the actual pressure tracings. Finally, the resistances are calculated and the use of "indices" as a means of comparing results across a population is introduced.

![TABLE II](image)

The Structure Of The Cardiovascular Pathophysiology Problems Used In Small Group Tutorials

<table>
<thead>
<tr>
<th>Signs and Symptoms</th>
<th>Hypotheses?</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Data Describing Pt Condition</td>
<td>Identify: Abnormalities</td>
</tr>
<tr>
<td>Calculate: Flows Thru Heart</td>
<td>Hypotheses?</td>
</tr>
<tr>
<td>Pressure Values</td>
<td>Identify: Abnormalities</td>
</tr>
<tr>
<td>Identify: Abnormalities</td>
<td>Hypotheses?</td>
</tr>
<tr>
<td>Cardiac Cath Tracings</td>
<td>Identify: Abnormalities</td>
</tr>
<tr>
<td>Calculate: Vascular Resistances</td>
<td>Hypotheses?</td>
</tr>
<tr>
<td>Calculate: &quot;Indices&quot;</td>
<td>Hypothesis?</td>
</tr>
<tr>
<td>Diagnosis?</td>
<td>Explanation?</td>
</tr>
</tbody>
</table>

At every stage the students are asked to consider the data presented, or the values of parameters calculated, to look for abnormal values or patterns of values. They are encouraged to generate hypotheses about the pathophysiology that might give rise to such data and to reject untenable hypotheses as more data becomes available. Eventually the students ought to be able to "home in" on a most probable explanation of what is going on in that patient.
We can examine two components of this sequence in a little more detail. In Table III we can see an example of the initial data from one of the patients. With this information the students ought to be able to do a Fick calculation to determine left and right ventricular outputs and then to calculate stroke volume. The students are asked to examine these data to see if any of the values are abnormal or if they suggest additional hypotheses about the pathophysiology that is present. Can any of the initially posed hypotheses be discarded at this point?

**Table III**

Example of Initial Cardiac Cath Data
Presented in Pathophysiology Problems;
Used to Calculate Right and Left Ventricle Outputs and Stroke Volume

<table>
<thead>
<tr>
<th>Metric</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (HR-beats/minute)</td>
<td>76</td>
</tr>
<tr>
<td>Ventilation (L/min)</td>
<td>5.16</td>
</tr>
<tr>
<td>O₂ consumption (cc/min)</td>
<td>255</td>
</tr>
<tr>
<td>Hemoglobin (gm%)</td>
<td>13.6</td>
</tr>
<tr>
<td>Pulmonary a-v O₂ difference (vol%)</td>
<td>4.4</td>
</tr>
<tr>
<td>Systemic a-v O₂ difference (vol%)</td>
<td>4.4</td>
</tr>
<tr>
<td>(Pulmonary artery O₂ - Systemic artery O₂)</td>
<td></td>
</tr>
<tr>
<td>(Aorta O₂ - Pulmonary artery O₂)</td>
<td></td>
</tr>
</tbody>
</table>

Figure 1 contains pressure tracings from the same patient. The ECG is used for timing purposes and pressure pulses from the left ventricle and the aorta are presented. The students must carefully examine the tracings to determine what they reveal about the pathophysiology that is present. Do they recognize that the contours of the ventricular and aortic pressure pulses are quite different, that the rate of rise of pressure is much slower in the aorta and the peak pressure there is much lower. Do they know if this is normal? At this point, the student ought to be nearly certain about the nature of the patient's problem.

After examining all of the data and having made the requested calculations, the group should now be ready to present a final hypothesis about the pathophysiology that is present and should be able to explain how that gives rise to all of the findings (signs and symptoms, hospital data, cath lab data). One way of organizing and presenting such an explanation is to generate a flow chart (Figure 2) in which the cause and effect relationships arising from the initiating pathology are diagrammed. Here we can see step by step - the consequences of an aortic stenosis: increased outflow resistance; giving rise to a murmur, and an increased pressure drop across the valve: near normal mean pressure, but chronic sympathetic stimulation. All of the patient's signs and symptoms as well as the physical findings can be seen to arise from such a sequence of cause and effect relationships. It is this approach to the analysis of a complex physiological system or problem that the students need to master.
Having worked through a problem in this way the students have hopefully integrated many previously separate pieces of information about the cardiovascular system, and have begun to learn how to attack problems of this kind so as to arrive at a useful "solution".

**SUMMARY**

As in any good lecture, there must be a take-home message. It is this. Unless we do something about it, the majority of our students are likely to finish their physiology course as competent "regurgitators" of facts but much less competent physiological "problem solvers". These necessary skills are best learned by solving problems...but in a setting that permits immediate feed-back, reinforcement, and correction. The small group tutorial is one format that is well suited for such learning. And pathophysiology problems, by virtue of their perceived relevance, represent a "carrot" that we may take advantage of in seeking to make our students active, thinking learners.
The traditional method of teaching, starting in the primary school, produces in the student a pedagogic distortion which we will call overprotection. Lessons that the children take home are supervised or even done by their parents. The result is that the young student becomes very dependent on his parents or siblings, refusing to make any effort to perform his job. A similar situation may occur at the secondary school level.

The examination for admission to the University depends on a lot of information which the student must keep in his memory. No test is applied in order to evaluate his initiative, attitude or problem solving ability.

At the University information is delivered to the student in "didactic" lectures. The student takes notes and during the examination reproduces exactly the words of the teacher. During the lectures, if he has questions he may be reluctant to interrupt the professor and thereby call attention to himself. However, the teacher, having heard no questions asked, feels happy thinking he has given a good lecture.

The questions presented to the students during the examination are similar to those of the previous year, according to the subject given in class.

Overprotection appears, clearly, when the teacher gives the lecture and the student takes notes on the lesson. A large number of students, receiving the information directly from the professor, remain passively waiting for the lecture in order to know what to study. So, it is not surprising that many students may finish the course without reading a single text-book of physiology.

During laboratory work, overprotection also occurs. The student attending a demonstration on the regulation of the blood pressure usually remains a passive spectator. He does not participate in the experiment; he does not anesthetize the animal and/or prepare the equipment to stimulate a nerve. Most importantly, he does not have an opportunity to commit errors or to discover, by himself, the way to reach the objectives of the demonstration.

When the student does perform the experiment he follows a laboratory manual containing more or less complete instructions and always works under the supervision of an assistant professor. The limitation of this approach to the laboratory experience is the student's anticipation that the results of the experiment can be found in the guide-book or revealed by the teacher. The student's pleasure in the discovery of knowledge is virtually precluded.

Conditioned by the traditional method of teaching, the student is not trained to take initiative and acquire self-confidence. At every step of the experiment he asks questions of the assistant that he could readily answer by himself. Questions such as the following are frequent: Is this the vagus nerve? Is the experiment correct?

Such questioning reveals the student's insecurity and is not in accord with the purpose of the experimental work. The student gets little benefit from the experiment, for the laboratory exercise is transformed into a mechanical act instead of serving to stimulate his curiosity to understand the physiological processes.

THE NON-DIRECTIVE APPROACH

The main purpose of the professor is to teach, that is, to create conditions for the student to learn. If the student does not learn, the professor has failed to reach his objective.

When we consider different methods of teaching, we are, indirectly, evaluating their efficacy and their costs. However, it is not easy to evaluate a teaching method. We think that the true teaching method is that which contributes to the formation of the student's personality, encouraging him to acquire new habits and attitudes, arousing his curiosity, and inducing him to think about the subject matter being studied. Obviously, however, these goals are usually not achieved.

In the great majority of courses in Physiology, the participation of the student is limited to receiving information from the professor during the lecture, while in the laboratory the experiments are conducted under the close supervision of the assistant professor.

In an attempt to find a method which gives the student the opportunity to develop his potentialities and acquire new abilities, in addition to facilitating personal growth, we decided to apply the non-directive method of psychotherapy (Rogers, 1951) to teaching physiology (Beraldo and Alvarenga, 1966).

With this approach the main role of the professor is to develop psychological conditions for the student so that, by his own effort, he can find solutions for his problems. This capacity to discern the true nature of a problem...
(the elucidating glimpse or insight) cannot be transmitted by the professor; it can only be arrived at by the student himself.

Rogers (1951) suggested that the application of psychotherapeutic techniques for the removal of emotional blocks could facilitate an active and reflective learning process. Non-directive therapy seeks to replace the purpose of the therapist by that of the client. To achieve such a goal in an educational setting there must be created a friendly atmosphere in which the student feels happy and free to talk about his problems, whether directly or indirectly connected with his life in school.

The student is stimulated to find his own way, studying and discussing the proposed subject. The professor does not give the direct answer for questions put forward for discussion; the group by itself is able to find the solutions.

THE METHOD

Discussion Groups

Each group is formed by 15 students, after the application of a sociometric test. The student chooses his own group. In the class room the chairs are arranged in a circle and the coordinator takes any one of the chairs. Each member of the group receives a guide-book containing the subject to be discussed.

The Group Coordinator

The assistant professors are instructed by a psychologist in the techniques of coordinating the group. They are trained to listen to the student, accepting criticism, and learn how to stimulate the group to become self-confident and independent.

The coordinator must respect and accept the student as he is, notwithstanding his ideas, behavior or sentiment; however, acceptance does not mean approval. He should cultivate an atmosphere of understanding, tolerance and friendship. The group leader is not designated ahead of time; the leadership appears during the discussion, in accordance with individual participation and activity in the group, and therefore it changes from time to time. Whether an individual becomes a leader depends on his temperament and/or on the amount of information he has obtained from the text-book and the literature.

When a few members of the group monopolize the discussion the coordinator, carefully, invites the participation of other members of the group. In achieving this objective, the coordinator should not discourage dominant members of the group, but should try to stimulate the less active students to participate. The coordinator usually asks the opinion of each member of the group about the subject that has been discussed, starting, for example, with the student sitting on the right of the coordinator.

When the students do not begin the discussion the coordinator waits for 10 minutes, usually enough time for the discussion to begin.

The activity of the coordinator brings out the potentialities of the students, giving them more responsibility for the discussion. The group will rarely reach a wrong conclusion because of the restricted participation of the coordinator, because when a group of 15 students is discussing a subject many of them have already read several text-books of physiology (contrary to what occurs when the classical method is used).

Another interesting result of the non-directive method is that the enthusiasm of the students is increased, so that when the class finishes the discussion continues in the corridor and other non-classroom sites.

The good relationship between students in the group during the discussion class and laboratory work contributes to their progress in the course. We have observed that if, for any reason, one of the members of the group is transferred to another group, his previous colleagues feel his absence.

Laboratory Work

The orientation of work in the laboratory is also non-directive. The group of 15 is divided into sub-groups of 5 students. A typed guide is given to them containing only the essential information needed to perform the experiment. The student is encouraged to discover the results himself. It is not important that he finds the correct result; the effort, curiosity and enthusiasm for the experimental work are the qualities that we intend to develop with the non-directive method applied to the study of physiology.

STUDENTS' EVALUATION OF THE NON-DIRECTIVE METHOD

When the students were asked which answer best expressed their thinking, they responded:

1. Did not study 2.6%
2. Studied only for the exam 23.4%
3. Studied to learn 87.0%

REFERENCES

A ROLE FOR MATHEMATICAL MODELS AND
COMPUTER SIMULATION IN THE TEACHING OF
PHYSIOLOGY?

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A variety of interesting mathematical models of biological phenomena have been developed in the past several years. These models, and the biological processes which they represent, range in scale from minute biochemical reactions buried within cells or even in parts of cells to interactions among organs within the body to the dynamics of whole populations. It is not clear at present whether or not these models will play an important role in the teaching of physiology in future years. Some of the most conspicuous positive and negative considerations are outlined below.

VOCABULARY

The use of terms such as "model" and "simulation" can lead to confusion. The term "model" generally refers to an imitation of an original, often in miniature, which bears a strong resemblance to the original. In science, "model" is often used to refer to an abstraction which faithfully captures the essence of the original but not necessarily details of lesser importance. As an example, constructs of plastic sticks and balls have often been successfully used to illustrate atomic interrelationships within molecules. Similarly, water, reservoirs and elastic tubing have been used to build models that illustrate basic hemodynamic principles. In the present context, a more restrictive definition has been selected: "model" means "mathematical model" or a mathematical description of a biological process.

"Simulation" in general terms refers to imitating a real process using substitutes such as props and actors. Professional actors can be used to simulate patients as a teaching aid at the onset of clinical training. In this context, however, a more technical and more limited definition must be used: "simulation" will mean "computer simulation" or the process by which mathematical models are analyzed using computers in order to reveal specific and general characteristics of the system under study. In a slightly expanded sense, the term "simulation" encompasses both mathematical model evaluation and the preceding steps of model building. Similarly, "modeling" is used herein to refer to the combination of mathematical model building and subsequent model evaluation.

These definitions for "model", "modeling" and "simulation" are not wholly satisfactory, but they probably would have been even less appropriate two or three decades ago. Rapid advances in applied mathematics and computer technology have brought these rather specialized meanings to the forefront, without fostering the creation of additional, concise descriptors. Struggling with this lack of precision may be temporary, however. Our vocabulary may become enriched in the future as computer-generated mathematical analyses become more prevalent and stimulate the use of new descriptive terms. In fact, such advances are probably essential to proper use of and further growth of mathematical modeling since inadequate communication due to an underdeveloped lexicon can only foster confusion and skepticism. For instance, there are not terms in existence today that concisely distinguish between mathematical models built on established fact and those built principally on speculative relationships.

Currently, definitions-in-context must suffice with the caveat that carelessness can cause confusion and that inexactness is sometimes required.

MODELING IN PHYSIOLOGY TEACHING TODAY

Standing and Tidball (9) have recently criticized physiological simulation. They argue that simulation can improve teaching efficiency and thereby reduce faculty work loads. Another direct consequence is that the learning experience for the student would be intensified. The analytical skills needed in clinical practice could be sharpened in simulated patient encounters that would surpass the rather constrained real encounters that are usually available to the medical student early in clinical training. Fortunately, these insights primarily document a potential for modeling in the teaching of physiology rather than a realization of that potential.

The editorial board of The Physiologist has been particularly receptive to papers describing mathematical models designed for teaching. Examples include an analysis of the renal excretory response to volume and osmolarity changes (5), an analysis of pulsatile hemodynamics in the aorta (4), an analysis of the evolution of the action potential and the subsequent refractory period (6) and an analysis of the determinants of cardiac output (8). These models generally demonstrate a single, well-founded physiological principle which also has an underlying computational or quantitative basis.

More complex physiological models also exist. These are generally described in internal reports of the agency of origin rather than in the scientific literature. Editorial constraints prevent detailed documentation of complex models in scientific journals. Examples of larger models include a cardiovascular model used primarily for research (3), a model of...
respiratory control (2) and a model of the interactions of several organ systems (7).

Generally, both large and small models are used most extensively at the site of origin. The most notable exception is the model by Dickinson (2) describing respiratory control (called MacPuf) which has been written in straightforward FORTRAN and has been widely disseminated. A model by Randall and Coleman (7) describing the interaction of several organ systems (called "HUMAN") has been configured for use on several popular microcomputers and this has facilitated dissemination.

To summarize, mathematical models have had little impact to date on the teaching of physiology—but it's probably way too soon for a final judgement.

WHY MODELS MAY REMAIN UNIMPORTANT

Models that are wedded to the peculiarities of a particular computer system cannot be easily transported to other systems, and this alone precludes widespread use. As an example, consider the generation of graphical images. There is such diversity in contemporary hardware that the simple act of changing from a computer terminal of one manufacturer to that of another often requires major reprogramming. Similarly, there are many dialects currently in existence for most high-level programming languages such as FORTRAN and software written on one computer system in one dialect is not easily transposed to another system and another dialect. Such restrictions discourage dissemination; yet it is not at all practical for each physiologist to develop his or her own teaching models just as it's not practical for each to write a physiology textbook.

Transportability

Developing analogies between teaching models and physiology textbooks seems natural enough. Each is used for communication, each has an author or authors, and so forth. Yet there are also some very striking differences which might prevent or at least slow the use of mathematical models in teaching. Certainly, the writing of texts is an attractive professional undertaking and authors are held in high regard by their colleagues; the same cannot be said (at this time at least) for the authors of models. And, the writing of models may be the more difficult of the two tasks. The author of a textbook must be familiar with the physiological concepts to be described and with the native language, namely English. The author of a model must be just as familiar with physiological concepts but he or she must also be skilled in the mathematical description of physical phenomena, computer programming and the numerical methods needed to produce accurate solutions in a reasonable amount of time. Hence, the pool of potential authors-for-texts is certainly much larger at this time than the pool of potential authors-for-models.

Ambiguity vs. Exactness

Some of the most interesting topics in physiology today are at the cutting edge of our scientific knowledge and therefore uncertainties and ambiguities must exist. The author of a text can list and discuss various explanations for a particular physiological phenomena without having to make an explicit evaluation of each possibility in terms of its relative and absolute importance. The author of a model is forced to quantitatively rank each and every documented and speculative physiological mechanism while the model is under construction. Misplaced emphasis in a text can remain hidden for years beneath the standard obfuscation; misplaced emphasis in a model readily becomes apparent as numerical solutions are generated and the solutions are quantitatively compared to laboratory and clinical observations. The thought processes of a model's author are placed in a scientific fishbowl, so to speak, and this exposure can be discouraging. One solution is to construct only models of relatively simple, straightforward, and well-understood phenomena. These phenomena can generally be described quite adequately using the format traditional to lectures and, therefore, modeling will offer only an alternative and not a superior alternative. Simplistic models cannot be expected to elevate simulation to the forefront since the greatest strength of simulation appears to be in analyzing complex processes and in minimizing ambiguity.

Hidden Conjecture

Models that describe and analyze broad physiological topics tend to be suspect. Large-scale models, probably without exception, contain in their structure a blend of established fact and unsubstantiated conjecture. As long as conjecture is included, these models must be considered to be quantitative hypotheses (1) and not pure repositories for commonly accepted knowledge. Further, the conjectural or hypothetical relationships are not necessarily evident in the performance of the model; they are embedded in the underlying structure and are available only from explicit descriptions provided by the model's author. Teachers have certain prejudices and they will want to select models as an adjunct to teaching that contain
mechanisms emerge later as interesting but of little causal importance. On the other hand, a concerted effort by the teacher to evaluate student in didactic presentations, often without underlying mechanisms are presented to the student (a) to the careful and humane treatment of experimental subjects, (b) to biological variation and (c) to the vicissitudes of biochemical determinations. Student laboratories are less successful in demonstrating dynamic

WHY MODELING MAY BECOME IMPORTANT

Two arguments that support modeling and suggest that it may become an important part of the teaching of physiology in the future are: 1) Modeling has the potential to offer a student a learning experience available neither in the lecture hall nor the student laboratory and 2) Recent advances in computer science have overcome a variety of technological and financial hurdles.

Homeostasis and Learning Opportunities

The first of these two ideas is built upon the concept of homeostasis. Homeostasis is a dynamic process or, rather, the sum total of many dynamic processes. Three sequential steps are needed to fully describe each component of homeostasis. They are:

1. Defining the basic, underlying mechanisms.
2. Demonstrating the interaction among these mechanisms, particularly as a function of time and changing environmental influences.
3. Cataloging the external signs and symptoms created by such interactions.

Traditional classroom instruction generally cannot satisfy all of these requirements in a uniform way and deficiencies emerge as emphasis is shifted from one aspect to another.

Underlying mechanisms. A complete knowledge of basic, underlying concepts is often not available. Indeed, researchers are continually at work looking for new mechanisms, adding additional descriptive detail to known mechanisms, and evaluating known mechanisms for quantitative importance. At any given time then, knowledge is advancing and uncertainties exist. Because of these uncertainties, a potpourri of underlying mechanisms are presented to the student in didactic presentations, often without a concerted effort by the teacher to evaluate each for quantitative importance. Some mechanisms emerge later as interesting but of little causal importance. On the other hand, a "safe", short-list of underlying mechanisms (as is often used in introductory texts) can rely too heavily on conventional wisdom and fall wide of the mark created by contemporary research.

Simulation can make a contribution here by theoretically investigating one basic mechanism at a time; each can be tested in a mathematical model that explores interactions and predicts the ultimate contributions of the mechanism to homeostasis. Such a theoretical undertaking does not prove causal importance and should never be construed to do so. But it can provide a tentative listing of quantitative importance among competing explanations while we await convincing experimental demonstration.

It is the authors' opinion that many important questions in physiology (and science in general) fall into this category. For instance, many different mechanisms have been proposed as the cause of essential hypertension. Yet, it is not currently clear if any known mechanism, one single mechanism or many mechanisms are actually involved. This question remains in need of experimental clarification. Through the imaginative use of experimental models, students might possibly become involved in the dialog that leads to clarification of unresolved scientific issues rather than being forced to accept an equivocal, unsubstantiated or over-simplified explanation on an interim basis.

Dynamic interrelationships. A second consideration involves dynamic interactions among the basic mechanisms. Lectures can be used to provide detailed descriptions of static conditions and sequential events. But, homeostasis usually involves simultaneous, time-dependent interactions and these are not easily described using conventional language. Worse yet, such interactions cannot be rigorously analyzed using conventional language. In contrast, groups of differential-algebraic equations and their solutions can be used to accurately explore dynamic interrelationships. Hence, one of the strongest features of the use of simulation is found in the analysis of and communication of the dynamic interactions that exist within homeostasis. Many existing models emphasize this point: the evolution of the action potential (6), the dynamics of respiratory control (2), the dynamics of blood pressure control (3) and other physiological processes (7).

The student laboratory theoretically provides an opportunity to demonstrate the dynamic interactions and complexities of homeostasis, but practically this is not the case. Tidball (10) has summarized the most attractive features of student laboratories. Among other things, laboratories introduce the student (a) to the careful and humane treatment of experimental subjects, (b) to biological variation and (c) to the vicissitudes of biochemical determinations. Student laboratories are less successful in demonstrating dynamic
interactions. Firstly, there are time constraints. The relevant time constants must lie well within the three to four hours allocated for a typical laboratory session. Hence, chronic diseases and many other important pathophysiological phenomena cannot be explored.

This is not true with simulation where there are no conventional time constraints and such topics as the evolution of myocardial hypertrophy, management of chronic renal disease or long-term consequences of defects in calcium metabolism, for instance, could be simulated conveniently. A second constraint on the conventional student laboratory comes from limits placed on the type of and the frequency of experimental measurements that can be conveniently implemented. For instance, in the study of insulin-glucagon-glucose interactions, it would be desirable to have repeated and instantaneous measurements of the blood concentrations of these substances over a relatively short interval in investigating the transient response to an applied hormonal or metabolic disturbance. Yet, rapid assay is not possible. Results are usually available only long after the experiment has been completed and possibly forgotten. And, the expense is not trivial. On the other hand, simulation can generally provide current values for all variables within a model as a function of time. Although the observed values are only theoretical, a strong sense of interdependency and time-dependency can be developed in the student by using simulation; this is less likely to be achieved using conventional laboratory procedures.

As another example, consider a popular laboratory protocol in the cardiovascular area which involves measuring pulsatile arterial pressure while short-acting vasoactive drugs are injected. This protocol satisfies the constraints of (a) relatively short time constants, (b) straightforward and instantaneous measurements and (c) reasonable costs. Yet, no one would argue that this protocol demonstrates one of the most important concepts in cardiovascular physiology—it's just convenient, that's all. Instead, with imaginative mathematical modeling, it might be possible to (theoretically) investigate the complex interactions of such cardiovascular phenomena as the acute and long-term control of blood volume, redistribution of blood flow in response to metabolic stimuli, neural-hemodynamic interactions or the long-term sequellae to reduced coronary blood flow. Such topics are outside of the purview of the traditional student laboratory at this time.

Descriptive vs. functional physiology. The third consideration in describing a dynamic process involves itemization of readily observable manifestations—that is, listing the signs and symptoms that are to become an important part of clinical medicine. Itemization does not absolutely require prior consideration of basic mechanisms and their interactions and, therefore, it can be undertaken in vacuo if desired. However, memorization of descriptive physiology is only partially effective at best. It has been reported by others at this symposium that a minimal amount of detailed information is retained by medical students several years after completion of a traditional medical physiology course.

When several complex systems are interacting, the total number of combinations of signs and symptoms must be close to uncountable. Hence, memorization of ultimate effects, while important, can also become mired in inefficiency in realistic situations. The debate concerning how much teaching emphasis should be placed on descriptive physiology and how much emphasis should be placed on functional relationships continues, but simulation may be used to emphasize and to strengthen the functional aspects of physiology and thereby offer some relief from the mental burdens associated with the descriptive components.

Technical Advances

Historically, it's been easier to build mathematical models than to solve them. Further, some of the most interesting features of real systems result from non-linearities; non-linear models (that is, families of non-linear differential-algebraic equations) are comparatively hard to solve.

The advent of the digital computer several decades ago and refinement of the necessary numerical methods shifted the status of all but the most elementary mathematical models from intractable to solvable, albeit with moderate to great difficulty in some cases. Models with severe non-linearities and widely ranging time constants can require considerable computer time to produce a single solution. Hence, large digital computers have traditionally been used most often in digital simulation and such computers are generally not readily available to physiologists—particularly for teaching-related use. Hence, the greatest successes to date have been found in aerospace and defense applications. One could argue that the use of simulation in physiological research and teaching has not yet been fairly and completely evaluated.

The historical picture is changing rapidly with several technological advances. Among other things, the number of solid-state computer elements that can be combined in a single package is increasing and the cost of computer memory is decreasing. In short, powerful computers are now available in compact configurations at reasonable prices. The potential impact of these developments on biomedical simulation is enormous. The current generation of small computers are inexpensive enough to be purchased by the teaching community in numbers which allow adequate student contact. These same machines are also powerful enough to solve complex mathematical models relatively rapidly.
Inexpensive display devices capable of generating detailed colored images are also now available and this may add to the attractiveness of simulation. Subsequent generations of small computers should be even more attractive. Hence, the utility of biological modeling may be about to get a fair test.

In 1978, Katz and colleagues (4) described a cardiovascular simulation for use in a student laboratory. Changes in arterial pressure were calculated in response to acute interventions and results were displayed on a polygraph. In addition to the requisite polygraph, a computing system costing approximately $70,000 was needed. It was also typical of that era that hardware configurations were not standardized and software could not be readily transported from one system to another. Today, this same simulation could be implemented on a $3,000 microcomputer having an increase in computing power of possibly 5- to 10-fold. Further, many popular microcomputers are available in large numbers and software can be transferred among similar machines with little or no alteration.

In total, many of the traditional computational and financial hindrances to successful simulation appear to be gone or disappearing rapidly. It remains to be seen whether or not this will be a decisive step in creating an important role for modeling in the teaching of physiology.

References


HEARTSIM: A CARDIOVASCULAR SIMULATION WITH DIDACTIC FEEDBACK.
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INTRODUCTION

Computer simulations are a comparatively recent addition to the body of methods that are used to teach physiology. Simulations share with other non-lecture techniques the potential for helping students to be active learners. They provide students with a means to observe, analyze and understand the interaction between the components of complex systems by simulating "experiments" many of which are difficult or impossible to carry out in the teaching laboratory.

We have used computer simulations at Rush in scheduled, faculty-supervised "laboratories". In these labs the students work in groups. We suggest that they first follow a specific protocol that illustrates the most important principles before going on their own, trying procedures that are more complex or less directly related to the course objectives. We encourage them to discuss each protocol step and try to arrive at a group consensus about the outcome of each procedure before they actually simulate it on the computer. The faculty circulate, question and challenge the students, and encourage group discussion. They point out phenomena or relationships that the students are likely to miss. They try to insure that the laboratory becomes an on-line learning experience.

However, there are some circumstances that make this process less than optimal. If the lab takes place before the students have studied the relevant material, they will be unable to make rational predictions or to explain or understand the behavior of the system being simulated. So, much of the teaching effectiveness of the exercise is lost. Also, some students feel hampered by having to work in a group or by having to work with peers who may be much faster or much slower than they. This discourages their participation and it may cause them to avoid the lab entirely.

For these and other reasons, we wanted to have the simulations available as free-standing units. Students could then use them whenever they felt ready. They could work alone if they wanted or in a group of their own choosing. However, we did not want the students to lose the positive benefits that derive from free discussion of the physiology, from the necessity of having to predict the outcome in advance, and from being challenged by a faculty member. We wanted to avoid the confusion that often accompanies using a simulation for the first time. We also wanted to make sure that the students were not tempted to slip into "cook-book mode", i.e., to carry out procedures and copy down the output data without trying to understand what is happening while it is happening. When students do this they honestly intend to review and make sense of the data later. However, they often do not or cannot do this. Then they have lost an opportunity to learn in this useful way and they have wasted their time.

To create our first stand-alone simulation we translated and reformatted the well known cardiovascular simulation MacMan (1,2) to run on PLATO. We then expanded the program in an important and we think unique way, by integrating an instructional component into it. This unit guides the students and provides didactic feedback based on the students' input, much like a teacher does. In fact the didactic component was designed to mimic the combined activity of a student group and an active, interested teacher in a laboratory setting.

We call this interactive version of the simulation HEARTSIM.

HEARTSIM

Heartsim starts by presenting a list of available procedures. These are stimuli to the CV system for which the program provides didactic feedback (Figure 1). The student starts by selecting one of these.

Briefly, what follows each protocol step is in sequence:

1) the student predicts the qualitative effect of the procedure,
2) the predictions are reviewed for logical consistency and to be sure that they agree with certain basic physiological relationships,
3) the program simulates the effects of the procedure providing both graphical and numerical output,
4) the qualitative results of the simulation are compared with the student's predictions, and finally
5) the program reacts to disagreements between the simulation output and the student's predictions, providing corrective and reinforcing feedback.
INSTRUCTIONAL INDEX

1. INTRODUCTION

Please select 2a if this is the first time you have used this exercise.

ARTERIAL RESISTANCE

2a. A sudden decrease to 50% of normal
2b. A patient with denervated baroreceptors
   - a decrease to 50% of normal $R_a$

3. CARDIAC CONTRACTILITY falls to 50% normal

4. VENOUS RESISTANCE increases to 200% normal

5. HEMORRHAGE
   - a 1 liter hemorrhage
   - an additional liter
   - an additional 1/2 liter

6. INTRATHORACIC PRESSURE
   - an increase to 8 mm Hg
   - an increase to 4 mm Hg
   - an increase to 8 mm Hg

Choose a topic and press one or two of these options to continue.

Figure 1. The Instructional Index lists the procedures that have guided instruction, i.e. provide interactive feedback to the student user. All of the figures in this paper are prints from the monitor screen. The prompts listed at the bottom of the figure (for example NEXT, BACK, shiftNEXT) allow the user to control the direction of the lesson. All of the available prompts are not shown in later figures.

All of the feedback is organized around a matrix, the Predictions Table. Students enter their predictions into the table. To make these predictions a student must visualize how each procedure will impact the CV system, then must apply physiological principles to known relationships. Thus, in filling out the Predictions Table a student partially emulates the group discussion that we encourage when the simulation is used in the laboratory.

The first time that a student uses Heartsim, the program slowly leads him through the Predictions Table. The student is first asked to predict the direct physical effect (DR) of the experimental procedure on 8 variables: heart rate (HR), stroke volume (SV), cardiac output (CO), cardiac contractility (CC), arterial resistance, ($R_a$), mean arterial blood pressure ($P_a$), atrial pressure ($P_at$), and capillary pressure ($P_c$). Entries are made by touching the monitor screen. One touch enters $+$, a second enters $-$ and the third enters 0 for increase, decrease and no change, respectively (see Figure 2). Usually all of the variables are listed in the table at the start of a procedure and the student must completely fill in the table before receiving any feedback. However, the first time that a student uses the lesson, the program provides definitions, instructions and reactive feedback immediately following each entry in the DR column.

When the DR column is completed, the student enters his predictions of the changes caused by the baroreceptor reflex response (RR) in the second column and shows the changes that he expects to be present in the final steady state (SS) in the third column (see Figure 3).

PREDICTIONS TABLE

<table>
<thead>
<tr>
<th>Parameters</th>
<th>DR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart Rate</td>
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</tr>
<tr>
<td>Art. Resist.</td>
<td></td>
</tr>
</tbody>
</table>

Figure 2. Students must predict the effects of each procedure before the computer simulation is executed. Step 2a, a 50% reduction in arterial resistance ($R_a$), provides the student with detailed instructions on how to enter predictions into the Predictions Table. The figure shows the start of this process, in which the student enters the direct physical effects (DR) of this procedure in the first column.
The Predictions Table is organized in this way to condition the students to think in terms of the causal sequence that occurs in the intact organism following some stimulus to the CV system. It also helps students to understand the source of the system transients and to begin to get a feel for how long these reactions take.

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<table>
<thead>
<tr>
<th>Parameter</th>
<th>DR</th>
<th>RR</th>
<th>SS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart Rate</td>
<td>#</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Stroke Vol.</td>
<td>#</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Cardiac Out.</td>
<td>#</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Card. Contr.</td>
<td>#</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Art. Resist.</td>
<td>#</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Mean B.P.</td>
<td>#</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Atrial P.</td>
<td>#</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Capillary P.</td>
<td>#</td>
<td>+</td>
<td></td>
</tr>
</tbody>
</table>

The statement below the Predictions Table in Figure 3, "...the final steady state (SS)..." is determined by the combination of DR \[\text{the direct response of a variable to the "stimulus"}\] and RR \[\text{the reflex response that follows...}\] refers to the need for a student's predictions to have internal logic (consistency). For example, in Figure 3, the student predicted that a 50% decrease in arterial resistance caused no direct change in cardiac contractility (Card. Contr.) and that the subsequent reflex response caused contractility to increase (DR = 0, RR = 1). It would now be illogical for him to predict that in the steady state (SS) the cardiac contractility would be either decreased or unchanged. If the student does not understand this, he may request HELP (see bottom of Figure 3). The logical system would then be discussed and he would be led through a "truth table" which gives all possible correct combinations of DR, RR and SS.

A student's predictions must also conform to the physiological relationships given below the Predictions Table in Figure 3. Any errors must be corrected before the simulation is carried out.

A student's predictions must also conform to the physiological relationships given below the Predictions Table in Figure 3. Any errors must be corrected before the simulation is carried out.

Arterial Resistance is decreased to 50%.
I feel faint when I try to stand up.

Figure 4. The computer simulation of the effects of a 50% decrease in Ra are shown. Arterial pressure and heart rate are plotted as a function of time. The table gives the normal, control and final steady state values of nine variables.

<table>
<thead>
<tr>
<th>Normal</th>
<th>Control</th>
<th>Steady State</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time</td>
<td>0</td>
<td>128 sec</td>
</tr>
<tr>
<td>Heart Rate</td>
<td>73</td>
<td>73</td>
</tr>
<tr>
<td>Stroke Vol.</td>
<td>60</td>
<td>60</td>
</tr>
<tr>
<td>Card. Output</td>
<td>4.96</td>
<td>6.19 L/min</td>
</tr>
<tr>
<td>Card. Contr.</td>
<td>1.3</td>
<td>2.1 L/min/mmHg</td>
</tr>
<tr>
<td>Art. Ven Rest</td>
<td>16/2.2</td>
<td>16/2.2 mL/min/mmHg</td>
</tr>
<tr>
<td>Mean B.P.</td>
<td>98</td>
<td>72 mmHg</td>
</tr>
<tr>
<td>RAP/Cap.P.</td>
<td>1.8/13</td>
<td>1.8/15 mmHg/mmHg</td>
</tr>
</tbody>
</table>

Press \# to continue or \#\# to see your predictions.
Press \#\# to compare the results with your predictions.
The simulation has two outputs (Figure 4). The graphic output in Heartsim is a plot of HR, systolic pressure ($P_s$) and diastolic pressure ($P_d$) against time. This gives students a view of how these events change in time and illustrates transients. Students often ignore or are unaware of transients in physiological responses. Heartsim's numerical output is a table with the normal, initial and steady state values of 9 variables.

Students may examine the simulation output at their leisure. Then the results are entered into the Predictions Table and disagreements between the student's qualitative predictions and the simulation's are outlined (Figure 5). Finally, the program reacts to each point of disagreement, providing appropriate feedback in each case.

The feedback may:

1. describe or discuss the underlying physiology,
2. test the student's understanding of specific facts or relationships, i.e. ask questions and respond to student answers,
3. summarize the changes observed in the simulation, or
4. at one point a small review lesson on the baroceptor reflex is provided. (This is one of a growing number of stand-alone, single topic computer lessons that we have written.)

When this review is completed, the student may select another (or the same) procedure from the protocol list.

## CONCLUSIONS

Computer simulations can help students to be active learners. They provide a basis for students to integrate the components of systems and see the way that these parts interact. Heartsim provides an additional benefit. It can detect, on-line, student misconceptions about the system's function and errors in the student's thinking. It provides immediate feedback to correct these mistakes while reinforcing correct facts, ideas and problem solutions. Heartsim has enough variety in the available procedures to uncover many, if not most, of the user's major misconceptions. Thus Heartsim's interactive didactic feature provides an added educational benefit over traditional simulations for the independent student learner.

## REFERENCES


WHAT ARE WE DOING OUTSIDE OF THE LECTURE HALL AND WHY ARE WE DOING IT: A SUMMARY

Joel A. Michael and Allen A. Rovick
Rush Medical College
Chicago, IL 60612

According to the recent survey on physiology teaching in the early 1980's (C. Rothe, The Physiologist 26, No. 3, 1983) lectures continue to be the dominant mode of instruction by a wide margin, but there is a great variety of other teaching methods that is used as well.

These non-lecture activities can be classified as labs ("wet" or "dry"), problem solving exercises, and various uses of computers. Regardless of the exact format, all seem to have as one of their goals the development of problem solving skills.

Three quite different approaches to laboratory instruction were described. In one (Richardson), the laboratory experiments are designed and carried out by students. This is surely the antithesis of the "cookbook" approach that conventional teaching laboratories often seem to foster. The active participation of all students would appear to be maximized in this way. In the second example (Traber et al) students carry out a series of experiments that integrate material across various organ systems and disciplines; the experience of dealing with "real", complex systems ought to provide the strongest possible message about the need to understand the function of an entire organism. Active participation is encouraged by the highly structured approach to the experiments and scheduled follow-up conferences. Yet a third kind of laboratory experience was described by Dr. Rothe a mechanical model of the heart of circulation is "exercised" by the students in order to gain an appreciation for the many interacting physical variables that determine system performance. Of interest is the experiential variety that is possible in the student laboratory.

The next three papers described non-laboratory approaches to problem solving. Dr. Caulson's problem-based learning modules represent a comprehensive approach to curriculum design which focuses on independent study in a problem solving environment. The papers by Michael and Rovick and by Beraldo and Alvarenga both discuss more limited problem-solving applications. Michael and Rovick describe the use of pathophysiology as a way of engaging student interest while focusing on integration (the interaction of system components) and problem solving. Beraldo and Alvarenga are concerned with the conditions that need to be created to encourage active, self-directed participation by the student in his own education. These two papers are complimentary in that the success of the tutorial sessions in which pathophysiology problems are considered requires exactly those conditions described by Beraldo and Alvarenga.

The three papers on computer-based exercises superficially appear to deal with quite different approaches to non-lecture teaching. Rovick and Brenner describe the use of a single system simulation (of the heart, circulation and baroreceptor reflex) as a stand-alone educational resource. The simulation is embedded in a program that requires students to predict system responses and provides appropriate feedback to correct errors. Hogan (Computer generated figures in physiology teaching; the "smart video slide") has developed a set of graphic displays of simple physiological systems that can be used either in a lecture/demonstration format, or in a laboratory in which the students may "exercise" the model. Coleman and Randall use of their experience with HUMAN, a very large model that encompasses most of the major organ systems to, discuss the benefits that can be derived from modelling.

But the seeming differences in these three approaches overlay a more important common feature. All of them encourage students to actively participate in the learning process and to focus on problem solving and the integration of information as key elements in the mastery of physiology.

In fact, these features characterize all of the non-lecture teaching exercises that have been described here. They are all designed to bring students out of their role as passive absorbers and memorizers of information (their behavior in the lecture hall). They all encourage students to become active problem solvers.

A variety of learning methods can be used to achieve these ends. For each we must carefully define the goals that we are seeking to achieve (and there are usually multiple goals for any teaching activity) and we must design the exercise to take advantage of features that will make the exercise attractive to the students and effective in working towards the stated goals; we must "human factor" all of our non-lecture activities if they are to be maximally beneficial.
Travel Grant Award Program
XXIX International Congress of IUPS
Sydney, Australia, Aug. 28–Sep. 3, 1983

The Physiologist, December 1981, contained an announcement of the XXIX International Congress of the International Union of Physiological Sciences to be held at the University of New South Wales, Sydney, Australia, August 28–September 3, 1983. In an effort to aid American scientists, who would not be able to attend without some financial assistance, the American Physiological Society submitted proposals to a number of Federal agencies and other organizations for travel grant awards designated specifically for the Congress. The APS proposed to handle the funds and administer the program by awarding the grants, with the US National Committee (USNC) of the IUPS sponsoring the program and selecting the award recipients. The travel grant award program was announced in The Physiologist (Vol. 25, No. 3, p. 153), June 1982, with a deadline date for receipt of applications of October 15, 1982—later extended to November 30, 1982, in conformance with an extension of deadline for Congress registration and abstract submission.

The USNC/APS travel grant program offered a limited number of travel awards to qualified physiologists, permanent residents of North America (US, Mexico, and Canada) and Hawaii, who required such assistance and who plan to participate fully in the XXIX Congress. The USNC/APS established a screening and selection committee, and the APS acted as fiscal agent and awarde of the travel grants. A major intention of the USNC/APS Selection Committee was to give particular attention to applications from younger physiologists.

Submission of proposals and allocation of funds by APS and USNC/IUPS resulted in $172,900 being available for travel grants, as follows:

<table>
<thead>
<tr>
<th>Organization</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>National Institutes of Health</td>
<td>$81,400</td>
</tr>
<tr>
<td>The Krocz Foundation</td>
<td>$25,000</td>
</tr>
<tr>
<td>The American Physiological Society</td>
<td>$14,000</td>
</tr>
<tr>
<td>US National Committee/IUPS</td>
<td>$15,000</td>
</tr>
</tbody>
</table>

In response to the announcement of the availability of travel grant funds, approximately 600 requests for applications were received and 411 were returned in time to be reviewed. A Selection Committee of five members of the USNC (Dr. James B. Bassingthwaighte, Chairperson, and Drs. David H. Cohen, Francis J. Haddy, Charlotte P. Mangum, and Loren J. Mullins), representing all of the adhering societies as well as different areas of expertise, appraised and scored the applications. In the selection procedure priority in scoring was given to plenary lecturers, symposia chairpersons, and invited symposia speakers and, in particular and in accord with commitments to the IUPS and funding organizations, emphasis was placed on physiologists who had received their highest earned degree most recently—within the last 15 years.

The Selection Committee scored each applicant by applying various points to an applicant's credentials. These included: "scientific age" as defined by 15 points minus one for number of years beyond the year of the highest earned degree (including 15 points for those about to receive a degree); congress participation (letter of invitation was received as documentation), namely, plenary lecturers and symposia chairpersons, symposia speakers and participants, planned free communication; publications, for which the standard was two per year, for the past five years in good quality journals (not more than five, excluding abstracts and papers in press, were requested); abstract of the Congress presentation (250 words only); resume of purposes of the trip other than attending the Congress (other meetings, satellite symposia, laboratory visits, collaboration).

The results were averaged and rank-ordered, and awardees were selected and approved in early December 1982 so as to advise applicants of their acceptance before the deadline for submission of registration fees for the Congress (January 31, 1983). Most of the award recipients were notified formally by the APS by letter of December 27, 1982. The stipend for each awardee was calculated to be approximately $300 less than the "super-saver" round-trip airfare from an awardee's nearest major airport to Sydney, Australia. This fare in turn was based on a Los Angeles-Sydney (or San Francisco-Sydney) specially negotiated fare of $849, which included unlimited stopovers en route.

There were 169 travel grants awarded. Of these a total of 124 went to awardees who had earned their highest earned degree within the last 15 years (71 within 5 years, 30 within 10 years, and 23 within 13 years). There were

Sustaining Associate Members
13 invited plenary lecturers and/or chairpersons and 71 invited symposia speakers.

In sponsoring travel grants, the Federal Government regulations restrict the expenditure of the monies to US residents and stipulate that, when flying from and to the United States, American air carriers must be used. Accordingly, the awardees were divided into two groups, those eligible for Federal grant funds and those who were not (non-US residents, US government employees). There were nine awardees who were US government employees and seven Canadian scientists. These 16 persons plus a few other special cases were funded by the private funds available from APS, USNC, and The Kroc Foundation sources (as noted above).

Membership held by applicants in any or none of the six societies was recorded from the applications submitted and evaluated. The following table shows the societies, the number of applicants per society, percent having received awards, the number of awardees per society, and percent having received awards.

<table>
<thead>
<tr>
<th>Society</th>
<th>Applicants</th>
<th>Awarded</th>
</tr>
</thead>
<tbody>
<tr>
<td>American Physiological Society</td>
<td>268</td>
<td>99</td>
</tr>
<tr>
<td>Society for Neuroscience</td>
<td>138</td>
<td>58</td>
</tr>
<tr>
<td>Society of General Physiologists</td>
<td>49</td>
<td>23</td>
</tr>
<tr>
<td>American Society of Zoologists</td>
<td>36</td>
<td>16</td>
</tr>
<tr>
<td>Microcirculation Society</td>
<td>28</td>
<td>10</td>
</tr>
<tr>
<td>Biomedical Engineering Society</td>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td>Not a Member of any of the above societies</td>
<td>51</td>
<td>27</td>
</tr>
</tbody>
</table>

(Percentages add up to over 100% because of multiple memberships of individuals.)

The award recipients represented persons from 35 states, Puerto Rico, and Canada, as follows:

California 30
New York and Massachusetts 14 each
Maryland 11
North Carolina 9
Pennsylvania 8
Illinois, Ohio, and Texas 7 each
Virginia and Washington 5 each
Alabama, Florida, Connecticut, and Oregon 4 each
Arizona, Colorado, and Michigan 3 each
New Hampshire, Nevada, Wisconsin, Indiana, and Iowa 2 each
Arkansas, Kansas, Louisiana, Maine, Mississippi, Missouri, Nebraska, New Jersey, Puerto Rico, Tennessee, Vermont, and Utah 1 each
Canada 5

To minimize administrative expense, since no allowance for overhead or indirect costs was included in the government grants, most recipients received their award in the form of a “credit” in their name with the travel agent (selected competitively by the US National Committee), Chevy Chase Travel, Inc., of Bethesda, MD. This use of a single travel agent for most awards allowed negotiations of a favorable airfare and blocking of space to assure awardees and other physiologists seats on appropriate schedules. Those awardees wishing to make travel arrangements independently were presented with travel vouchers to be submitted for reimbursement on completion of the travel.

### Symposia for 1984 Spring Meeting

<table>
<thead>
<tr>
<th>Title</th>
<th>Organizer</th>
<th>Section</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regulation of phosphoprotein phosphatase activity</td>
<td>J. DiSalvo</td>
<td>Society for Experimental Biological Medicine</td>
</tr>
<tr>
<td>The Control of Cell Volume</td>
<td>A. L. Finn</td>
<td>Society of General Physiologists</td>
</tr>
<tr>
<td>Theoretical trends in neuroscience (2 sessions)</td>
<td>H. Lecar and J. Rinzel</td>
<td>General Physiology Section</td>
</tr>
<tr>
<td>Regulation of phosphoprotein phosphatase activity</td>
<td>J. DiSalvo</td>
<td>Cardiopulmonary Council</td>
</tr>
<tr>
<td>Histamine and the lung’s circulation</td>
<td>H. V. Sparks, Jr.</td>
<td>Nervous System Section</td>
</tr>
<tr>
<td>Membrane ATPase function in vascular smooth muscle during hypertension</td>
<td>R. K. Hersmeyer</td>
<td>Cardiovascular Section</td>
</tr>
<tr>
<td>Mediator mechanisms in shock</td>
<td>R. F. Bond</td>
<td>Nervous System Section</td>
</tr>
<tr>
<td>A history of neurophysiology and the latest developments</td>
<td>J. Trubatch</td>
<td>Neurobiology of Aging</td>
</tr>
<tr>
<td>Sexual differences in neural development/sexual dimorphism of CNS</td>
<td>C. D. Toran-Allerand</td>
<td>Nervous System Section</td>
</tr>
<tr>
<td>Neurobiology of aging</td>
<td>C. E. Finch</td>
<td>Cell and General Physiology Section</td>
</tr>
<tr>
<td>Functional interaction of developing neurons with their target tissue</td>
<td>G. Pilar</td>
<td>Biomedical Engineering Section</td>
</tr>
<tr>
<td>Role of guanine nucleotide binding proteins in biology</td>
<td>A. G. Gilman</td>
<td>Metabolism Section</td>
</tr>
<tr>
<td>Role of tyrosine phosphorylation in the action of hormones and growth factors</td>
<td>J. Avruch</td>
<td>Endocrinology and Metabolism Section</td>
</tr>
<tr>
<td>Membrane biogenesis</td>
<td>G. Blobel</td>
<td>Endocrinology and Metabolism Section</td>
</tr>
</tbody>
</table>

*Jointly sponsored by the following APS Sections: Cell and General Physiology, Epithelial Transport, Gastrointestinal, and Renal Physiology.
*Membrane component turnover
Organized by G. Ashwell

*Membrane modification by fusion events
Organized by Q. Al-Awqati

*Intestinal transport: structural and functional adaptive responses
Organized by H. J. Binder

*Renal transport: structural and functional adaptive responses
Organized by J. B. Wade
Regulation of renal phosphate transport
Organized by V. Dennis
Sponsored by Renal Physiology Section
Central mechanisms in the control of salt and water intake
Organized by D. J. Ramsay
Sponsored by Water and Electrolyte Homeostasis Section

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**Announcements**

**Comparative Physiology Section**

The usual joint meeting of APS-American Society of Zoologists was scheduled for Fall 1984. Due to a scheduling conflict with an international symposium which will heavily involve ASZ, the next joint meeting will occur in the Fall of 1985 (information communicated by Dr. John Roberts on behalf of ASZ). Suggestions or proposals for symposia for Fall 1985 should be addressed to Dr. Donald C. Jackson, Program Officer for Comparative Physiology, Division of Biology and Medicine, Brown University, Providence, RI 02912.

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**Burroughs Wellcome Clinical Pharmacology Award**

Advancements in the medical sciences have brought new therapeutic concepts and drug entities. The elucidation of disease processes, the development of new drugs and the determination of their relative efficacy and safety, and continued research to establish improved methods for measuring the effects of drugs in man require the skills of trained clinical pharmacologists. The unfilled needs for clinical pharmacology manpower to respond to these requirements, and also to function in teaching capacities, continue at a high level. In response to this need the Burroughs Wellcome Fund is offering a Clinical Pharmacology Award for 1984 in the amount of $200,000, payable in annual installments of $40,000. The aim of the Clinical Pharmacology Award is to support an individual who has chosen Clinical Pharmacology as a career objective and who will promote research, strengthen teaching programs, and attract young men and women interested in a career in this discipline. The Award recipient is known as a Burroughs Wellcome Scholar in Clinical Pharmacology. The Award is available to full-degree granting US medical schools to initiate and develop a new Division in Clinical Pharmacology or, alternatively, to provide for the salary of a faculty member in an established division. Invitations to apply for the 1984 Clinical Pharmacology Award are being sent to the Deans of medical schools and to the Chairmen of the Departments of Medicine and Pharmacology. **Deadline for applications nominating candidates for the 1984 Award: November 1, 1983.** The Award recipient, or recipients, will be announced in early Spring 1984. **For further information contact**: The Burroughs Wellcome Fund, Research Triangle, NC 27709. Phone: (919)248-3000.

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**Election to the American Academy of Arts and Sciences**

APS member Dr. Christina Enroth-Cugell of the Departments of Engineering Sciences (Biomedical Engineering Division) and Neurobiology and Physiology of Northwestern University has been elected Fellow of the American Academy of Arts and Sciences. Professor Enroth-Cugell is a native of Finland and attended the Karolinska Institutet in Stockholm, Sweden, where she obtained her M.D. and doctorate degrees. Her research is devoted to physiological studies of the properties of the neural circuitry of the mammalian retina.

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**Second International Congress on Myocardial and Cellular Bioenergetics and Compartmentation**

The Second International Congress on Myocardial and Cellular Bioenergetics and Compartmentation will be held February 16-18, 1984, at the University of Southern California, Los Angeles. Topics: Microcompartmentation and Energy Transport; Respiration Control—Cellular and Organ Level; Myocardial Preservation and Ischemia; Pathophysiology of Energy Compartmentation; Calcium, Magnesium and Bioenergetics; P31 NMR. There will be Free Communications (abstracts), 2 sessions; Poster Session, 1 session; and Poster Discussion Groups. **For more information contact**: N. Brautbar, M.D., USC/LAC Medical Center, Dept. of Medicine, 2025 Zonal Ave., Los Angeles, CA 90033. Phone: (213)226-4768 or (213)226-7337.

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The Physiologist, Vol. 26, No. 4, 1983
APS Committees, Their Principal Functions and Membership (1983-1984)

Publications Committee
Manages all Society publications including the appointment of editors and editorial boards. A subcommittee of this committee is responsible for developing an annual symposium as the basis for an APS publication in the basic and clinical sciences.

H. E. Morgan, Chairman
Dept. of Physiol.
Hershey Med. Ctr.
Hershey, PA 17033

L. E. Farhi
Dept. of Physiol.
State Univ. of New York
Buffalo, NY 14214

E. E. Windhager
Dept. of Physiol.
Cornell Univ.
New York, NY 10021

Finance Committee
Reviews the proposed annual budget and fiscal plan for all Society activities and recommends a final budget and implementation plan to Council. Supervises the investment of the Society's financial resources subject to approval by Council.

P. C. Johnson, Chairman
Dept. of Physiol.
Univ. of Arizona
Tucson, AZ 85724

F. J. Haddy
Dept. of Physiol.
Uniformed Services Univ.
Baltimore, MD 20814

E. H. Wood
Dept. of Physiol./Biophys.
Mayo Med. Sch.
Rochester, MN 55901

Education Committee
Conducts educational and teaching programs and develops teaching resource material that may be required by the Society. This includes naming tutorial lecturers, organizing teaching sessions and the refresher course conducted at APS meetings.

J. A. Spitzer, Chairman
Dept. of Physiol.
Louisiana State Univ.
New Orleans, LA 70112

M. Anderson-Olivo
Dept. of Biol. Sci.
Clark Sci. Ctr.
Northampton, MA 01063

P. M. Hogan
Dept. of Physiol.
State Univ. of New York
Buffalo, NY 14214

B. A. Horwitz
Dept. of Animal Physiol.
Univ. of California
Davis, CA 95616

J. A. Michael
Dept. of Physiol.
Chicago, IL 60612

M. L. Entman (ex officio)
Houston, TX 77030

Program Executive Committee
Selects the scientific symposia and special sessions to be organized or supported by APS, develops policies regarding the conduct of scientific sessions and names the recipients of the Caroline tum Suden Travel Fellowship.

M. J. Jackson, Chairman
Dept. of Physiol.
George Washington Univ.
Washington, DC 20037

E. J. Masoro
Dept. of Physiol.
Univ. of Texas
San Antonio, TX 78284

B. L. Umminger
Reg. Biology Program
National Sci. Fndn.
Washington, DC 20550

J. B. West (ex officio)
Dept. of Med.
Univ. of California
La Jolla, CA 92039

Program Advisory Committee
Recommends to the Program Executive Committee scientific programs for APS meetings. Members of this committee also organize contributed abstracts into sessions, select session chairmen and introductory speakers, nominate candidates for the Caroline tum Suden Travel Fellowship.

Cardiovascular
F. D. Harris
Dept. of Physiol./Biophys.
Univ. of Louisville Med. Sch.
Louisville, KY 40292

J. W. Covell (ex officio)
Dept. of Med./Bioeng.
Univ. of California
La Jolla, CA 92039

Cell & General Physiology
R. B. Gunn
Dept. of Physiol.
Emory Univ.
Atlanta, GA 30322

F. M. Abboud
Dept. of Med.
Univ. of Iowa Hosp.
Iowa City, IA 52242

Comparative Physiology
D. C. Jackson
Brown Univ.
Providence, RI 02912

Endocrinology & Metabolism
M. S. Smith
Dept. of Physiol.
Univ. of Pittsburgh
Pittsburgh, PA 15260

Environmental, Thermal & Exercise Physiology
C. V. Gisolfi
Dept. of Physiol./Biophys.
Univ. of Iowa
Iowa City, IA 52242

Gastrointestinal Physiology
L. Lichtenberger
Dept. of Physiol.
Univ. of Texas Med. Sch.
Houston, TX 77023

Muscle Physiology
M. J. Siegman
Dept. of Physiol.
Philadelphia, PA 19107

Nervous System
J. Trubatch
The Federal Building
NIH/NINCDS
Bethesda, MD 20205

Neural Control & Autonomic Regulation
R. D. Foreman
Dept. of Physiol./Biophys.
Univ. of Oklahoma
Oklahoma City, OK 73190

Renal Physiology
P. S. Aronson
Dept. of Med.
Yale Sch. of Med.
New Haven, CT 06510

Respiratory Physiology
A. J. Berger
Dept. of Physiol./Biophys.
Univ. of Washington
Seattle, WA 98195

Environmental, Thermal & Exercise Physiology
C. V. Gisolfi
Dept. of Physiol./Biophys.
Univ. of Iowa
Iowa City, IA 52242

Water & Electrolyte Homeostasis
R. F. Shade
Dept. of Physiol.
Univ. of South Carolina
Columbia, SC 29008

Epithelial Transport Group
J. S. Handler
Lab of Kidney/Electrolyte Metabolism
NIH, NHLBI
Bethesda, MD 20005

Detailed functional statements for each committee are included in the APS Operational Guide distributed annually to officers and committee chairmen.
Public Affairs Executive Committee
Advises Council on all matters pertaining to public affairs that affect physiologists and implements public affairs activities in response to Council guidance.

J. T. Shepherd, Chairman
Director of Education
Mayo Clinic
Rochester, MN 55901

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Cardiovascular. 23(S): 5, 1980. Send a letter requesting affiliation to the Membership Services Department of APS.


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