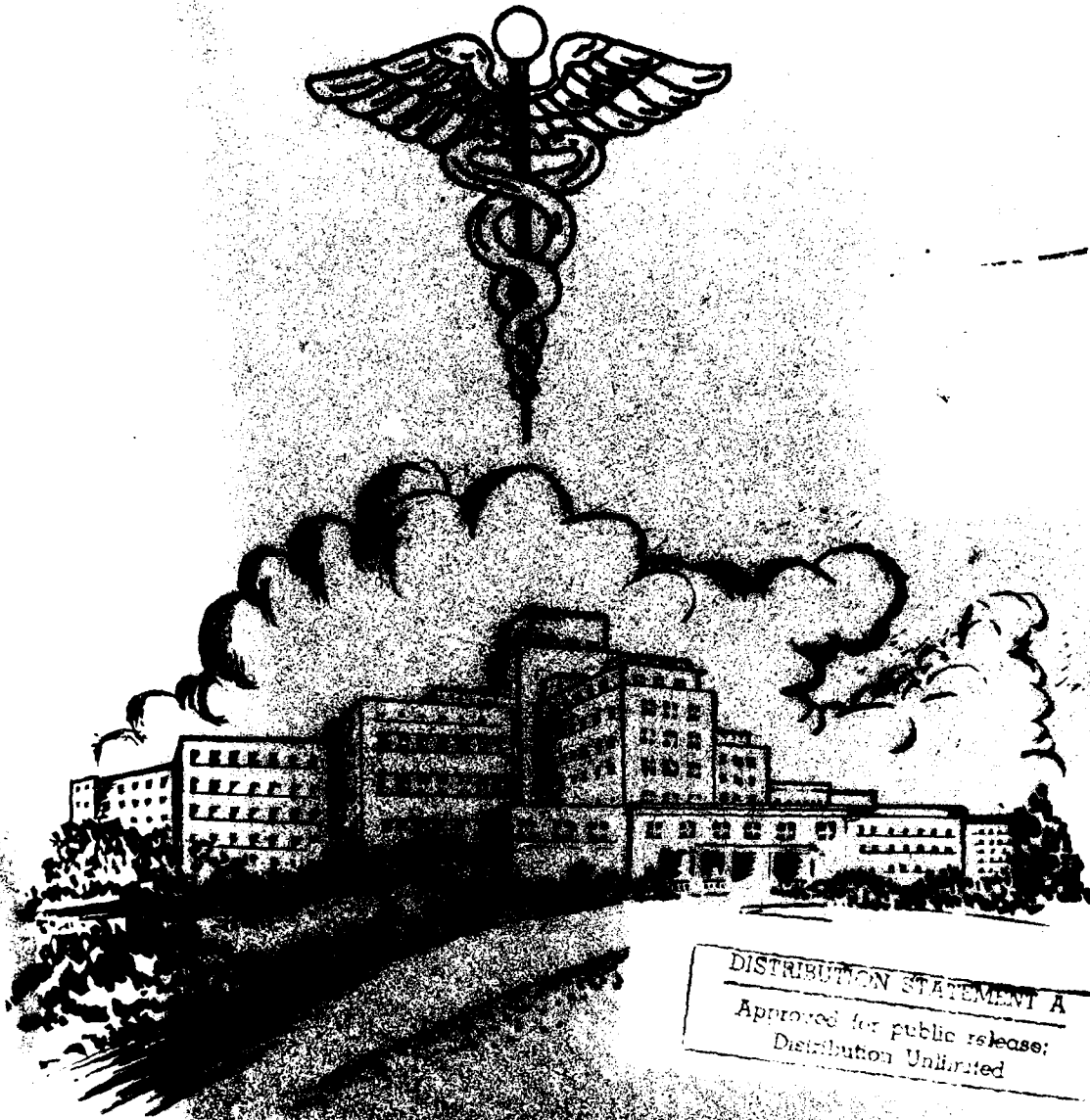


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REPORT DOCUMENTATION PAGE		READ INSTRUCTIONS BEFORE COMPLETING FORM
1. REPORT NUMBER MLD-300	2. GOVT ACCESSION NO. AD-A103166	3. RECIPIENT'S CATALOG NUMBER
4. TITLE (and Subtitle) CLINICAL INVESTIGATION PROGRAM. Annual Progress Report		5. TYPE OF REPORT & PERIOD COVERED ANNUAL - FY 79
		6. PERFORMING ORG. REPORT NUMBER
7. AUTHOR(s) SAMUEL A. CUCINELL / M.D., COL, MC Chief, Clinical Investigation Service		8. CONTRACT OR GRANT NUMBER(s)
9. PERFORMING ORGANIZATION NAME AND ADDRESS Clinical Investigation Service Tripler Army Medical Center Tripler AMC, Hawaii 96859		10. PROGRAM ELEMENT, PROJECT, TASK AREA & WORK UNIT NUMBERS 7-119
11. CONTROLLING OFFICE NAME AND ADDRESS Commander HQ, Tripler Army Medical Center Tripler AMC, Hawaii 96859		12. REPORT DATE 1 October 1979
14. MONITORING AGENCY NAME & ADDRESS (if different from Controlling Office) Office of The Surgeon General Department of The Army Washington, D.C. 20314		13. NUMBER OF PAGES
		15. SECURITY CLASS. (of this report) UNCLASSIFIED
16. DISTRIBUTION STATEMENT (of this Report) APPROVED FOR PUBLIC RELEASE: DISTRIBUTION UNLIMITED		15a. DECLASSIFICATION/DOWNGRADING SCHEDULE
17. DISTRIBUTION STATEMENT (of the abstract entered in Block 20, if different from Report)		
18. SUPPLEMENTARY NOTES THE FINDINGS IN THIS REPORT ARE NOT TO BE CONSTRUED AS AN OFFICIAL DEPARTMENT OF THE ARMY POSITION UNLESS SO DESIGNATED BY OTHER AUTHORIZED DOCUMENTS.		
19. KEY WORDS (Continue on reverse side if necessary and identify by block number) Clinical investigations; experimental projects; research protocols; in-house research; publications, presentations of research data; protocol status; experimental design.		
20. ABSTRACT (Continue on reverse side if necessary and identify by block number) Subject report identifies those individuals who are conducting investigative protocols at Tripler Army Medical Center. An abstract of each protocol giving abbreviated technical objectives, methods, and progress is presented.		

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ANNUAL PROGRESS REPORT

CLINICAL INVESTIGATION PROGRAM
Reports Control Symbol MED-300

FISCAL YEAR 1979
1 October 1979

CLINICAL INVESTIGATION SERVICE
TRIPLER ARMY MEDICAL CENTER
Tripler AMC, Hawaii 96859

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McCurdy, J. A.: Manometric Measurement of Eustachian Tube Ventilatory Function. 82nd Annual Meeting, Triological Society, Scottsdale, AZ, Jan 1979. DEPT OF SURGERY

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UNIT SUMMARY SHEET

CLINICAL INVESTIGATION OF TRIPLER ARMY MEDICAL CENTER

OBJECTIVES. Providing the opportunity for professional development by scientific inquiry to the entire patient care staff is the goal of the Clinical Investigation Service. Professional development requires that the whole process of scientific study be completed. The investigator starts with an idea or observation, completes a literature search, and designs a study. Experimentation requires support and technical assistance. The accumulated data must be organized, collated, and written in an appropriate form. The final product, in order to be meaningful both to the investigator and to medicine, must now be published.

Success in completing a scientific study is a measure of professional development. Few tyros at research succeed without help. The Clinical Investigation Service is the mechanism for this help. The main barriers at Tripler at present are time and motivation. Since residency is time-consuming and there is no immediate benefit to the individual from scientific investigation, few wish to assume the extra burden. Incentives in addition to "professional development" will have to be found if clinical investigation at the medical center level is to reach its full potential.

TECHNICAL APPROACH.

1. MANPOWER. During FY 79, four officers, eight enlisted personnel, seven civilians (six full-time and one part-time) implemented the Clinical Investigation program. A manpower survey team in FY 77 recognized the requirements of a staff of 20, to be composed of four officers, eight enlisted personnel, and eight civilians:

1	Officer (MC)	Chief
1	Officer (MS)	Biochemist
1	Officer (MS)	Microbiologist
1	Officer (VC)	Veterinarian
1	Enlisted (NC)	Biomedical Scientific NCO
1	Enlisted (NC)	Animal Specialist NCO
3	Enlisted	Animal Specialists
2	Enlisted	Medical Laboratory Specialists
1	Enlisted	Nuclear Medicine Specialist
1	Civilian	Physiologist
1	Civilian	Biomedical Engineer
2	Civilian	Medical Technologists
1	Civilian	Microbiology Technician
1	Civilian	Animal Caretaker
1	Civilian	Administrative Specialist
1	Civilian	Clerk typist

2. FUNDING. In FY 79, \$56,797 in OPA funds and \$268,356 in O&MA funds were spent, which greatly expanded our research capability through the purchase of instrumentation and laboratory hardware. Funds in the amount of \$80,000 for consumable supplies were requested for FY 79, with the exact O&MA allocation to be forthcoming.

PROGRESS. Eighty-four projects are reported, of which 22 have been terminated, 13 completed, and 49 are ongoing. There have been 15 publications, four resulting from research projects, and 18 presentations at national and regional scientific meetings, nine resulting from research projects. The detail sheets should be examined for specific information on the individual projects.

TITLE: Evaluation of the Cardioesophageal Sphincter Competence by Comparison of Intraluminal Esophageal Sphincter and Gastric Pressure with Thoracic, Hiatal, and Abdominal Pressure

PROJECT NO.: 138/75 - Ongoing

INVESTIGATORS: Gordon H. Bryant, Clin Invest Svc
Tom R. DeMeester, M.D., Univ of Chicago

FUNDING: FY 79 - \$1000,; FY 80 - \$1000.

OBJECTIVES: To obtain comparative gastric and cardioesophageal sphincter pressures during 24-hour pH testing for nocturnal reflux.

TECHNICAL APPROACH: For more exact analysis of causative factors of nocturnal reflux and its surgical correction, the direct measurement of gastric and cardioesophageal pressures are to be made simultaneously with pH in 24-hour studies. Reduction of errors due to perfused side hole catheter pressure measurements in the cardioesophageal sphincter are to be made by utilizing a three-channel, semiconductor, gastro-esophageal probe presently available. This device is to be modified so as to incorporate both a Dent sleeve system in the center section and a pH probe.

PROGRESS: Results from the previous section of this study reporting results from measurements of intra-abdominal pressures versus cardioesophageal pH have been published in Surgical Forum 1978, American Journal of Surgery, 1979, and Archives of Surgery (in press). Collaboration with Dr. Tom R. DeMeester of Department of Surgery, University of Chicago continues.

DeMeester, TR, Wernly, JA, Bryant, GH, Little, AG, Skinner, DB: Clinical and In Vitro Analysis of Determinants of Gastroesophageal Competence: A Study of The Principles on Antireflux Surgery. Am J Surg 137:39-45, Jan 1979.

Wernly, JA, DeMeester, TR, Bryant, GH, Wang, C-I, Smith, RB and Skinner, DB: Intra-Abdominal Pressure and Manometric Data of the Distal Esophageal Sphincter. Arch Surg (in press).

TITLE: The Development and Utilization of a New Method of Ballistocardiography to Monitor Fetal Heart Rate during Maternal Exercise

PROJECT NO.: 15/77 - Terminated

INVESTIGATORS: Gordon H. Bryant, Clin Invest Svc
LTC Richard A. Bronson, MC, Dept of OB-GYN

FUNDING: FY 79 - none; FY 80 - none

OBJECTIVES: (a) Development of a technique that would allow continuous monitoring of the fetal heart rate in pregnant women during maternal exercise. (b) To ascertain whether maternal exercise can be used as a "stress test" to define a group of women with occult placental insufficiency. (c) To determine whether changes in fetal heart rate during maternal exercise may have predictive value in defining a group of women at risk for subsequent development of toxemias of pregnancy.

TECHNICAL APPROACH: A method of fetal heart rate monitoring during maternal exercise is being developed. It is felt that the highest likelihood of success will be with ballistocardiography. Following development of such a fetal monitor, fetal heart rate will be measured during maternal exercise. Utilization of such a monitor of fetal heart rate during maternal ambulation and exercise should be of value in identifying high risk pregnancies.

PROGRESS: Due to the lack of time and the departure of one of the investigators, the project is terminated.

TITLE: Fabrication of a Catheter for the Determination of Liver Blood Flow in Dog and Man

PROJECT NO.: 34/79 - Ongoing

INVESTIGATORS: Gordon H. Bryant, Clin Invest Svc
COL Samuel A. Cucinell, MC, Clin Invest Svc

FUNDING: FY 79 - none; FY 80 - \$1200.

OBJECTIVES: Development of a thermodilution catheter which will easily and repeatedly give an accurate measure of hepatic vein blood flow in larger animals.

TECHNICAL APPROACH: Thermistors will be removed from used Swan-Ganz catheters. Various size polyethylene or Teflon catheters will be tested for acceptability for the insertion of the thermistors. The thermistor leads will be connected to a gang of Wheatstone bridges supplied by a polygraph. The catheter will be tested in both an in vitro and in vivo system. Previous experience has demonstrated that the in vitro system is good for calibration of the system, but this rigid system does not permit the detection of the physiological variations which plague the development of new techniques. Experience with dogs will be used in the course of previously approved experiments for the evaluation of the production of lactic acid in shock.

PROGRESS: No progress as yet; protocol just recently approved.

TITLE: The Effect of Exercise in Man on Plasma Renin Activity and Plasma and Urine Antidiuretic Hormone (ADH), and Aldosterone Concentration.

PROJECT NO.: 158/75 - Completed

INVESTIGATORS: John R. Claybaugh, Ph.D., Clin Invest Svc
Charles Wade, Univ of Hawaii
LTC Harry M. Thomas, Jr., MC, Dept of Medicine

FUNDING: FY 79 - \$7,200.; FY 80 - none.

OBJECTIVES: To determine whether exercise will stimulate the release of ADH and renin, thereby resulting in increased release of aldosterone.

TECHNICAL APPROACH: Blood and urine samples were collected for ADH and renin analysis before, during, and after controlled exercise on a treadmill with workload adjusted to achieve a maximum heart rate or one-hour running sessions at 70% and 35% of maximum. Blood pressure was recorded prior to and immediately after run, with EKG being continuously monitored. Other measurements include urine creatinine, sodium and potassium concentration, osmolality and volume, and plasma sodium and potassium concentration, osmolality and hematocrit.

PROGRESS: Seven subjects have completed two series of graded maximal exercise tests, one dehydrated, and a second following ingestion of 300 ml of water. The responses in both treatments are similar. There is a decrease in urine flow after exercise with an increase in free water clearance and a decrease in osmotic clearance. Plasma osmolality is elevated and plasma volume decreased. Plasma renin activity (PRA) is elevated to the same degree regardless of the state of hydration. Plasma ADH concentration is increased significantly more in normally hydrated subjects than in subjects that had 300 ml supplemental water. The submaximal exercise workloads demonstrated statistically significant correlation between exercise intensity and plasma osmolality, renin activity, ADH concentration, and volume reduction.

Wade, C. E. and Claybaugh J. R.: Plasma Renin Activity, Vasopressin Concentration, and Urinary Excreting Responses to Exercise in Man. (Submitted) J. Appl. Physiol.

Wade, C. E. and Claybaugh J. R.: Responses of ADH, Renin, and Urinary Excretion to Graded Exercise in Man. Fed. Proc. 38:967, Abstract 3889, 1979.

TITLE: Further Studies on the Site of Action of Circulating Angiotensin II on Plasma ADH Concentration

PROJECT NO: 38/76 - Ongoing

INVESTIGATORS: John R. Claybaugh, Ph.D., Clin Invest Svc
MAJ Bradford S. Goodwin, VC, Clin Invest Svc
David P. Brooks, University of Hawaii

FUNDING: FY 79 - \$500.; Fy 80 - \$1,500.

OBJECTIVES: To determine if circulating angiotensin II exerts its effects on stimulating ADH release via augmentation of osmotic stimulation of ADH. Studies are centered around the determination of angiotensin potentiation of osmoreceptor control of ADH of osmoreceptors located in the brain and liver.

TECHNICAL APPROACH: Previous approaches have included a comparison of carotid arterial and peripheral venous infusions of angiotensin II with the results clearly showing no difference in the ability of angiotensin II to stimulate ADH release. We then tied off the vertebral arteries on both sides at about C-6 and repeated the above experiments. These results were difficult to interpret because of probable reanastomosis of the vertebral blood supply. Several pilot experiments have been attempted recently in which we are testing two hypotheses. First, since it is felt that angiotensin stimulates ADH release by potentiating osmotic stimuli, we are attempting to demonstrate a central osmotic effect on ADH release by infusing hypertonic NaCl into two exteriorized carotid arteries in conscious dogs. Alternatively, we have ligated one carotid artery, and infused into the remaining carotid artery. Having established this, we will then infuse angiotensin II either peripherally (I.V.) or via the carotid arterial circulation; thus we hope to establish whether the osmotic site and angiotensin could be the same or are, indeed, in different locations. Secondly, we are testing the angiotensin II potentiation of osmotically stimulated ADH release via stimulation of liver osmoreceptors by infusion of hyperosmotic NaCl into a chronic indwelling portal vein cannula.

PROGRESS: One dog with bilateral exteriorized carotid loops has been prepared; no experimental runs have been conducted. One dog with one carotid artery ligated and one carotid artery exteriorized in a loop has been prepared, with one experiment conducted to determine a central effect of hypertonic NaCl. The analysis has not been completed.

Several dogs have been prepared with chronic indwelling portal vein cannulae and an exteriorized carotid arterial loop. We have achieved stimulation of ADH by infusions of hypertonic NaCl into the portal vein. However, the potentiation of this response by angiotensin II is not

Further Studies on the Site of Action of Circulating Angiotensin II on Plasma ADH Concentration

convincing at present. In addition, the only previous report of hepatic osmoreceptor control of ADH release indicates that the magnitude of the ADH response is greater than we have observed. Although, in our opinion, the ADH response we have observed is more within the expected "physiological" response range than theirs, further experiments will be necessary for our findings to be of significant additional information to be publishable. This is anticipated because our experimental protocol allows for simultaneous measurement of the osmolality of the portal venous plasma; thus, the correlation of plasma osmolality with plasma vasopressin levels can be obtained.

TITLE: The Role of Glucocorticoids in the Diuresis Associated with Alcohol Ingestion

PROJECT NO.: 39/76 - Completed

INVESTIGATORS: John R. Claybaugh, Ph.D., Clin Invest Svc

FUNDING: FY 78 - \$1000.; FY 79 - \$3000.

OBJECTIVES: To determine if factors other than a reduction of anti-diuretic hormone (ADH) release contribute to the acute diuretic response to alcohol ingestion.

TECHNICAL APPROACH: Consenting patients with diabetes insipidus (DI) were given alcohol (0.75 ml/kg) after ADH injections which resulted in a state of slight antidiuresis, in the hope that any effects of alcohol on the tubular effects of ADH would also be revealed.

PROGRESS: Water and electrolyte studies on 20 male subjects have confirmed for the first time that the diuresis associated with alcohol ingestion is accompanied by a reduction in ADH release as determined by a radioimmunoassay of urinary ADH in urine pools at hourly intervals after alcohol consumption (manuscript in preparation). Thus far, one patient with DI has been studied, and no diuretic response was observed to alcohol ingestion when he received no ADH, or when ADH was given at doses (2 used) which achieved an intermediate urine flow.

Kwon, W.-J., Hanna, J. M., and Claybaugh, J. R.: Effects of Acute Ethanol Administration on Water and Electrolyte Excretion in Man. Fed Proc 35:706, 1976. (Abstract E2754).

Kwon, W.-J., Hanna, J. M., and Claybaugh, J. R.: The Effects of Acute Ethanol Ingestion on Water and Electrolyte Metabolism in Man. Fed Proc 37:815, 1978. (Abstract #3146)

TITLE: The Effect of Sodium Balance on the Vasopressin Response to Blood Volume Reduction

PROJECT NO.: 9/7T - Ongoing

INVESTIGATORS: John R. Claybaugh, Ph.D., Clin Invest Svc
MAJ Bradford S. Goodwin, Jr., VC, Clin Invest Svc
COL Peter J. Barcia, MC, Dept of Surgery

FUNDING: FY 79 - \$1,500.; FY 80 - \$300.

OBJECTIVES: To determine whether the typical increase in plasma vasopressin in concentration observed after hemorrhage is altered by the state of sodium balance.

TECHNICAL APPROACH: Conscious dogs will be hemorrhaged 10% of the estimated blood volume after two weeks of low, normal, or high sodium intakes. Blood samples will be obtained prior to and five minutes after hemorrhage, and one hour after the return of hemorrhaged blood. Six dogs will be prepared with exteriorized carotid loops and with chronic indwelling, left atrial cannulae. The dogs will be hemorrhaged at a rate of 0.4 ml/kg/min with blood samples taken at time 0, 10, 20, and 30 minutes, corresponding to 5, 10, and 15 percent hemorrhages. This regimen will be conducted four times, once on normal diet, once on low sodium diet, once on low sodium diet with simultaneous infusion of angiotensin converting enzyme inhibitor, and once in a control with no hemorrhage on normal sodium diet, with similar experimental procedures.

PROGRESS: The 10% hemorrhage series has been completed on six dogs, and the plasma ADH and plasma renin activity increased in response to hemorrhage only on normal and low sodium diets. The high sodium diet completely blunted the response. With the arrival of replacement personnel, this study has been altered in an attempt to extend the findings and possibly learn more of this mechanism. These results show that the ADH response to equal volumes of hemorrhage is significantly greater in dogs maintained on low sodium diet, and that the inhibition of the formation of angiotensin II in response to hemorrhage results in an even greater increase in plasma vasopressin and greater reduction in mean arterial blood pressure. These results demonstrate that the renin-angiotensin system plays an important role in maintaining blood pressure in face of blood volume reduction of less than 20%, and that the ADH response to hemorrhage is not significantly influenced by a concomitant increase in angiotensin II.

Claybaugh, J. R.: Effect of varying sodium intake on vasopressin and renin responses to nonhypotensive hemorrhages in conscious dogs. XXVII International Congress of Physiological Sciences, Paris, France, Abstract No. 406, July 18-23, 1977.

Claybaugh, J. R., Wade, C. E., Goodwin, B. S., and Barcia, B. J. ADH, renin, and cardiovascular responses to slow continuous hemorrhage in conscious dogs on low Na diet with inhibition of converting enzyme. Fed. Proc., 38:967, Abstract 3890, 1979.

TITLE: The Role of the Renin-Angiotensin System in the Antidiuretic Hormone Response to Dehydration

PROJECT NO.: 14/77 - Ongoing

FUNDING: FY 79 - \$200. FY 80 - \$1,500.

INVESTIGATORS: John R. Claybaugh, Ph.D., Clin Invest Svc
MAJ Bradford S. Goodwin, VC, Clin Invest Svc
David P. Brooks, University of Hawaii

OBJECTIVES: These experiments are designed to determine if endogenously generated angiotensin can influence the normal release of antidiuretic hormone in response to dehydration.

TECHNICAL APPROACH: Since it has been previously shown in this laboratory that the renin-angiotensin system may influence ADH release when dogs are dehydrated, these experiments were designed to determine if the normal response of increased ADH during dehydration is dependent upon the concomitant increased plasma renin and angiotensin. Thus, before and after 48 hours of dehydration, venous blood samples will be obtained, once when the dogs are on normal sodium intake, and once after two weeks of low sodium diet.

Theoretically, if angiotensin II has an effect in stimulating ADH during dehydration, this should be greater when endogenous levels of angiotensin II are higher, i.e., after the low sodium diet and 48 hours of dehydration. Infusion of an angiotensin converting enzyme inhibitor after 48 hours of dehydration when the animals have been maintained on a low sodium diet should be followed by an acute drop in plasma ADH concentration which should be greater than in the dogs dehydrated while maintained on a normal sodium diet.

PROGRESS: To date, we have successfully demonstrated a greater increase in plasma ADH concentration in response to 48 hours of dehydration when maintained on low sodium diet (four dogs have been run). More dogs will have to be completed on this series to substantiate this finding and the effect of converting enzyme inhibitor evaluated.

Claybaugh, J. R. and Balk, M. W.: Effect of Low Sodium Diet on the ADH Responses to Dehydration in the Dog. Abstract #206, Fed. Proc. 36:310, 1977.

TITLE: Acute Effect of Hormonal Regulation of Water and Electrolyte Balance at High Altitude in Man

PROJECT NO.: 12/78 - Completed

INVESTIGATORS: John R. Claybaugh, Ph.D., Clin Invest Svc
COL Samuel A. Cucinell, MC, Clin Invest Svc
Charles E. Wade, Univ of Hawaii
LT John Lane, Barbers Point Naval Air Station, HI
Aileen K. Sato, Clin Invest Svc

FUNDING: FY 79 - \$1000.; Fy 80 \$200.

OBJECTIVES: To determine the pattern of hormonal and water and electrolyte excretory changes that occur during 48-hour exposure to 11,000 feet simulated altitude.

TECHNICAL APPROACH: Volunteer subjects free from known endocrine, respiratory, or cardiovascular diseases were selected from a male military population. Two subjects were studied during the same experimental run. After a 24-hour control period, the chamber housing was decompressed to a pressure equivalent to 11,000 (10,500-11,500) feet. During the control day and the first day at high altitude, three blood samples were obtained, at 1000, 1200, and 1800 hours, with urine collections every two hours until 2200 hours. On days 3 and 4, blood was obtained at 1000 hours, and on day 4 the subjects returned to sea level just after the 1000-hour blood and urine samples were obtained. At 1200 hours on day 4, final blood and urine samples were obtained. Plasma concentrations of aldosterone, renin activity, antidiuretic hormone (ADH), cortisol, and prolactin were determined in addition to urinary ADH concentration. Creatinine, osmometry, and electrolyte were conducted.

PROGRESS: Two subjects developed symptoms of acute mountain sickness and did not complete the entire experimental protocol. However, one of those subjects had a clearly different pattern of ADH release; plasma concentration and urinary excretion of ADH were elevated several fold after only 6 hours of exposure to high altitude. This was accompanied by a pronounced antidiuresis and oliguria. The other symptomatic subject did not demonstrate this pattern of ADH release, but did exhibit urinary excretion of ADH at a base rate of 3 to 5 times normal. The possible role of ADH in this disorder is being further studied in another protocol.

The nonsymptomatic subjects in general exhibited no change in plasma ADH concentration, a slight but statistically significant increase in urinary excretion of ADH during the first day of exposure to high altitude and then a reduction to original levels, and a diuresis, predominantly during the morning hours of high altitude exposure with the ensuing hemoconcentration. Plasma aldosterone, renin, and prolactin were decreased during high altitude exposure while cortisol was increased.

Acute Effect of Hormonal Regulation of Water and Electrolyte Balance at High Altitude in Man

The urinary losses of sodium were increased with exposure to high altitude which were not explained by changes in GFR or dietary intake. Thus, the diuresis can be explained in these experiments by an increased loss of sodium via a reduction in tubular reabsorption, probably as a result of the decreased activity of the renin-angiotensin-aldosterone system. On the other hand, the oliguria associated with acute mountain sickness would appear to be a consequence of inappropriate secretion of ADH.

An abstract entitled "Effects of 48 Hours of Mild Hypoxia on the Endocrine Regulation of Urinary Excretion of Water and Electrolytes in Man", Claybaugh, J. R., S. A. Cucinell, C. E. Wade, J. Lane, and A. E. Sato, was accepted and presented to the Hypoxia Symposium sponsored by the Arctic Institute of North America, Calgary, Alberta, Canada in February 1979. A manuscript is in preparation.

TITLE: Studies on the Occurrence of Increased Antidiuretic Hormone (ADH) Release Upon Rapid Ascent to High Altitude and the Role of Diamox in Prevention of Acute Mountain Sickness (AMS) - A Field Study at 13,800 Feet

PROJECT NO.: 13/79 - Ongoing

INVESTIGATORS: John R. Claybaugh, Ph.D., Clin Invest Svc
COL Samuel A. Cucinell, MC, Clin Invest Svc
Al Cymerman, Ph.D., US Army Research Institute of Environmental Medicine, Natick, MA

FUNDING: FY 79 - \$50.; FY 80 - \$1000.

OBJECTIVES: To confirm earlier observations made in studies using high altitude chambers that at some time during the first 24-hour period of exposure to high altitude there is an increased urine ADH excretion, and hopefully correlate this with increased plasma ADH concentration. The latter was not previously accomplished. We would like to see if the increased urine ADH excretion rate occurs at the same time as that in those individuals who have greatly increased urinary ADH excretion rates associated with AMS symptoms. The proposed studies should demonstrate whether or not these changes actually do occur in the "field," when many other factors such as decreased temperature, humidity, and a less confining environment will be superimposed on the effects of hypobaric hypoxia.

TECHNICAL APPROACH: Twelve subjects will be studied. Six will receive Diamox as a preventative for AMS symptoms and six will be untreated. The hormonal responses and water and electrolyte balance will be studied during four days prior to, and four days during exposure to an altitude of 13,800 feet. A two day post-control period will also be conducted. During the preexposure and high altitude exposure periods, two maneuvers known to affect renal handling of water and electrolytes and hormonal responses will be performed--a 16-hour dehydration and an exercise experiment. Hopefully, we will be able to detect differences in these responses between high altitude and sea level, and between the Diamox treated and untreated groups. With these differences in responses, we can perhaps find a mechanism for the ability of Diamox to ameliorate the AMS symptoms.

PROGRESS: We are still awaiting approval from Health Services Command.

We have received approval from the University of Hawaii (lessee of the land) for use of the site selected. The site selected is Puu Poliahu, a cinder cone on the top of Mauna Kea which is approximately 13,600 feet. The site provides adequate level ground for camp facilities, landing facilities for helicopter transportation of subjects, road access for emergency evacuation and trucking of equipment, and is sufficient distance from existing telescope facilities so as not to interfere with their ongoing astrological research.

Studies on the Occurrence of Increased Antidiuretic Hormone (ADH) Release Upon Rapid Ascent to High Altitude and the Role of Diamox in Prevention of Acute Mountain Sickness (AMS) - A Field Study at 13,800 Feet

We have received verbal approval from the Hawaii State Department of Land and Natural Resources on the basis of a request for land use prepared for us by the University of Hawaii Planning Office. The formal approval is expected in the next week.

We have made a site visit with the probable helicopter pilot to assess the possible landing areas. All transportation has received approval. Equipment is being acquisitioned through the support of the 25th Division.

Dr. Al Cymerman has been contacted. He is willing to collaborate and a formal request to USARIEM for his assistance has been issued.

Subject solicitation has begun with many interested volunteers.

TITLE: Comparison of Control of Vasopressin Release from Isolated Hypothalamoneurohypophyseal (HNS) Explants Obtained from Normal and Hypertensive Rats

PROJECT NO.: 22/79 - Ongoing

INVESTIGATORS: John R. Claybaugh, Ph.D., Clin Invest Svc
Kuuleialoha Cornette, Univ of Hawaii School of Medicine
CPT John C. O'Brien, MSC, Clin Invest Svc
MAJ Bradford S. Goodwin, VC, Clin Invest Svc

FUNDING: FY 79 - \$2000.; FY 80 - \$3900.

OBJECTIVES: Certain rat models of hypertension have elevated pituitary content, plasma concentration, and urinary excretion rates of vasopressin. The mechanism for this increased release of vasopressin is not clear and may be due to an alteration in the sensitivity of the hypothalamus to various known stimuli. By removing the hypothalamus with the stalk connection to the neurohypophysis still intact, we can eliminate many uncontrollable inputs to vasopressin release and test the sensitivity to acetylcholine, angiotensin, and osmotic stimuli, and possibly others, in order to test the hypothesis.

TECHNICAL APPROACH: Five-week-old, male, spontaneously hypertensive rats will be selected from the colony at Clinical Investigation Service, Tripler Army Medical Center, Okamoto-Aoki strain. Age-matched normotensive male control rats will be of the WKY strain. The rats will be surgically prepared with indwelling carotid arterial cannulae and placed individually into metabolism cages. Two days after surgery, daily collections of urine will be begun for analysis of flow rate, and urine concentrations of Na⁺, K⁺ and antidiuretic hormone (ADH), and urine osmolality. Daily measurements of systolic and diastolic blood pressure will be made via the carotid arterial cannulae. After 5 days of measurements and urine collections, the rats will be sacrificed by guillotine and trunk blood collected for analysis of plasma osmolality and Na⁺, K⁺ and vasopressin concentration, and plasma renin activity. The HNS will be dissected and prepared for incubation. Osmolality will be determined by vapor pressure method, Na⁺ and K⁺ by flame photometry. Vasopressin will be assayed by radioimmunoassay and plasma renin activity by the New England Nuclear radioimmunoassay kit. All methods are ongoing in our laboratory.

PROGRESS: The surgical skills necessary for successful dissection of the HNS preparation and the procedures involved in organ culture have been routinely performed. We have been able to demonstrate an osmotic stimulation of vasopressin from the HNS preparation in a 3-hour exposure period. Control experiments indicate a steady vasopressin production can be achieved during the necessary 12-hour block of time on the fourth day of organ culture. Changing the osmolality of the incubation medium from 310 to 375 mOsm/kg elicits identical responses on the same day, with a control period interspersed between the two stimulation periods.

Comparison of Control of Vasopressin Release from Isolated Hypothalamoneurohypophyseal (HNS) Explants Obtained from Normal and Hypertensive Rats

We are now at the stage where we feel confident to study the potentiation of this response with certain agents, e.g., angiotensin II, aldosterone, catecholamines, and cholinergic agents. The variability in baseline vasopressin production may preclude the distinction between hypertensive and normotensive rats unless the production rates are widely different. To date, we have studied only the normotensive control rats, and the hypertensive rat colony has had to be reestablished because the existing colony had apparently exceeded a reproductive age. Investigation into hypertensive rats will begin in May 1980.

TITLE: Body Fluid Balance and Associated Hormonal Changes in Man in Response to 13 Days at 31 Atmosphere Absolute (ATA) Pressure

PROJECT NO.: 31/79 - Completed

INVESTIGATORS: John R. Claybaugh, Ph.D., Clin Invest Svc
CPT John C. O'Brien, MSC, Clin Invest Svc

FUNDING: Fy 79 - \$1200.; FY 80 - None

OBJECTIVES: To assess the water and salt balance and associated hormonal control mechanism at 31 ATA. To assess these parameters in response to exercise and immersion at the simulated depth of 1,000 feet.

TECHNICAL APPROACH: Four professional saturation divers employed by Japan Marine Science and Technology Center (JAMSTEC) were studied for 3 days at sea level, during 3 consecutive days of increasing compression at increments of 10 ATA per day, then for 14 days at 31 ATA (1000 ft sea water), 6 days of decompression to sea level, and 3 postcompression days. During these periods, water and electrolyte balance, renal function, and hormonal parameters were determined. Studies were conducted in chamber facilities at JAMSTEC which is equipped with a wet pot. The wet pot was used to assess the added known stimulus for diuresis, immersion, which was conducted at sea level barometric pressure, at 31 ATA, and again at sea level after compression. Again, parameters to assess renal function, water and electrolyte balance, and hormonal control were determined.

PROGRESS: All studies have been completed but thousands of samples were obtained, and are not quite through complete analysis. Our studies were only a portion of all the physiological measurements being made, including respiratory function, cardiac function, electroencephalogram recordings, and some hematological studies.

Several important new observations were made in our area of study. Compression to 1000 feet is accomplished by two types of diuresis. First, during compression, there is an immediate increase in urine flow probably due to an increased urinary loss of sodium, the cause of which we have not yet been able to determine. Hormonal analysis on these samples has not been completed. This occurred during each of the three compression phases. Secondly, there is a substantial diuresis during the period of steady pressure of 31 ATA. Interestingly, this is typified by a highly significant reversal in the normal diurnal urine flow pattern. That is, during 31 ATA, nocturnal urine flow increased by about 50%. At least part of this diuresis can be explained by suppressed levels of vasopressin, but the factors which cause vasopressin to be abnormally low at night while at high pressure are unresolved.

Body Fluid Balance and Associated Hormonal Changes in Man in Response to 13 Days at 31 Atmosphere Absolute (ATA) Pressure

Immersion caused a diuresis at sea level, at high pressure, and at sea level (post pressure). The immersion was accompanied by a greater reduction in the urinary excretion of vasopressin at sea level than at high pressure, an observation we have seen before. The diuresis results from an increased free water clearance and osmotic clearance. The lower baseline levels of vasopressin probably account for the reduction in the magnitude of suppressed vasopressin seen during immersion at high pressure.

Nakayama H, Hong SK, Claybaugh J, Matsui N, Park YS, Ohta Y, Shiraki K, and Matsuda M: Energy and Body Fluid Balance During a 14-Day Dry Saturation Dive at 31 ATA (SEADRAGON IV). Mini-paper submitted to the Undersea Medical Society, VII Symposium on Underwater Physiology, Athens, Greece, 5-10 July 1980 (in conjunction with European Undersea Biomedical Society).

Nakayama H, Hong SK, Arita H, Lin YC, Claybaugh J, Lundgren C, and Smith, RM: Physiological Responses to Immersion at 31 ATA (SEADRAGON IV). Mini-paper submitted to the Undersea Medical Society, VII Symposium on Underwater Physiology, Athens, Greece, 5-10 July 1980 (in conjunction with European Undersea Biomedical Society).

TITLE: Studies on the Occurrence of Increased Antidiuretic Hormone (ADH) Release Upon Rapid Ascent to High Altitude

PROJECT NO.: 32/79 - Terminated

INVESTIGATORS: John R. Claybaugh, Ph.D., Clin Invest Svc
Al Cymerman, Ph.D., US Army Research Institute of Environmental Medicine, Natick, MA

FUNDING: FY 79 - none; FY 80 - none

OBJECTIVES: To confirm earlier observations that at some time during the first 24-hour period of exposure to high altitude there is an increased urine ADH excretion, and hopefully correlate this with increased plasma ADH concentration. The latter was not previously accomplished. We would like to see if the increased urine ADH excretion rate occurs at the same time as that in those individuals who have greatly increased urinary ADH excretion rates associated with acute mountain sickness (AMS) symptoms.

TECHNICAL APPROACH: The study will be a collaborative effort between the U. S. Army Research Institute of Environmental Medicine (USARIEM) and Tripler Army Medical Center (TAMC) in Honolulu, Hawaii. It will be conducted in the hypobaric chamber at USARIEM, with the majority of sample analysis being done at the Clinical Investigation Service of TAMC. Twelve healthy young men experienced with high altitude exposure in the chamber will be used as volunteer subjects.

PROGRESS: It was planned to conduct this study in the chamber facilities at USARIEM. However, their scheduling of this project was delayed, and since we felt that most these questions could be answered satisfactorily by conducting a field study in Hawaii, we have decided not to continue this particular study. Probably a follow-up study will be scheduled later.

TITLE: Clinical Significance of Antidiuretic Hormone Levels in Disorders of Fluid and Electrolyte Metabolism

PROJECT NO.: 6/79 - Ongoing

INVESTIGATORS: COL Samuel A. Cucinell, MC, Clin Invest Svc
John R. Claybaugh, Ph.D., Clin Invest Svc

FUNDING: FY 79 - \$2000.; FY 80 - \$2000.

OBJECTIVES: As a continuing part of our investigation into the influence of the antidiuretic hormone (ADH) in human metabolism, we wish to determine what influence this hormone has in a variety of clinical states.

TECHNICAL APPROACH: The main technical alteration in this protocol is that we are not doing plasma volumes in conjunction with the ADH levels. In patients with secondary hyperaldosteronism syndrome, the total blood volume is not a meaningful estimation of the state of total body hydration.

PROGRESS: The antidiuretic hormone activity has been determined in over 25 patients at Tripler Army Medical Center under varying clinical conditions. It is clear that the ADH takes part as a major response to multiple syndromes of cardiac, renal, and hepatic disease. The only consistent finding to date is the presence of a marked ADH change to position and dehydration in untreated hypertensive patients. These changes are either an increase or decrease. This is in contrast to normotensive controls who had no ADH changes at all to the same stimulus. As a control on the sampling technique, renin was shown to have an increase in all persons tested with orthostasis and dehydration.

TITLE: Determination of Liver Blood Flow and Improved Technique for Sampling Hepatic Vein Blood

PROJECT NO.: 26/79 - Ongoing

FUNDING: FY 79 - \$1000.; Fy 80 - \$2000.

INVESTIGATORS: COL Samuel A. Cucinell, MC, Clin Invest Svc
Gordon H. Bryant, Clin Invest Svc
COL Paul L. Shetler, MC, Dept of Surgery

OBJECTIVE: To determine liver blood flow and to develop an improved technique for sampling hepatic vein blood.

TECHNICAL APPROACH: Methods now available for the determination of hepatic blood flow are either invasive or based on indirect chemical clearances. None of these methods is satisfactory for the accurate noninvasive quantitation of liver blood flow necessary for our continued studies into the lactic acid metabolism by the liver. It should be possible to place a thermistor catheter in the vena cava (VC) at the level of the renal and hepatic veins. Blood flow at these points might be determined by thermodilution. Hepatic vein blood flow could be estimated by subtraction of the blood flow in the vena cava at the level of the renal veins from the vena cava blood flow at the level of the diaphragm. This should be liver blood flow. It should be possible to sample pure hepatic vein blood by inflation of a balloon-equipped, double lumen catheter at the level just above the renal veins. This should cut off blood coming from the renal veins and below from entering the vena cava in the area of the hepatic veins. Blood samples from just above the balloon should be hepatic vein blood.

PROGRESS: It has been established by a series of dog experiments using the electromagnetic flow meter that the blood flow in the inferior vena cava between the renal veins and the right atrium can be adequately determined by two thermodilution flow probes. The flow between these two points represents the efflux of blood from the hepatic veins. The correlation is statistically highly significant and response to the usual physiological mechanism of increasing and decreasing liver blood flow. This includes glucagon administration, vasopressin administration and exsanguination and transfusion. The efflux of blood from the liver by way of hepatic veins is the easiest and most direct means of determining hepatic blood flow. At present, the thermodilution flow probes are being designed for rapid and facile use.

TITLE: Mechanism of Action and Antidote for Tricyclic Antidepressants

PROJECT NO.: 28/79 - Ongoing

FUNDING: FY 79 - \$1000.; FY 80 - \$2500.

INVESTIGATORS: COL Samuel A. Cucinell, MC, Clin Invest Svc
LTC Harry M. Thomas, MC, Dept of Medicine
Bert Lum, M.D., Univ of Hawaii

OBJECTIVES: The tricyclic antidepressants (TCA) have become widely used in medicine and psychiatry with resultant overdoses and toxicities becoming more common. The cardiovascular effects of these compounds are known to include a muscarinic blocking action (atropine-like) and blockade of the re-uptake of norepinephrine. It is the intent of this study to try to define more precisely the cardiovascular toxicity of the TCA and to suggest the most rational antidote for the cardiotoxicity.

TECHNICAL APPROACH: A preliminary review of all cases of TCA overdose at Tripler Army Medical Center will be made to determine the cardiovascular pattern which may be peculiar to these patients in this area. A correlation with other cardioactive compounds the patient may have taken will be made.

An animal model of cardiotoxicity of the TCA will be developed in the dog and rabbit. The animal will be sedated with the TCA itself. Recordings of the EKG, electrolytes, and blood gases will be made. Doses of TCA will be given to produce EKG toxicity. In some animals it will be necessary to allow the complete cardiotoxicity to evolve in order to determine the pattern of conduction abnormality leading to cardiac arrest. Once this pattern is defined, antidotes and mechanisms of altering the EKG pattern will be made. It is anticipated that a drug so rich in autonomic actions would have a cardiac effect which would operate through the autonomic nervous system. Blockade of this system at known points, i.e., ganglionic blockade, cholinergic receptor blockade, adrenergic transmitter and receptors blockade, as well as autonomic stimulants at the same levels, should alter the pharmacological pattern of TCA. If the TCA proves resistant to these manipulations, a direct quinidine-like action may exist and direct pacing may be of value.

PROGRESS: The intraperitoneal toxicity of imipramine in cats has been determined in preparation for development of an antidote. Work done at the University of Hawaii has shown that the anesthetized rabbit does not develop lethal arrhythmia after the administration of imipramine by any route. The influence of anesthesia may be paramount in these studies.

TITLE: Effect of Single Dose Intra-articular Corticosteroid on Post-operative Infection Rate in Rabbits' Knees

PROJECT NO.: 152/75 - Terminated

INVESTIGATORS: Gerald Dericks, Jr., M.D., Honolulu, Hawaii
CPT Carroll R. Dotson, MSC, Clin Invest Svc
MAJ Bradford S. Goodwin, VC, Clin Invest Svc

FUNDING: FY - none; FY 80 - none.

OBJECTIVES: To investigate the effect of single dose intra-articular steroid in conjunction with antibiotics on the postoperative infection in rabbits' knees.

TECHNICAL APPROACH: Twenty New Zealand white rabbits (3-4 kg body weight) were anesthetized, and their knees were shaved and surgically prepared. All rabbits received 100 mg of Kefzol (IM) followed by 0.1 ml of Staphylococcus aureus (2×10^8 organism) injected into both knee joints. One-half of the animals also received 0.1 ml of Decadron phosphate into the knee joint along with the bacteria. Animals were observed twice daily for changes in feeding habits, joint swelling as determined by measurement, loss of joint mobility, and increased thermal reaction of the joints. All animals still alive were sacrificed 15 days following initial injections. Knee joints were cultured and then fixed in PAF for histological examination. On the basis of the above data, knees were classified as definitely affected or normal.

PROGRESS: No further work has been performed since the last report. The project is being terminated.

TITLE: Evaluation of Three Rapid Diagnostic Methods for the Identification of Haemophilus influenzae in Comparison to Standard Microbiological Procedures

PROJECT NO.: 30/78 - Ongoing

INVESTIGATORS: CPT Carroll Ray Dotson, MSC, Clin Invest Svc
CPT Dean D. Ettinger, MC, Dept of Pediatrics
MAJ Charles G. Jackson, MC, Dept of Pediatrics
Paul Rudoy, M.D., Univ Of Hawaii

FUNDING: FY 79 - \$3,000.; FY 80 - \$500.

OBJECTIVES: To determine the magnitude of diagnostic correlation between typical culture, serological, and microscopic techniques for the identification of clinical isolates of H. influenzae and immunological methods (counterimmunoelectrophoresis \pm CIE1, Latex particle agglutination, and Staphylococcus-A agglutination slide tests).

TECHNICAL APPROACH: Cerebrospinal fluid (CSF), serum, urine, and sputum specimens from clinical cases of suspected H. influenzae at Tripler and other Oahu hospitals will be prepared for testing. On some occasions, these specimens may be stored at -70 F and tested as a group at a later date. The principal source will be bacterial meningitis presentations in pediatric patients. Additionally, similar specimens from aseptic meningitis, bacterial meningitis other than Haemophilus, and inflammations of noninfectious nature will be examined by the same techniques to establish specificity.

When possible or necessary, fluid specimens will be concentrated by standard physical and biochemical techniques. Nonspecific (positive) reactions will be eliminated by pretreating the specimen as needed; i.e., heating CSF to 100°C for 15 minutes for latex agglutination tests. The tests will be performed to detect the bacterial antigen in the body fluids. Purification and modification of the antisera, parameters of testing and specimens will be performed as needed. In particular, increased sensitivity of these reactions is expected with immunochemical purification of the antisera used.

The principal tests will be CIE, latex particle agglutination and Staphylococcus-A coagglutination, and other determinations may be made by immunoelectrophoresis, various immunological gel diffusion reactions, and ELISA. These results will be compared to that of the clinical bacteriology laboratory and to the patient's medical course.

Evaluation of Three Rapid Diagnostic Methods for the Identification of Haemophilus influenzae in Comparison to Standard Microbiological Procedures

Antisera will be prepared to the representative bacterial organisms and to the dominant surface antigen of H. influenzae type B (HITB). This antigen has been shown to be polyribose phosphate (PRP). It can be purified and used to quantitate the amount of HITB antigen in the specimen. Sterile body fluids similar to those provided by the patients will be "seeded" with known members of H. influenzae type B organisms and the limits of bacterial cell detection quantitated.

PROGRESS: Counterimmunoelectrophoresis has been established for use in diagnosis of bacterial meningitis. Currently, the specificity controls are being collected, and only preliminary results are in.

Latex particle agglutination (LPA) is approximately 100x more sensitive than CIE for detection of HITB antigen in CSF and serum. LPA reagents have been absorbed with cross-linked, pooled, normal human serum proteins to remove nonspecific, false-positive reactions.

Staphylococcal (protein-A) coagglutination (SAC) has been tested for HITB and appears to be equal to LPA in sensitivity. Specificity tests for SAC are underway. SAC preparations for other bacterial meningitis agents are being tested.

Several hundred patient specimens have been collected and clinical charts for each are now being reviewed to classify these body fluids. All specimens will be tested simultaneously by all techniques, if quantities allow, to eliminate variability.

TITLE: Isolation of a Pyrogenic Exotoxin from Staphylococcus aureus

PROJECT NO: 27/79 - Ongoing

INVESTIGATORS: CPT Carroll R. Dotson, MSC, Clin Invest Svc
Marion E. Melish, M.D., Univ of Hawaii School of Medicine
and Kapiolani Children's Medical Center

FUNDING: FY 79 - \$1000.; FY 80 - \$1400.

OBJECTIVES: To establish methods and procedures for production and isolation of staphylococcal pyrogenic exotoxin.

TECHNICAL APPROACH: Recent isolates of Staphylococcus aureus suspected of elaborating this exotoxin and implicated in clinical disease will be procured. Isolation of S. aureus suspected of producing pyrogenic exotoxin in local hospitals will be made. Suspected organisms will be grown in air and 5% CO₂ atmospheres in several media to determine if toxin production can be promoted or enhanced in in vitro conditions. Culture supernates will be tested for pyrogenic factors by the rabbit bioassay. Positive pyrogenic cell-free filtrates will then be further processed to isolate the pyrogen and characterize it biochemically.

The crude toxin-containing filtrate will be treated by one or more of the following processes: ethanol precipitation, ammonium sulfate precipitation, and column chromatography as necessary. The partially purified toxin will then be isolated by thin-layer isoelectric focusing. Bioassays for pyrogenicity and epidermolytic toxin will be performed on the crude and purified forms of the isolated factors.

PROGRESS: Isolates of S. aureus have been secured from two mainland hospitals that are believed to produce new toxins which manifest clinically as toxic shock or elaboration of pyrogenic exotoxins. These isolates do not produce epidermolytic toxin as measured by bioassay in mice and are being checked by radioimmunoassay for this toxin.

The isolate suspected of producing a pyrogen has been grown on beef-heart dialysate, trypticase soy broth and dialysate, brain-heart infusion and dialysate and CCY medium (chemically defined). Cell-free filtrates of each grown in 5% CO₂ have been tested in the rabbit pyrogen assay for activity without further purification. The rabbits used to date have failed to give positive pyrogenic responses to standardized bacterial lipopolysaccharide pyrogens; thus, invalidating the tests. It was later determined that some strains and sub-strains have better responses and some have vastly diminished responses to the same pyrogen. Dutch belted rabbits are believed to be good responders and have been ordered. Further work on isolation and purification has been deferred until a reliable detection system for pyrogens is established.

TITLE: Amylase Excretion in Laboratory Animal Models

PROJECT NO: 1/79 - Ongoing

INVESTIGATOR: MAJ Bradford S. Goodwin, Jr., VC, Clin Invest Svc

FUNDING: FY 79 - \$1000.; FY 80 - \$1000.

OBJECTIVES: To determine which laboratory animal is the best model for the study of amylase excretion. To determine the laboratory animal model that responds to glucagon by increased excretion of amylase.

TECHNICAL APPROACH: Small laboratory animals to be studied include the mouse, rat, rabbit, and cat. Each laboratory animal species will be divided into a control group and a study group. Saline diuresis will be administered if necessary to allow adequate determination of total urine output and the levels of amylase and creatinine in urine samples. The diuresis will provide an adequate sample size from the small animal species. Food and water will be available ad libitum. Normal values of amylase and creatinine have not been reported for these laboratory animals; therefore, baseline normal values will be determined for each species. The study group of laboratory animals will receive varying doses of glucagon along with the intraperitoneal saline diuresis as administered to the controls. A correlation between the concentration of glucagon administered and the increase in amylase excretion will be made. The laboratory animal species which demonstrates the most profound increase in amylase clearance after injection of glucagon should provide an excellent laboratory animal model for the study of human pancreatitis. Large animal studies will include dogs and monkeys (sheep and pigs, if necessary). Anesthetized animals will have a continuing saline diuresis with control period followed by I.V. Glucagon (approximately 1 mg). Urine will be collected during these periods for analysis.

PROGRESS: The mouse, rat, rabbit, cat, dog, and monkey have been evaluated for the effects of glucagon on amylase excretion. The cat and dog respond similarly to the human, but the effect is of short duration, and concentrations of amylase are very small. The monkey does not respond, and the rat and rabbit show a decrease in amylase excretion under the effects of glucagon I.V.

The data collected to date was presented at the AALAS annual meeting in Atlanta, GA., in Sep 1979. The mouse and rat need to be reevaluated, and, once completed, a publication will be submitted to the Laboratory Animal Science Journal.

TITLE: Enzyme Immunoassay of Arginine Vasopressin (formerly titled Enzyme Immunoassay of Steroids)

PROJECT NO: 11/77 - Ongoing

INVESTIGATORS: CPT John C. O'Brien, MSC, Clin Invest Svc
John R. Claybaugh, Ph.D., Clin Invest Svc

FUNDING: FY 79 - none; FY 80 - \$1,500.

OBJECTIVES: (a) To develop the technology for and assess the clinical and research efficacy of enzyme immunoassay methods for arginine vasopressin (AV) measurements in biological fluids in comparison with now standard radioimmunoassays; and (b) to partially automate enzyme immunoassay techniques so as to allow for greater productivity in hormone measurement by routine laboratory personnel.

TECHNICAL APPROACH: This study consists of two phases: (1) The validation of enzyme immunoassay for AV using hormone coupled B-galactosidase, comparing results to currently available radioimmunoassays; (2) partial automation of the enzyme immunoassay for B-galactosidase.

PROGRESS: We have established the conditions for the enzyme assay of B-galactosidase. Recently we have conjugated AV to B-galactosidase, and after dialyzing out the free AV have found high enzyme activity of the AV-enzyme conjugate. Presently we are evaluating the conditions required for second antibody precipitation of the (AV-enzyme)-anti-AV antibody complex. There has been no recent progress because of shortage of technicians.

TITLE: The Effect of 5-Bromodeoxyuridine on the Tumorigenicity of Hepatoma Tissue Culture Cells

PROJECT NO.: 42/78 - Ongoing

INVESTIGATORS: CPT John C. O'Brien, MSC, Clin Invest Svc
MAJ Bradford S. Goodwin, VC, Clin Invest Svc

FUNDING: FY 79 - \$3500.; FY 80 - \$4000.

TECHNICAL APPROACH: The research will be organized into three separate areas: (a) standardization of the techniques for HTC tumor growth in the athymic nude mouse and buffalo rat; (b) effects of BUdR on tumor growth of HTC cells using previously determined standard methods; and (c) test for the retention of tumorigenicity in HTC clones selected for their ability to survive with a high level of BUdR in their DNA.

PROGRESS: The project has progressed well. It has been determined that hepatoma tissue culture (HTC) cells were tumorigenic in both the athymic nude mouse and the adult host, the buffalo rat. If HTC cells were cultivated in 10 μ M 5-bromodeoxyuridine (BUdR) for 10 days, the cells were still tumorigenic in the athymic nude mouse, but not in the buffalo rat. The significance of the effect of BUdR is that the only known metabolic fate of BUdR is to replace thymidine in DNA. At the 10 μ M concentration used, there is no change in the growth rate. Presently, we are testing whether or not the buffalo rat, which did not develop tumors when treated with BUdR-grown HTC cells, will still grow tumors with control HTC cells. This project will need to be extended due to the long-term nature of these experiments.

TITLE: Lactic Metabolism in Isolated Liver Cells with Regard to Anoxia, Acidosis, Alkalosis, and Temperature

PROJECT NO.: 46/78 - Ongoing

INVESTIGATORS: CPT John C. O'Brien, MSC, Clin Invest Svc
COL Samuel A. Cucinell, MC, Clin Invest Svc

FUNDING: FY 79 - \$2,000.; FY 80 - \$4,500.

OBJECTIVES: To study lactate metabolism in primary cultures of rat hepatocytes.

TECHNICAL APPROACH: It is planned to systematically determine if increasing and decreasing pH causes a reversal of the usual role of the liver from a consumer of lactic acid to a producer of lactic acid. The effects of graded doses of hormones (epinephrine, glucagon, steroid, insulin, and others) will be studied for possible effects. Recognized treatments for shock will be studied to determine influence on acidosis. Those to be studied include sympathomimetic amines (alpha, beta and dopamine, vasodilators, dextran, and diuretics).

PROGRESS: The project has progressed well, and a preliminary publication is being prepared. A method for obtaining rat hepatocyte monolayer cultures was developed and characterized. The cells were found to readily use lactate, converting approximately 45% of that consumed to glucose. At a concentration of 8 mM, lactate was utilized at a constant rate to 120 min. The rate of consumption was found to increase in a linear fashion as the median concentration of lactate increased from 1 to 8 mM, and less than 1 mM lactate was produced. At constant P_{O_2} and P_{CO_2} , lactate consumption was constant over a pH range of 7.1 to 7.7. Below 7.1, the rate of lactate utilization was inhibited. The inhibition was reversed by restoring the pH to above 7.1. At constant pH, P_{CO_2} of from 4.3 to 100.2 mmHg had no effect on lactate consumption.

TITLE: Recovery Patterns of Renal Function During Unusually Prolonged Multi-day Endurance Running

PROJECT NO.: 25/79 - Completed.

INVESTIGATORS: Charles E. Wade, Ph.D., Clin Invest Svc
John R. Claybaugh, Ph.D., Clin Invest Svc
MAJ Richard Stor, MC, Dept of Medicine
Rudy Dressendorfer, Ph.D., Univ of California, Davis

FUNDING: FY 79 - \$1200.; Fy 80 - \$200.

OBJECTIVES: Single bouts of competitive endurance exercise greatly affect fluid and electrolyte regulation, and the resulting changes in kidney function may persist for days. With repeated endurance efforts on a daily basis, inadequate recovery of normal blood and urine chemistry may limit continued physical performance. In this study we investigated the recovery patterns of renal regulation and function during 18 days of running an average distance of 17.7 miles per day under race conditions.

TECHNICAL APPROACH: Ten experienced runners participating in "The Great Hawaiian Footrace" volunteered as subjects. The race consisted of 20 consecutive days, during which the runners ran distances varying from 22.6 to 12.5 miles each morning with three exceptions. On the last morning only 6.2 miles were run, and on the mornings of days 11 and 12, no miles were run. Eight sample times were scheduled throughout the race. The samples were taken on the morning of day 1 before the race started, on the mornings after runs of distances 18.0 miles or greater, and on the morning after the two-day midpoint rest period. The samples consisted of a timed over-night urine sample and a blood sample.

PROGRESS: The results indicate no significant variations in urine flow rate, creatinine clearance, osmotic clearance, free-water clearance, or urinary excretion of vasopressin. The amount of filtered sodium being reabsorbed by the kidneys was significantly greater during run days, and returned to normal during the midpoint rest period. This was probably due to elevated production of renin and aldosterone during the run days. It is important to recognize that these analyses represent the morning after a run which occurred the previous morning, i.e., the samples were obtained before they started running on the morning of the sample day. Thus, these values represent a lack of complete recovery of the water and electrolyte and associated hormonal status, even after about 20-22 hours of relative rest and normal fluid and dietary intake.

PUBLICATION:

Wade, C., O'Brien, J., Claybaugh, J., Starr, V.R., and Dressendorfer, R. Effects of repeated long distance running on "Athletic Pseudonephritis". Submitted to The Physician in Sports Medicine.

TITLE: The Behavioral Effects of Antihypertensive Therapy in the Elderly

PROJECT NO.: 29/79 - Ongoing

INVESTIGATORS: MAJ John E. Aoki, MC, Dept of Family Practice
Marvelu Peterson, R.N., University of Hawaii
MAJ David Gillooly, MSC, Dept of Psychiatry
COL Samuel A. Cucinell, MC, Clin Invest Svc

OBJECTIVES: To investigate the possible untoward effects of antihypertensive medications on intellectual function and related behaviors in the elderly.

TECHNICAL APPROACH: Active medications will be replaced by a non-active form of the drug or placebo for a period of 30 or 60 days. Two groups of subjects will be studied and compared in a cross-over design: Group I (APP) - subjects will receive active medications for 30 days and then placebos for 60 days; and Group II (PAA) - subjects will receive placebos for 30 days and then active medications for 60 days. Data on the behavioral effects of and blood pressure response to the active and nonactive medications will be collected at 30-day intervals. The subject will participate in the study for a period of 90 days.

PROGRESS: Awaiting OTSG approval.

TITLE: Biodetermination of Scombroid Toxin

PROJECT NO.: 17/79 - Ongoing

INVESTIGATORS: LTC Thomas I. Clements, MC, Dept of Medicine
MAJ Bradford S. Goodwin, VC, Clin Invest Svc

FUNDING: FY 79 - \$500.; FY 80 - \$1000.

OBJECTIVES: To design a bioassay to determine presence of unknown toxin in fish responsible for clinical scombroid poisoning. This will be attempted by correlating known patients, fish, specimens, and suspected outbreaks.

TECHNICAL APPROACH: A bioassay will be developed which may utilize radioactive-tagged human serum used in rabbits. Intradermal injections of the fish extract gives a "wheal and flare" which can be measured by amount of radioactivity in the area. This is most tentative. Other possibilities would include oral ingestion in laboratory animals with modified guts to watch for histamine-type response. Whatever test we develop will be correlated with retrospective analysis of the 30 to 50 cases seen in Hawaii in the last two years. The fish specimens come from these suspected cases. In addition, the investigators have made arrangements to be notified as soon as possible about any new suspected cases.

PROGRESS: The above-mentioned radioactive assay has been developed and is being tested on all fish specimens. In addition, filtrates, autoclaved, cooked, and raw variations of the specimens will be tested.

TITLE: Anatomic Effects of Exercise on the Coronary Arteries of Hypertensive Rats

PROJECT NO.: 20/77 - Completed

INVESTIGATORS: COL James E. Hastings, MC, Dept of Medicine
MAJ Bradford S. Goodwin, VC, Clin Invest Svc

FUNDING: FY 79 - \$1000.; FY 80 - none

OBJECTIVES: To determine if forced exercise has significant effect on the coronary arteries of the hypertensive rat. The effect of antihypertensive drugs will be determined in this model, as well as the overall survival of hypertensive rats with regular exercise and sedentary.

TECHNICAL APPROACH: The "spontaneous hypertensive rat" was obtained. Animals were given food ad lib. One group was given regular daily exercise of the forced swimming type. After two weeks, all animals were sacrificed and the anatomy of the coronary arteries determined by the vinyl acetate technique. Further studies evaluated antihypertensive medication with and without exercise and variation in the duration of exercise. The rat blood pressure was determined twice daily, immediately after exercise and at a time remote from the exercise.

PROGRESS: There was a clear separation of the survival of rats with swimming males dying first followed by swimming females, control males, and control females.

TITLE: Prospective Study of von Hippel-Lindau Disease

PROJECT NO.: 7/78 - Completed

INVESTIGATORS: CPT James M. Lamiell, MC, Dept of Medicine
MAJ Fernando G. Salazar, MC, Dept of Surgery
CPT William L. Fill, MC, Dept of Radiology
Y. Edward Hsia, M.D., Univ of Hawaii
Margaret Marshall, Univ of Hawaii
Juliet Yuen, Kapiolani Medical Center, HI

FUNDING: FY 79 - \$7000; FY 80 - \$500.

OBJECTIVES: (1) To search for and identify an appropriate marker present in those individuals with von Hippel-Lindau disease (vHL). (2) To clinically examine all the members of the kindred known to have vHL in order that any occult cases of vHL may be identified. (3) To perform a detailed genetic and historical study of the kindred. (4) To determine the effectiveness of indirect ophthalmoscopy and abdominal ultrasound in a prospective study of vHL. (5) To study the psychological impact of such a study on the individuals of the kindred and of the identification of any occult cases of vHL.

TECHNICAL APPROACH: A detailed historical study of the kindred in question was made including obtaining relevant hospital records and pathology reports, contacting involved local physicians, and locating the various members of the kindred. A careful physical examination, indirect ophthalmoscopy and abdominal ultrasound was performed on each member of the kindred. In addition, the following laboratory tests were done: CBC, ESR, SMA-12, and urinalysis. If indicated, serum norepinephrine, urine VMA, brain scan, fluorescein angiography, and IVP were performed. HLA blood typing was performed on all members of the kindred. A search was made for red cell gene linkage and saliva protein gene linkage markers on specimens obtained from members of the family. A total of some 40 markers were searched for in each specimen. The psychological impact of this study on the members of the kindred was observed and documented.

PROGRESS: A kindred spanning six generations and containing 221 individuals was studied. In this kindred, 42 individuals were afflicted with von Hippel-Lindau disease. Through a simple presymptomatic screening program, we were able to make the new diagnosis of von Hippel-Lindau disease in 27 instances. Many new manifestations of von Hippel-Lindau disease were discovered in the kindred. This included four cases of bilateral renal adenocarcinoma in young individuals, all of whom were treated with bilateral nephrectomies and hemodialysis. One of those individuals has received a successful cadaveric renal transplant.

Prospective Study of von Hippel-Lindau Disease

The history and literature of von Hippel-Lindau disease has been reviewed and generally tends to confirm the results of previous reviews. Information from the literature plus some of our own cases lead us to include pancreatic carcinoma as part of von Hippel-Lindau disease.

Two papers were presented at the 29th Annual Meeting of the American Society of Human Genetics in Vancouver in October 1978.

Publications:

- (1) Fill, WL, Lamiell, JM, and Polk, NO: The Radiographic Manifestations of von Hippel-Lindau Disease. Radiology (in press).
- (2) Lamiell, JM, Stor, RA, and Hsia, YE: von Hippel-Lindau Disease Simulating Polycystic Kidney Disease. Urology (in press).
- (3) Salazar, FG and Lamiell, JM: Early Identification of Retinal Angiomas in a Large Kindred with von Hippel-Lindau Disease: Am J Ophthalmol (in press).
- (4) Lamiell, JM, Salazar, FG, and Hsia, YE: von Hippel-Lindau Disease. In preparation.

TITLE: Immunogenic Studies of Reduced Mitogen Response in Patients with Rheumatoid Arthritis

PROJECT NO.: 13/78 - Terminated

INVESTIGATORS: LTC Martin I. Leftik, MC, Dept of Medicine
Mark Barton Frank, Univ of Hawaii

FUNDING: FY 79 - none; FY 80 - none

OBJECTIVES: To determine (1) if reduced in vitro lymphocyte response to certain mitogens (as found in rheumatoid arthritis patients) is inherited, and, if so, the mode of inheritance, and (2) if there is a correlation between the response to mitogens and disease severity.

TECHNICAL APPROACH: Ten cc of blood will be drawn for mitogen and mixed lymphocyte culture (MLC) response studies, and another 10 cc will be drawn for HLA typing from patients with rheumatoid arthritis. A group of patients and relatives will be chosen at random to study the reproducibility of results within family members, and a group of patients with notable remission or advancement of the disease will be asked to return for a second donation to study the relationship of mitogen and MLC response to the course of the disease and disease severity. As osteoarthritis patients do not appear to have a reduced mitogen response but use the same drugs for treatment as rheumatoid arthritis patients, they will be studied primarily as controls. Volunteers will be used as normal healthy controls with an attempt made to obtain a representative sample of the disease group with respect to age, sex, and race. The same procedures will be followed for the control groups as for the disease group.

PROGRESS: Project has been terminated.

TITLE: Continuation of Chemotherapy and Immunotherapy

PROJECT NO.: 43/78 - Terminated

INVESTIGATORS: LTC Ray O. Lundy, MC, Dept of Medicine
MAJ William C. Waterfield, MC, Dept of Medicine
LTC David A. Maybee, MC, Dept of Pediatrics
LTC Constance P. Hastings, MC, USA Health Clinic

FUNDING: FY 79 - none; FY 80 - none.

OBJECTIVES: To provide appropriate chemotherapy for cancer patients.

TECHNICAL APPROACH: To continue the use of the following chemotherapy agents at Tripler: (1) CIS-platinum, (2) high-dose Methotrexate, (3) BCG-immunotherapy, and (4) Daunomycin.

PROGRESS: Disapproved by OTSG.

TITLE: Lactic Acid Metabolism in Laboratory Models

PROJECT NO.: 45/78 - Completed

INVESTIGATORS: MAJ Dean J. Nickles, MC, Dept of Medicine
COL Samuel A. Cucinell, MC, Clin Invest Svc

FUNDING: FY 79 - \$9,000; FY 80 - \$150.

OBJECTIVES: To define the influence of the reversal of the liver's role from clearing lactic acid out of the blood to increasing lactic acid (lactategenesis).

TECHNICAL APPROACH: Initial studies in animals will be designed to determine the most practical methods of sampling hepatic venous blood. The hepatic venous blood will be compared to arterial blood levels of lactic acid (although we believe pyruvic acid determinations are of limited clinical value, they will be determined in all cases). Efforts will be made to cause the liver to undergo lactategenesis by controlled hemorrhage, pharmacologically induced hepatic artery and portal vein vasoconstriction, acidosis, alkalosis, or pharmacologically induced shock.

PROGRESS: In order to explore the compensating ability of the liver in controlled shock, anesthetized dogs were subjected to graded exsanguination. Catheters were placed in the hepatic vein, the portal vein, the pulmonary artery, and the aorta. Blood gases, lactic acid, and pyruvic acid were determined. During the control period the hepatic vein lactic acid was always lower than both the arterial and portal vein levels. With the onset of shock, hepatic vein lactic acid exceeded all other sampling ports, indicating that the liver not only was no longer clearing the acid from the aorta and portal vein blood, but was now contributing lactic acid to the body burden. With retransfusion, the hepatic vein lactic acid fell more rapidly than the aorta and portal vein, indicating that the liver was again functioning to clear lactic acid. In animals with irreversible shock, the lactic acid transiently responded to retransfusion, but the hepatic vein level continued to exceed aortic and portal vein levels. Pyruvic acid increased in hepatic vein, aorta, and portal vein more slowly than lactic acid, reaching a constant concentration of about 0.25 mEq/L despite continued shock, while lactic acid levels continued to increase for the duration of shock. Irreversible hemorrhagic shock had lactate concentrations of over 8 mEq/L. Acidosis of below 7.0 and oxygen tension below 20 mmHg were seen in severely shocked dogs in the hepatic vein. It is suggested that there is a critical pH below which spontaneous recovery of liver clearing lactic acid may not be possible and the acidosis is progressive.

Presented at the Annual Meeting of the American Society for Pharmacology and Experimental Therapeutics, Portland, Oregon, August 1979.

Manuscript submitted to Proceeding of the Society for Experimental Biology and Medicine.

TITLE: Glucose Modulation of Insulin Binding

PROJECT NO.: 2/79 - Ongoing

INVESTIGATORS: MAJ Shiao W. Shen, MC, Dept of Medicine
John R. Claybaugh, Ph.D., Clin Invest Svc
CPT John C. O'Brien, MSC, Clin Invest Svc

FUNDING: FY 79 - \$1,000.; FY 80 - \$4,000.

OBJECTIVES: To investigate the effect of glucose concentration on insulin binding; to investigate the effect of glucose preincubation on insulin binding; and to study glucose transport under varying insulin and glucose concentrations.

TECHNICAL APPROACH: Epididymal fat pads are removed from male Sprague-Dawley rats. Isolated fat cells are prepared by shaking at 37° C for 60 minutes in Krebs-Ringer bicarbonate buffer containing collagenase (3 mg/ml) and albumin (40 mg/ml) by the method of Rodbell. Isolated fat cells are then suspended in a buffer containing 35 mM Tris, 120 mM NaCl, 1.2 mM Mg SO₄, 2.5 mM KCl, 1% bovine serum albumin, pH 7.6, and varying concentrations of glucose in a Dubnoff metabolic shaker at 37° C for 45 minutes. At the end of incubation, cells are washed and ready to be used for either ¹²⁵I insulin binding or glucose transport studies. ¹²⁵I insulin binding is carried out with ¹²⁵I insulin prepared at a specific activity of 100-150 µCi/µg according to the Freycht et al. modification of the method of Hunter and Greenwood. Glucose transport studies are carried out by incubating cells with 2-deoxy-II-¹⁴C-D-glucose (specific activity 2 mCi/mM) in Krebs-Ringer bicarbonate, pH 7.4, containing bovine serum albumin (10 mg/ml) at 24° C. This assay measures the total uptake of the radio-labeled 2-deoxy-glucose and is based on the principle that while 2-deoxy-glucose is transported and phosphorylated by the same process as D-glucose, it cannot be further metabolized. Calculation of glucose transport is based on the method of Olefsky.

PROGRESS: Progress has been limited due to supply problems. Silicon oil has not been available until recently. M.A.S.H. II (Multiple Automated Sample Harvester) will be purchased during FY 80.

TITLE: Free and Total Insulin Levels in Insulin-Treated Diabetics

PROJECT NO.: 3/79 - Ongoing

INVESTIGATORS: MAJ Shiao W. Shen, MC, Dept of Medicine

FUNDING: FY 79 - \$500.; FY 80 - \$1,000.

OBJECTIVES: To measure free and total insulin levels in insulin-treated diabetics, to characterize the insulin-binding antibodies in these patients, and to correlate the free insulin levels and the characteristics of the insulin-binding antibodies to control of diabetes.

TECHNICAL APPROACH: Patients will be classified with regard to their diabetic control on the basis of personal knowledge, examination of the clinic notes, and 24-hr urine glucose. Heparinized blood, 10 ml, will be drawn from subjects after an overnight fast and again at 4 pm for plasma glucose, insulin determinations, and characterization of insulin antibodies. Free insulin and total insulin will be extracted by a modified method of Nakagawa et al. Radioimmunoassay for free insulin and total insulin will be done by dextran-coated charcoal method. Deinsulinization is accomplished by combining one part plasma with 1.25 (V/V) 0.12N HCL and 0.5 parts dextran-coated charcoal suspension. The mixture is Vortex-mixed before adding 1.25 parts 0.12 N NaOH and centrifuging twice at 2500 rpm for 30 minutes at 4°C to completely remove the charcoal particles with the adsorbed insulin. The supernatant is also used for binding assay to characterize the insulin antibodies.

PROGRESS: Free and total insulin levels have been measured in six diabetics and ten normals. Tentative conclusions are that there is no relationship between insulin dosage and free insulin levels in patients; insulin binding to monocytes in each patient is not correlated with bound insulin or insulin dosage, but is inversely correlated to the free insulin level; and the maximal binding site of insulin antibody is inversely proportional to the ratio of free insulin to bound insulin.

TITLE: Beta Blocker Heart Attack Trial

PROJECT NO.: 19/79 - Ongoing

INVESTIGATOR: LTC Harry M. Thomas, Jr., MC, Dept of Medicine

FUNDING: FY 79 - none; FY 80 - none

OBJECTIVES: To determine the efficacy of propranolol in decreasing the incidence of sudden death and/or recurrent myocardial infarction.

TECHNICAL APPROACH: The test subjects will be patients who have recently had an acute myocardial infarction. After screening to see that they meet the admission criteria of the study, a careful history and physical examination will be performed and arrhythmia monitoring will be done.

PROGRESS: Awaiting OTSG approval.

TITLE: Evaluation of Amiodarone for the Therapy of Cardiac Arrhythmias

PROJECT NO.: 33/79 - Ongoing

INVESTIGATOR: LTC Harry M. Thomas, Jr., MC, Dept of Medicine

FUNDING: FY 79 - none; FY 80 - \$1200.

OBJECTIVES: To control symptomatic cardiac arrhythmias which have not been responsive to the conventional and accepted forms of treatment or whose control is dependent on the use of a drug which has been shown to be harmful to or in other ways not tolerated by the individual.

TECHNICAL APPROACH: Patients with recurrent supraventricular and/or ventricular arrhythmias, requiring therapy because of symptoms and/or signs due to the arrhythmia or because of potential harmful effects from the arrhythmia, but in whom the arrhythmia is either not responsive to conventional drug therapy or who have had reactions to the usually utilized drugs, will be considered for the study. Each patient will be evaluated initially with a complete history and physical examination, routine ECG, exercise ECG, chest x-ray, CBC, urinalysis, TSH, T-3, T-4, SMA-13, VDRL, and prothrombin time. Prior to initiation of therapy, 48 hours of continuous ambulatory ECG tape monitoring will be undertaken to provide a baseline of the arrhythmias. Ophthalmologic evaluation will be obtained. Amiodarone will be given once a day, 1-4 capsules daily, depending on the individual patient. In addition, patients will be given eye drops to lubricate the cornea and sclera to decrease the occurrence of microdeposits. Patients will be monitored throughout the study with frequent 24-hr ECG, standard ECG, blood tests, urinalysis, ophthalmology examination and physical examination. The study will be conducted over a 6-month period.

PROGRESS: Awaiting OTSG approval.

TITLE: Combination Chemotherapy with BCG Immunotherapy in High-Risk Melanoma Patients

PROJECT NO.: 28/78 - Terminated

INVESTIGATORS: MAJ William C. Waterfield, MC, Dept of Medicine
CPT Nadine Maslowski, ANC, Dept of Nursing
CPT Patricia Nishimoto, ANC, Dept of Nursing

FUNDING: FY 79 - none; FY 80 - none

OBJECTIVES: To determine if improvement in survival can be obtained by the use of combination chemotherapy and BCG immunotherapy in patients with stage II or stage III malignant melanoma.

TECHNICAL APPROACH: BCG by the scarification technique will be given on one of four extremities near lymph node bearing areas weekly for three weeks during the first two months of therapy, and then monthly for a total of one year of treatment. Combination chemotherapy with 1,3--BIS--(2--chloroethyl)--1--nitrosourea (BCNU), hydroxyurea, and dimethyl triazeno imidazole carboxamide (DTIC) will be given monthly for a total of 12 months. Evaluation of the patient with history, physical examination, and appropriate laboratory studies will be done on a monthly basis. Survival will be compared to the survival of patients treated with conventional therapy, i.e., historical controls from the literature.

PROGRESS: Terminated due to departure of principal investigator.

TITLE: Naloxone Prior to Chemotherapy to Prevent Nausea and Emesis

PROJECT NO.: 4/79 - Terminated

INVESTIGATORS: MAJ William C. Waterfield, MC, Dept of Medicine
CPT Carl Suchar, MC, Clinical Support Div
Mary McMillan, Pharmacy Svc

FUNDING: FY 79 - none; FY 80 - none

OBJECTIVES: To determine if a decrease in nausea and emesis secondary to chemotherapy can be obtained by prior injection of Naloxone.

TECHNICAL APPROACH: Patients in trial are to be on one or more of the following drugs: Adriamycin, DTIC (Dacarbazine) or Cis-platinum. Patients who report nausea secondary to other chemotherapeutic agents will be eligible. Patients taking large doses of narcotics will be ineligible. Patients are to receive either 1 cc of 0.4 mg Narcan (A) or 1 cc of sterile saline (B) 30 minutes prior to chemotherapy. Every patient will receive a total of two doses of A and two doses of B over four separate cycles. A and B will be randomized by the Pharmacy without physician or patient knowledge. Patients are to treat any nausea or emesis with Prochlorperazine, either 5 mg tablets every 3 hours or one 25 mg suppository every 3 hours. Evaluation of effects will be done by recording absence or presence of nausea, number of episodes of emesis and quantity of Compazine required.

PROGRESS: Project was not approved by OTSG.

TITLE: The Genetic Origin of Hydatidiform Moles

PROJECT NO.: 16/78 - Terminated

INVESTIGATORS: LTC John A. DeMersseman, MC, Dept of OB-GYN
Terry J. Hassold, Ph.D., Univ of Hawaii
Patricia A. Jacobs, D.Sc., Univ of Hawaii

FUNDING: FY 79 - None; FY 80 - None

OBJECTIVES: To determine whether genetic material of molar pregnancies is derived from maternal or paternal sources.

TECHNICAL APPROACH: Chromosomes of hydatidiform moles will be compared with those of its parents to determine which chromosomes are paternal in origin and which, if any, are maternally derived. A small tissue sample from the mole will be obtained for chromosomal analysis at the time of D and C which is the required treatment for termination of molar pregnancies. Additionally, because hydatidiform moles and hydatidiform degenerations are apparently two distinct entities, a complete pathology work-up on each sample will be performed. Routine cytogenetic tests on blood samples from the parents will be performed.

PROGRESS: Project terminated due to the departure of the principal investigator.

TITLE: Postpartum and Postgynecological Surgery Enzyme (Serum) Changes

PROJECT NO.: 1/78 - Terminated

INVESTIGATORS: CPT Daniel R. Eisemann, MC, Dept of OB-GYN
LTC C. Willis Sherrer, MC, Dept of OB-GYN

FUNDING: FY 79 - none; FY 80 - none

OBJECTIVES: The goals of this project will be to determine and quantify the serum enzymatic changes seen in various gynecological procedures postoperatively as well as in the puerperium.

TECHNICAL APPROACH: The patients will be divided into the following groups: (1) uncomplicated pregnant patients, EKG also obtained at 34 weeks; (2) repeat C-sections, which would be further subdivided into procedures with tubal ligation procedures and those without tubal ligation; (3) total abdominal hysterectomy and bilateral salpingo-oophorectomy; (4) total abdominal hysterectomy without bilateral salpingo-oophorectomy; (5) total vaginal hysterectomy; (6) diagnostic laparoscopy without associated surgical procedures. Serum enzyme levels including CPK, LDH, SGOT, AND SGPT will be drawn prior to the delivery or surgical procedure (in the pregnant patients with the 34th week, and in the surgical patients at the preoperative clinic visit). The enzyme levels will be repeated on the day of the procedure or delivery and daily for the next three days, with a final level obtained at the sixth week return clinic visit. EKG's will be performed pre- and postoperatively.

PROGRESS: Project terminated due to departure of principal investigator.

TITLE: A Comparison Evaluation of Terbutaline and Magnesium Sulfate as Tocolytic Agents

PROJECT NO.: 10/79 - Terminated

INVESTIGATORS: MAJ Steven H. Golde, MC, Dept of OB-GYN
MAJ Kenneth W. Meade, MC, Dept of OB-GYN

FUNDING: FY 79 - none; FY 80 - none

OBJECTIVES: To study the efficacy and comparative safety of these agents when used for tocolysis.

TECHNICAL APPROACH: Labor: Uterine activity strip charts, cervical examinations at the time of admission and at the time of termination will be reviewed. Treatment failures will be classified into two categories. True method failures will consist of labors that were not stopped by the administered drug. Patients will be matched for number of fetuses, duration of pregnancy (menstrual dates), parity, and degree of cervical dilation at the time of admission to the study. Side-effect failures will constitute the other group. All side effects requiring the discontinuance of the study agent will constitute such failures. These patients will also be matched for parity, duration of pregnancy, presence of multiple gestation, and maternal age.

Neonate: All offspring will be assessed for APGAR scoring by the pediatrician in attendance at th delivery. A sample of cord blood for initial cord gases and pH will be obtained by the obstetrician. Additionally, a separate sample of cord blood will be obtained in those babies born to mothers receiving magnesium sulfate. This will be analyzed for serum magnesium, calcium, and albumin. The infants will be monitored in the newborn nursery and their neonatal course annotated. A Dubowitz examination will be performed on each infant to substantiate gestational dating. A separate venous sample will be obtained from the mother at the time of delivery for magnesium, calcium, and albumin determinations.

Side effects: A record of each drug's adverse reactions will be maintained and compared for each matched group of patients. Only side effects requiring termination of the study protocol will be considered.

PROGRESS: Project was not approved by OTSG.

TITLE: The Reduction of Neonatal Morbidity by Long-term, Low-Dose Insulin Infusions: A Pilot Study

PROJECT NO.: 24/79 - Terminated

INVESTIGATORS: MAJ Steven H. Golde, MC, Dept of OB-GYN
CPT Lawrence Nance, MC, Dept of OB-GYN
LTC Philip G. Pettett, MC, Dept of Pediatrics
MAJ Shiao W. Shen, MC, Dept of Medicine

FUNDING: FY 79 - none; FY 80 - none

OBJECTIVES: This study is designed as a pilot study to assess the effect of long-term, low-dose infusions of insulin on neonatal outcome.

TECHNICAL APPROACH: Study population will consist of all insulin-dependent diabetics admitted to the hospital at their 34th gestational week. They will initially be given their current insulin dose by subcutaneous depot administration. Beginning the second hospital week, a continuous infusion of low-dose insulin will be started subcutaneously. All patients will be maintained on their diabetic diet calculated on present body weight. Activity will include standard OT given these patients under our current management regime. Except for brief walks they will remain largely at bedrest. Patients will be monitored with blood glucose determinations throughout the study. Infusion will be carried on through labor and delivery, but switched to the IV route to avoid contaminating abdominal wall should cesarean section be necessary. One researcher will be present at each delivery to assure adequate collection of specimens from cord blood and the neonate. Neonates will be followed for morbidity and mortality; all outcomes will be classified against the degree of control obtained by their mothers.

PROGRESS: The study is being terminated.

TITLE: Effect of Intrauterine Irrigation with Antibiotic Solution at Cesarean Section

PROJECT NO.: 18/79 - Ongoing

INVESTIGATORS: CPT William H. Long, MC, Dept of OB-GYN
MAJ Michael B. Dillon, MC, Dept of OB-GYN
CPT Eugene G. Rudd, MC, Dept of OB-GYN

FUNDING: FY 79 - \$500.; FY 80 - \$950.

OBJECTIVES: To determine if intrauterine irrigation with antibiotic solution will decrease the febrile morbidity and the sequelae associated with pelvic infections following cesarean section.

TECHNICAL APPROACH: All patients undergoing cesarean section at Tripler Army Medical Center without history of allergy to cephalosporins will be asked to participate in the study. Each patient will be randomly placed into one of three groups as follows: Group 1 - cesarean sections with no irrigation of the intrauterine cavity; Group 2 - cesarean section with intrauterine cavity irrigated with normal saline; Group 3 - cesarean sections with intrauterine cavity irrigated with cefamandole nafate solution (2 grams per 800 cc of normal saline). The two irrigation groups will be doubly blinded and evaluation of all charts will be done without knowing which group patients were assigned to and before breaking the code. Serum cefamandole levels will be obtained at one and two hours postoperatively. Data will be gathered as temperatures above 99° with individual temperature readings taken from each patient postoperatively every 4 hours. Daily CBC with differential will also be obtained. The total study group will include an initial 90 patients, 30 per group. Various statistical techniques will be used to treat the data obtained.

PROGRESS: Since final approval of this project was obtained in July 1979, it is only now on the verge of being underway. At the present rate of cesarean sections at Tripler, it is estimated that approximately three to four months will be necessary before the 90 patients will be obtained.

TITLE: Microsurgical Anastomosis of the Rabbit Oviduct

PROJECT NO.: 40/78 - Ongoing

INVESTIGATORS: LTC C. Willis Sherrer, MC, Dept of OB-GYN
MAJ Bradford S. Goodwin, VC, Clin Invest Svc

FUNDING: FY 79 - \$400.; FY 80 - \$500.

OBJECTIVES: To perfect skills and increase proficiency in microsurgical techniques.

TECHNICAL APPROACH: Rabbits will have bilateral ligation of the fallopian tubes with microsurgical reconstruction. The reconstruction will be either bilateral or unilateral.

PROGRESS: The project continues as a training protocol. MAJ David A. Kattenberger will be principal investigator as LTC Sherrer is no longer at TAMC.

TITLE: Development of Clinical Assays

PROJECT NO.: 21/77 - Ongoing

INVESTIGATORS: LTC Peter Angritt, MC, Dept of Pathology
MAJ William G. Kavanaugh, MC, Dept of Pathology
John R. Claybaugh, Ph.D., Clin Invest Svc
CPT John C. O'Brien, MSC, Clin Invest Svc
COL Samuel A. Cucinell, MC, Clin Invest Svc
COL James E. Hastings, MC, Dept of Medicine

FUNDING: FY 79 - \$400.; FY 80 - \$1000.

OBJECTIVES: This study is designed to (a) familiarize the clinical pathology resident with the field of new and developing assay kits; (b) give him an opportunity to evaluate the various assay kits for cost, effectiveness, and technique; and (c) determine which of the kits would be of greatest service to TAMC.

TECHNICAL APPROACH: All new laboratory tests which become available commercially will be evaluated by sending for information from the manufacturer. A number of kits will be purchased from various manufacturers. Clinical specimens will be obtained from patients with established diagnoses as well as from appropriate controls. Each kit will be compared for accuracy, sensitivity, ease of performance, cost, shelf life, etc. The investigator will estimate, based on current and future hospital requirements, which test (if any) is best.

PROGRESS: The diagnostic kit for the determination of antibody to Hepatitis A virus has just become available, and steps are being taken to order it in conjunction with kits for HBsAg and HBs antibody.

One hundred charts of patients with a recent diagnosis of hepatitis will also be reviewed and samples of their blood will be included in the present study.

TITLE: Amylase Excretion with Exercise

PROJECT NO.: 44/78 - Ongoing

INVESTIGATORS: MAJ William G. Kavanagh, MSC, Dept of Pathology
COL Samuel A. Cucinell, MC, Clin Invest Svc
CPT John C. O'Brien, MSC, Clin Invest Svc

FUNDING: FY 79 - \$200.; FY 80 - \$2000.

OBJECTIVES: To determine if under conditions of controlled exercise there is a relationship between the concentration of glucagon in the serum and the clearance of amylase.

TECHNICAL APPROACH: This experiment will make use of military volunteer marathon runners, male and female. Control (resting) levels of chemical and physiological measures will be obtained. The subjects will then run at least 20 miles. At intervals of five miles, specimens of blood and urine will be obtained, as well as physiological measures. A correlation of the plasma glucagon, which should increase continuously during the exercise, and amylase excretion will be made. No other change in the routine of marathon running will be made. Water, food, and additional stops will be made ad lib. A maximum of 12 subjects will be studied. It is best for logistical purposes, as well as competitive performance, to do the study at a practice marathon rather than the real competition, although studies at the conclusion of a true competitive marathon may yield maximal changes.

The following will be studied on the blood: lactate, pyruvate, CBC, amylase (the amylase will be fractionated for the S and the P types), vasopressin, glucagon, cortisol, electrolytes, creatinine, and BUN (a total of 25 ml of blood at each stop). Urine will be collected for: amylase, creatinine, volume, time, BUN, hemoglobin, and total protein. Physiological studies will include: weight, blood pressure, pulse, and oxygen uptake.

PROGRESS: Experiments to date with marathon runners have indicated a significant increase in the amylase-creatinine ratio after a four-day rest period which followed eight days of exercise. Subsequent exercise returns amylase-creatinine ratio to the previous exercise level. There appears to be an amylase excretion control mechanism which is altered by exercise which continues to function when exercise is withdrawn resulting in increased amylase-creatinine ratios at the end of the four-day rest period. A hormone such as glucagon may be involved in the mechanism. Glucagon levels remain to be analyzed. The type of the amylase (i.e., isoenzyme) is also to be analyzed. If glucagon levels correlate with the observed changes, we may have a hint as to how amylase secretion varies under stress. If we find no correlation with glucagon levels, this project will be terminated and a different approach to our interesting findings will be proposed.

TITLE: Role of Complement and Antibodies in Protection Against Neonatal Group B Streptococcal Infection

PROJECT NO.: 41/78 - Ongoing

INVESTIGATORS: MAJ Charles G. Jackson, MC, Dept of Pediatrics
CPT Carroll Ray Dotson, MSC Clin Invest Svc
LTC Philip G. Pettett, MC, Dept of Pediatrics
MAJ David K. Ohashi, MSC, Dept of Pathology

FUNDING: FY 79 - \$1500.; FY - \$500.

OBJECTIVES: To evaluate the integrity of the classical and alternative pathways of complement and the presence of type specific antibodies in mothers and neonates in relation to colonization and infection with group B beta hemolytic streptococci.

TECHNICAL APPROACH: Serum from maternal-infant pairs where the infant is infected and/or colonized with GBS will be obtained in two ways. The first is retrospective, i.e., recognized by finding an infected or colonized infant in the nursery. The second method is prospective starting with maternal GBS carriers recognized during pregnancy. Since the carrier rate for GBS is roughly 25% with sensitive bacteriologic techniques, and since the incidence of GBS infection in infants is only about 3 per 1,000 live births, the prospective approach will yield primarily colonized maternal-infant pairs with only a small chance of identifying infected infants in advance.

PROGRESS: Project is being completed and will be submitted for publication in FY 80.

TITLE: Utilizing Direct Contact Agar Plates (Rodac) as a Method of Assessing Colony Counts of Infants with Pathogenic Staphylococcus aureus

PROJECT NO.: 5/79 - Completed

INVESTIGATORS: MAJ Tommy Leonard, JR., MC, Dept of Pediatrics
COL Joseph Brown, III, MC, Dept of Pediatrics
LTC Philip G. Pettett, MC, Dept of Pediatrics

FUNDING: FY 79 - \$2750.; FY 80 - \$1000.

OBJECTIVES: To determine the epidemiologic characteristics of skin colonization of newborn infants and to evaluate quantitative skin colony counts as a predictor of pyoderma and/or impetigo.

TECHNICAL APPROACH: Utilizing Rodac plates, 200 consecutive newborns admitted to the routine newborn nursery were cultured by direct contact to the right groin area. Cultures were taken prior to commencing rooming-in and/or at 24 hours of age. The same infants were recultured at 72 hours of age or at the time of discharge, whichever came first. All infants were followed two weeks later as outpatients. The right groin of each infant was again cultured using the dry swab technique and plated on blood agar media. All positives were evaluated for coagulase activity and phage typing. Data were compiled for (1) colonization rate, (2) prevalence of specific phage types, and (3) relation of colony counts with subsequent pyoderma.

PROGRESS: All pertinent data from the patients has been gathered. This information is currently being analyzed and prepared for publication.

TITLE: Effects of Perinatal Alcohol Consumption on Various Adult Behaviors of Male Rats

PROJECT NO.: 5/78 - Completed

INVESTIGATORS: LTC Philip G. Pettett, MC, Dept of Pediatrics
Marcia Henderson, Univ of Hawaii
Milton Diamond, Ph.D., Univ of Hawaii

FUNDING: FY 79 - \$500.; FY 80 - \$1000.

OBJECTIVES: To assess the role of maternal ingestion of ethanol on the developing neural and behavioral systems of postnatal weanling rats.

TECHNICAL APPROACH: Fifteen adult female Wistar rats were bred and reared at the Tripler Army Medical Center Animal Facility. At parturition, the mothers and their pups were divided into three groups based on the maternal diet. Group I received a 20% of total calorie liquid ethanol diet; Group II received a 30% of total calorie liquid ethanol diet; and Group III received the same liquid diet but with sucrose as 30% of the total calories instead of ethanol. The pups received only breast milk until weaning, then conventional rat chow appropriate for age. Between 30-45 days of age, all offspring were tested for alterations in open field behavior. Between 50-60 days of age, male offspring in each group were subjected to testing of adult sexual behavior. After behavioral testing was complete, subjects were weighed, sacrificed, and autopsied. Blood serum was analyzed for plasma testosterone concentrations using a radioimmunoassay technique.

PROGRESS: Both groups of dams lost weight on the liquid diets; however, the ethanol-fed dams were lighter than their pair-fed controls throughout the lactation period. Litters of ethanol-fed dams gained weight less rapidly during lactation than litters of control-fed dams. Deficiencies in weight gain continued for the first 100 days of life, although the pattern differed from males to females. Alcohol-nursed females had reduced open field behavior at 60 days of life. Ethanol in the diet of nursing rat dams affects both dams and their offspring. There appears to be a sex difference in the ethanol effects on growth.

TITLE: Mechanism of Action of Tromethane (THAM) in Producing Respiratory Depression

PROJECT NO.: 9/78 - Terminated

INVESTIGATORS: LTC Philip G. Pettett, MC, Dept of Pediatrics
David Crowell, Ph.D., Univ of Hawaii

FUNDING: FY 79 - \$1,800.; FY 80 - none.

OBJECTIVES: To determine whether or not Tromethane (THAM) produces apnea through cholinergic dysfunction.

TECHNICAL APPROACH: Experiment I: To establish whether THAM induces respiratory dysfunction, namely, prolonged apnea. Following a basal recording period, THAM will be infused intravenously. Respiratory function will be monitored by the use of a pneumotachometer and sequential arterial blood gases. Time to apnea, time to recovery, and total apnea time will be recorded.

B₁(basal)_____I₁(THAM induction)_____B₂(basal/recovery)

Experiment II: To determine whether acetylcholine by itself will prevent or delay apnea presumed due to THAM. Respiratory function will be monitored as above.

B₁(basal)_____I₁(Physostigmine)_____I₂(THAM)_____B₂(recovery)

PROGRESS: Data collection has been completed and is being incorporated into work being done at the University of Hawaii. Data collected is not sufficient to warrant independent publication.

TITLE: Intubation and Chest Tube Placement in Small Laboratory Animals

PROJECT NO.: 12/79 - Ongoing

INVESTIGATORS: LTC Philip G. Pettett, MC, Dept of Pediatrics
MAJ Tommy Leonard, Jr., MC, Dept of Pediatrics
MAJ Leedell Reuben, MC, Dept of Pediatrics

FUNDING: FY 79 - \$500.; FY 80 - \$350.

OBJECTIVES: To provide a teaching model for medical trainees in the proper techniques of endotracheal intubation and chest tube insertion.

TECHNICAL APPROACH: Young kittens and rabbits housed at the Tripler Army Medical Center Animal Facility will serve as animal models. The anatomy of the thorax and airway closely approximates that of the premature human infant. Standard intubation and thoracotomy equipment will be set up on a weekly basis at a time prearranged with Clinical Investigation Service and the Newborn Medicine Service. One of the above-named investigators will accompany 1-2 junior house staff officers to the facility and provide instruction in proper technique. Each house staff officer will then use the animal models to refine his own abilities.

PROGRESS: House staff officers continue to rotate through the program with a current schedule set up through October, 1979.

TITLE: Assessment of Maternal Fever in the Immediate Prenatal Period as a Predictor of Perinatal Newborn Infections

PROJECT NO.: 30/79 - Ongoing

INVESTIGATORS: MAJ Leedell Reuben, MC, Dept of Pediatrics
LTC Philip G. Pettett, MC, Dept of Pediatrics
(Cooperative study with MAJ Howard Kilbride, MC, and
LTC Gerald B. Merenstein, MC, at FAMC, Denver)

FUNDING: FY 79 - none; FY 80 - \$1000.

OBJECTIVES: To determine the incidence of serious perinatal infections in infants born to febrile mothers.

TECHNICAL APPROACH: The study population will consist of all infants born at TAMC, FAMC, and MAMC to mothers who are febrile within 24 hours prior to delivery. A supplemental application for clinical investigation will be submitted at FAMC and MAMC. A mother will be considered febrile if she has a temperature of 38° C. on two readings at least four hours apart. A control population will be determined by matching each study infant with the next infant born to an afebrile mother and matched by weight, gestational age, Apgar scores, and duration of ruptured membrane (<12 hr, 12-24 hr, >24 hr). Each study and control mother will have a blood culture and placental culture. Each study and control infant will have a peripheral blood culture (minimum of 1 cc of blood obtained after Betadine scrub for two minutes), stool and umbilical cultures, CBC and platelet count, and C-reactive protein within six hours of birth. Each study infant will have a chest x-ray. A gastric aspirate for gram-stain and culture will be obtained in the delivery room or immediately on arrival to the nursery for each infant. The CBC and platelet count will be repeated at 24 hours of life. A lumbar puncture for cerebrospinal fluid evaluation will be done on those infants to be treated with antibiotics or as otherwise clinically indicated. Each infant will be treated with antibiotics according to the clinical situation at the discretion of the physician in charge of his care. If an infant is born to a mother who received antibiotics prior to the delivery and he is not started initially on antibiotics, a second blood culture will be obtained from that infant at 24 hours of life. Acute and convalescent viral titers will be obtained at birth and at 3-4 weeks, respectively, on all study and control infants. Viral cultures of nasopharynx, stool, and urine will be obtained from all infants at TAMC. The placentas of study and control infants will be examined grossly and histologically by a pathologist for evidence of chorioamnionitis, as is now routinely done by the Pathology Department at TAMC in all situations where this diagnosis is suspected. A data collection sheet will be used to collect all pertinent maternal and infant information and culture results. At the end of the study period, the data will be analyzed to determine the clinical course of infants born to febrile mothers and the incidence of

Assessment of Maternal Fever in the Immediate Prenatal Period as a Predictor of Perinatal Newborn Infections

bacterial and viral infection in those infants compared to control infants. This information will assist the obstetrician in management of the febrile prenatal patient and will clarify the significance of maternal fever relative to an infectious disease complication in the newborn infant.

PROGRESS: Awaiting OTSG approval.

TITLE: Percutaneous Lung Biopsy in Rabbits

PROJECT NO.: 10/78 - Terminated

INVESTIGATORS: MAJ James L. Wilson, MC, Dept of Pediatrics
LTC Philip G. Pettett, MC, Dept of Pediatrics
CPT Dean D. Ettinger, MC, Dept of Pediatrics
MAJ Bradford S. Goodwin, VC, Clin Invest Svc

FUNDING: FY 79 - \$500.; FY 80 - none.

OBJECTIVES: To determine the feasibility and safety of obtaining lung tissue by percutaneous needle biopsy.

TECHNICAL APPROACH: Rabbits, 2-3 kg, will be anesthetized with ketamine and sterilely prepared. A variety of biopsy needles will be used under direct fluoroscopic control to determine the feasibility of safely obtaining a sample of lung tissue large enough for cytologic examination and culture. The incidence of complications (pneumothorax, bleeding) will be recorded. Some animals will be sacrificed immediately after the biopsy to examine the immediate effect on the lung. Others will be sacrificed after complete healing, examining the long-term effect of percutaneous biopsy.

PROGRESS: On inspection of the data collected and because the technique is not applicable to newborns, the project is being terminated.

TITLE: A Prospective Analysis of Physiologic Factors Involved in Neonatal Hyperviscosity Syndrome

PROJECT NO.: 14/78 - Completed

INVESTIGATORS: CPT Thomas E. Wiswell, MC, Dept of Pediatrics
LTC Philip G. Pettett, MC, Dept of Pediatrics

FUNDING: FY 79 - \$700.; FY 80 - \$900.

OBJECTIVES: To determine the potential etiologic factors and the pathogenesis of polycythemia in newborn infants.

TECHNICAL APPROACH: Twenty-five neonates with polycythemia (central venous hematocrit in excess of 65%) had partial exchange transfusions done based on calculations to lower the above hematocrit to the 50-55% range. The initial blood withdrawn during the partial exchange transfusion was sent to the laboratory for the following tests: serum erythropoietin, total protein, fibrinogen, reticulocyte count, and RBC morphology and indices. Twenty-five neonates of similar sex, gestation, and age who were having blood drawn for reasons unrelated to polycythemia also had the above studies done and served as a control population. A retrospective chart review of normal and polycythemic infants was also done to supply additional data on total protein, reticulocyte count, and RBC morphology and indices.

PROGRESS: Both the prospective and retrospective portions are completed. The highest incidence of polycythemia occurs in growth retarded infants. No evidence of hypoxic bone marrow stimulation could be found. Serum erythropoietin, reticulocyte count, NRBC count, and Apgar scores were similar in subjects and controls. By far, the majority of polycythemic infants were asymptomatic pointing up the inefficiency of clinical screening. No elevation of fibrinogen or serum proteins was found. Methods for detecting polycythemia must, at present, rely on hematocrit evaluation to define at-risk infants.

TITLE: Childhood Psychosis and Trifluoperazine Therapy: Placebo Comparison (Double-Blind Study)

PROJECT NO.: 16/79 - Ongoing

INVESTIGATORS: COL Nicholas L. Rock, MC, Dept of Psychiatry
LTC Robert D. Shearer, MC, Dept of Psychiatry
SSG Paul Skogberg, Dept of Psychiatry

FUNDING: FY 79 - \$330.; FY 80 - \$950.

OBJECTIVES: To compare in a double-blind manner the therapeutic effects of trifluoperazine (Stelazine) in the treatment of childhood psychosis (infantile autism, childhood schizophrenia, atypical development).

TECHNICAL APPROACH: Children stabilized on a maintenance dose of trifluoperazine will be entered into the study which will consist of the random distribution of coded medication by the TAMC pharmacy. At least half the children at one time should be on placebo and the other half on the regular medication. Each week the rating scale will be completed by parents, special program, and TAMC staff to evaluate the level of psychotic behavior. After one month, the procedure will be reversed, in that those on placebo will be given drugs and those who have been on regular drugs will receive placebo. This procedure will proceed for the third and fourth months so that each group will have received an alternating placebo dose and therapeutic dose over the four months. After the fourth month, the code will be broken.

PROGRESS: Approximately two-thirds of the group has completed the first phase of the study, i.e., placebo/drug regime. The remainder of the group is expected to complete this phase within the next month. Analysis of data (i.e., breaking of code) is in progress. Results are too incomplete at this time to make any conclusions.

TITLE: Clinical Evaluation of Cisternography Utilizing Indium-111 DTPA

PROJECT NO: 14/76 - Ongoing

INVESTIGATORS: MAJ Anna K. Chacko, MC, Department of Radiology

FUNDING: FY 78 - none; FY 79 - none.

OBJECTIVES: Since there is currently a moratorium on the use of RISA in cisternography, it is our purpose to substitute Indium-111 DTPA for RISA in this procedure. Indium-111 DTPA (Diethylene Triamine Penta Acetic Acid) is presently in the third phase of investigation under the FDA. The agent will be used for the following: (1) detection of communicating hydrocephalus; (2) detection of noncommunicating hydrocephalus; (3) aid in determining whether a cerebrospinal fluid shunt would be required; (4) detection of rhinorrhea; and (5) study of cerebrospinal fluid dynamics.

TECHNICAL APPROACH: Radionuclide cisternography will be performed utilizing Indium-111 DTPA in those patients with the above-described medical problems. Results obtained from these procedures will be compared with results obtained with earlier RISA cisternography and with results obtained by other laboratories. The results will be correlated with the results of clinical findings, by roentgenographic studies and autopsy or surgical material where available to determine the accuracy and limitations of this procedure in each of the categories of disease studied.

Approximately 0.5 mCi Indium-111 DTPA will be administered by intrathecal or intraventricular injection to patients referred to the Nuclear Medicine laboratory for scintigraphic evaluation of cerebrospinal fluid pathways. The patients will meet the following criteria: (1) non-pregnant and over the age of 18 years unless special indications for study exist; (2) all will have either known or suspected alterations of cerebrospinal fluid flow. No subject without manifest or suspected disease will be studied.

PROGRESS: Cisternography was performed on 13 patients during FY 79. The study has provided useful information in patient diagnosis.

TITLE: Clinical Evaluation of Fluorescent Scanning of the Thyroid with Americium-241

PROJECT NO.: 31/76 - Ongoing

INVESTIGATORS: MAJ Anna K. Chacko, MC, Department Radiology

FUNDING: FY 78 - none; FY 79 - none.

OBJECTIVES: To determine the value of fluorescent thyroid imaging as compared with other modalities of thyroid imaging in the diagnosis and treatment of a variety of thyroid abnormalities.

TECHNICAL APPROACH: Dual studies are intended to involve both conventional thyroid scanning and fluorescent technique scanning in patients studied in the Thyroid Clinic at TAMC.

PROGRESS: To date, fluorescent scans have been performed on 43 patients. The original protocol was approved for 50 patients. At present, the fluorescent scanner is inoperative due to a leak in the liquid nitrogen storage tank. This tank has been sent back to the manufacturer for repair. As soon as the tank is returned and the scanner put back in operation, the remaining seven patients' studies will be completed.

TITLE: The Diagnostic Value of the Barium Enema Examination in the Preoperative Evaluation of Inguinal Hernia

PROJECT NO.: 34/78 - Terminated

INVESTIGATORS: MAJ Richard L. DeJournett, MC, Dept of Radiology
MAJ Lennard A. Nadalo, MC, Dept of Radiology
CPT Roger L. Cronk, MC, Dept of Radiology
CPT Richard F. Nelson, MSC, Dept of Radiology

FUNDING: FY 79 - none; FY 80 - none.

OBJECTIVES: To assess the value or lack of value in the performance of routine barium enema in the preoperative evaluation of patients with inguinal hernia.

TECHNICAL APPROACH: To review all charts of patients treated for colon cancer at TAMC from 1973 through 1978 and currently, in order to screen for concurrent inguinal hernia. To review all charts and x-rays of patients treated for inguinal hernia repair since 1973 to evaluate for possible occult carcinoma or other obstruction of the colon. To establish a prospective study preparing an age-matched control group consisting of all other barium enema examinations performed on clinically asymptomatic patients. To establish the mean average gonadal dose which is incurred in the performance of the routine barium enema examination as performed in our clinic.

PROGRESS: Because of problems in obtaining films, this project is terminated.

TITLE: The Application of Ultrasonography to Evaluation of Extremity Masses

PROJECT NO.: 7/79 - Completed

INVESTIGATORS: MAJ Lennard A. Nadalo, MC, Dept of Radiology
CPT Hector Ramirez, MC, Dept of Radiology

FUNDING: FY 79 - none; FY 80 - \$1000.

OBJECTIVES: To demonstrate the utility and reliability of ultrasonographic examination of the extremities in the preoperative and follow-up management of extremity mass lesions.

TECHNICAL APPROACH: Teaching file cases from the Ultrasound Service, Tripler Army Medical Center, were reviewed and appropriate clinical summaries, pathological reports and operative notes obtained. The accuracy and reliability of diagnostic ultrasound as it is applied to extremity masses was determined by a radiographic-pathological correlation.

PROGRESS: Project has been completed and an exhibit is being prepared for presentation.

TITLE: Complications of Catheterization: A Radiographic Atlas and Scientific Exhibit

PROJECT NO.: 8/79 - Completed

INVESTIGATORS: MAJ Lennard A. Nadalo, MC, Dept of Radiology
CPT Michael McCabe, MC, Dept of Radiology
CPT S. Keith McMurdo, MC, Dept of Radiology

FUNDING: FY 79 - none; FY 80 - \$1000.

OBJECTIVES: To document, assess, and organize the radiographic appearance of malpositioned catheters within the vascular, CNS, and intra-peritoneal spaces. This will be an attempt to familiarize clinicians and radiologists concerning the normal as well as the abnormal position of such catheters, and to illustrate some of the potential complications which can occur with the use of catheters.

TECHNICAL APPROACH: All catheter malplacements as described within the Department of Radiology were collected, documented, and photographed. Certain specific complications were evaluated via chart review in an attempt to establish the frequency of such complications.

PROGRESS: Project has been completed and exhibit is being prepared for presentation.

TITLE: The Radiographic Differential Diagnosis of Lower Extremity Bowing

PROJECT NO.: 9/79 - Terminated

INVESTIGATORS: MAJ Lennard A. Nadalo, MC, Dept of Radiology
MAJ Richard L. DeJournett, MC, Dept of Radiology

FUNDING: FY 79 - none; FY 80 - none

OBJECTIVES: To formulate a method of organization concerning abnormal curvatures of the lower extremities which will allow for a differential diagnosis by radiographic means.

TECHNICAL APPROACH: The orthopedic section of our x-ray teaching file will be examined for examples of lower limb bowing. For this purpose the use of material from other institutions will also be considered. A manuscript in atlas format will be prepared for publication and an illustrated display for presentation.

PROGRESS: Terminated due to departure of the principal investigator.

TITLE: Creation of Peripheral Vascular Access Sites (A-V Fistulas) for Delivery of Cancer Chemotherapy

PROJECT NO.: 31/78 - Terminated

INVESTIGATORS: LTC Charles A. Andersen, MC, Dept of Surgery
MAJ William C. Waterfield, MC, Dept of Medicine

FUNDING: FY 79 - none; FY 80 - none

OBJECTIVES: (1) To determine whether or not the creation of peripheral vascular access sites will ease the administration of cancer chemotherapy. (2) To determine whether or not the acute and chronic complications of cancer chemotherapy are altered by administration through peripheral vascular access sites.

TECHNICAL APPROACH: Patients with a variety of malignancies, who will be treated with cancer therapeutic agents known to cause venous sclerosis, will be eligible for this study. They will be fully counseled as to the procedure, its possible risks and complications, and the rationale for its use by both investigators. Complications related to the fistula will be documented. Informed consent will be obtained from each patient.

PROGRESS: This project has been terminated.

TITLE: Regrowth of Small Intestinal Mucosal Surface Area

PROJECT NO.: 6/77 - Ongoing

INVESTIGATORS: LTC Peter J. Barcia, MC, Dept of Surgery
MAJ Bradford S. Goodwin, VC, Clin Invest Svc

FUNDING: FY 79 - \$300.; FY 80 -\$1000.

OBJECTIVES: To explore methods of increasing small intestinal mucosal absorptive area following massive resections, and to determine the technical feasibility and functional results of certain specific procedures.

TECHNICAL APPROACH: Laparotomy will be performed in dogs and a 30 cm onlay graft of jejunum devised by splitting the intestine along the antimesenteric border and sewing this to the serosa of the transverse colon; this segment is defunctionalized by means of a Roux-en-Y connection. As a second procedure, these animals undergo resection of all other small bowel with continuity reestablished through the graft.

PROGRESS: An initial series of dogs has provided us with the following data: (1) A new small intestinal mucosa will grow across the serosa of the colon under these circumstances; and (2) the graft is mechanically functional, i.e., food is propelled in a relatively normal fashion through the graft, and these animals do not develop small intestinal obstruction. All animals in this series succumbed after the second operation due to starvation. Another group of ten dogs has had the first-stage procedure and seven are available for a second stage. A new group of animals had neogut procedure April-May 1978 and were studied for in vitro tissue transport. These animals will be used for studies of the functional characteristics of small bowel.

This project won second prize in the Hawaii American College of Surgeons Annual Essay Contest, Honolulu, Hawaii, June 1977. Presented to the William Beaumont Gastrointestinal Symposium, El Paso, Texas, in March 1978.

TITLE: Saluting with a Supracondylar Fracture

PROJECT NO.: 2/78 - Ongoing

INVESTIGATORS: CPT B. Hudson Berrey, Dept of Surgery
CPT Bruce W. Wulfsberg, MC, Dept of Surgery
COL Bruce F. LaFollette, MC, Dept of Surgery

FUNDING: FY 79 - \$850.; FY 80 - \$500.

OBJECTIVES: To assess the efficacy of positioning the forearm to control rotation of the distal fragment in a supracondylar fracture.

TECHNICAL APPROACH: Patients who sustain a supracondylar fracture of the humerus are carefully examined for rotary malalignment of the fracture clinically and radiographically. If reduction and skeletal traction are chosen as the method of treatment, management of rotation is attended to by positioning of forearm. The results of treatment regarding deformity of the elbow are assessed by clinical and radiographic examination.

PROGRESS: Ten patients have been treated in this fashion who were noted to have abnormal rotation prior to reduction and had reduction and maintenance of reduction by this method. This is an ongoing project and will be continued until a significant number of patients have been evaluated.

Presented at the Society of Military Orthopedic Surgeons Meeting in November 1977.

Submitted and accepted as a scientific exhibit at the meeting of the American Association of Orthopedic Surgeons to be held in February 1979.

TITLE: Knee Hinged Cylinder Cast - Sprained Knee Study

PROJECT NO.: 37/76 - Ongoing

INVESTIGATORS: CPT B. Hudson Berrey, MC, Dept of Surgery
LTC Dennis J. Sullivan, MC, Dept of Surgery

FUNDING: FY 79 - \$800.; FY 80 - \$500.

OBJECTIVES: To determine the feasibility of nonoperative early ambulation and physical therapy in a knee hinged cylinder cast as treatment for acute severe sprains of the knee.

TECHNICAL APPROACH: Patients with clinical history and physical examination compatible with sprained medial or lateral collateral ligaments of the knee will be evaluated radiographically by means of quantitatively reproducible stress x-ray to demonstrate gapping open or instability of the affected side of the joint. If the patient, by means of the physical examination and x-ray picture, is deemed to be grossly unstable and may be treated operatively, he will be offered the choice between treatment in a cast brace with early ambulation and protected rehabilitation versus surgery. Those treated nonoperatively will then be started on a painless, permissive progressive protected rehabilitation to deter quadriceps atrophy and apply physiologic stresses to the knee. These patients will be followed at one-month intervals up to six months and then at one year. At six months they will be re-examined with stress x-ray and also at one year. Patients will be compared to the operated cases regarding changes in stability, range of motion, and thigh girth at the end of treatment and at six months, and function in regard to return to former activity.

PROGRESS: Thirteen patients were treated in this fashion with results that appear comparable to a previous study of operatively treated knees. There are several more patients whose end point of treatment has not yet been reached.

Presented at the Annual Meeting of the Western Orthopaedic Association, October 1977.

TITLE: The Value of Gallium Scans in Determining Prosthetic Aortic Graft Infections in Canines

PROJECT NO.: 39/78 - Ongoing

INVESTIGATORS: CPT John H. Brown, MC, Dept of Surgery
LTC Charles A. Andersen, MC, Dept of Surgery
MAJ Anna K. Chacko, MC Dept of Radiology
MAJ Bradford S. Goodwin, VC, Clin Invest Svc
CPT Carroll R. Dotson, MSC, Clin Invest Svc

FUNDING: FY 79 - \$2000.; FY 80 - \$2000.

OBJECTIVES: To find a safe, noninvasive tool in determining whether or not a graft is infected.

TECHNICAL APPROACH: To undertake a randomized, double-blind, prospective study in canines in which 50% of the aortic vascular prostheses will be infected. All dogs in the study will be generally followed with gallium scans to determine which grafts are infected. At completion, all grafts will be removed and cultured, then correlated with the above scans to determine effectiveness.

PROGRESS: The first group is currently underway. Aortic grafts are surgically placed in the dogs and are infected with Staphylococcus aureus. The dogs are being monitored monthly with gallium scans and twice weekly for bacterial status of blood.

TITLE: The Early Diagnosis of Pyogenic Arthritis with the NBT Test of Synovial Fluid

PROJECT NO.: 35/78 - Terminated

INVESTIGATORS: CPT Robert M. Campbell, Jr., MC, Dept of Surgery
CPT B. Hudson Berrey, Jr., MC, Dept of Surgery

FUNDING: FY 78 - none; FY 79 - \$1050.

OBJECTIVES: To establish the specificity and sensitivity of the NBT test for pyogenic arthritis when used on synovial fluid.

TECHNICAL APPROACH: Extra fluid obtained from joint fluid aspirations for routine studies will be examined by the NBT test. Two orthopedic housestaff will process the fluid and make the slides. To eliminate observer bias, the actual counting of NBT positive cells on these slides will be done by laboratory personnel during normal working hours. Results of the NBT test of the joint fluid of patients with pyogenic arthritis will be compared to a control group of patients with joint effusions due to other causes.

PROGRESS: This project is terminated because of the departure of the principal investigator.

TITLE: Subcutaneous Mastectomy

PROJECT NO: 11/76 - Ongoing

INVESTIGATOR: LTC Maxwell A. Cooper, MC, Dept of Surgery

FUNDING: FY 79 - none; FY 80 - none.

OBJECTIVES: To determine the efficacy and results of the procedure over a prolonged period of time for prevention of signs and symptoms of fibrocystic disease and/or mastodynia; additional objective, to decrease risk factor for breast cancer especially in high-risk patients.

TECHNICAL APPROACH: Maintain long-term contact with patients undergoing subcutaneous mastectomy and compare their quantity and quality of life with (a) female population at large, (b) females with benign breast diseases, and (c) females with breast malignancies. Determine risk factors from medical history and pathological specimens; compare results of conservative surgery versus radical surgery for benign, premalignant, and malignant diseases.

PROGRESS: Plan to add no new patients to the series and follow just the present group to 10 years postoperative.

Presented to American Academy of Gynecology and Obstetrics in October 1975, and to the Military Plastic Surgery Symposia in January 1976.

TITLE: Microvascular Training Protocol

PROJECT NO.: 25/78 - Ongoing

INVESTIGATOR: LTC Maxwell A. Cooper, MC, Dept of Surgery

FUNDING: FY 79 - \$1300; FY 80 - \$700.

OBJECTIVES: To develop and maintain microvascular suture technique among the Plastic Surgery Service staff, TAMC, and to familiarize general surgery and other specialty residents with the techniques of microvascular anastomosis.

TECHNICAL APPROACH: To divide and reanastomose the common femoral artery and vein of rats. One pair of vessels per week with delayed evaluation of patency is planned. Later expansion to other models such as the rabbit ear and dog intestine and vas deferens is possible.

PROGRESS: Arrival of a second plastic surgeon in August 1979 should permit utilization of the protocol as the plastic surgery workload per physician should decrease.

TITLE: Human Implantation of Intraocular Lenses

PROJECT NO.: 17/78 - Ongoing

INVESTIGATORS: LTC Geoffrey Davis, MC, Dept of Surgery
LTC Anthony P. Martyak, MC, Dept of Surgery
COL John J. Kearney, MC, Dept of Surgery
MAJ Fernando G. Salazar, MC, Dept of Surgery

FUNDING: FY 79 - none; FY 80 - none

OBJECTIVES: The adjunctive study of the effects of implantation of intraocular lenses in humans and establishment of a satisfactory technique.

TECHNICAL APPROACH: Standard intracapsular and extracapsular techniques will be utilized, followed by insertion of Choyce style anterior chamber lenses. Additional types of intraocular lenses may be included in this study as time progresses.

PROGRESS: There has been significant progress and experience in the use of intraocular lenses. To date more than 35 lenses have been implanted. There have been excellent results in all of these cases. Two patients required additional surgery because of malposition of the foot plate; however, both of these patients have had satisfactory results following the second surgical intervention. Four lenses were rejected for imperfections including warped foot plates and scratches on the optic portions. It has been noted that there has been a significant post-operative astigmatism associated with lens insertion. The astigmatism, however, has been reversed by releasing tension in the corneal scleral sutures 8-10 weeks postoperatively. There have been no cases of endophthalmitis, and no lenses have had to be removed since the beginning of this study. The conclusion as reached thus far in this study is that Choyce style of intraocular lens manufactured by Precision-Cosmet Lens Company appears to be satisfactory without any significant intraocular complications.

TITLE: Ocular Manifestations of Decompression Sickness

PROJECT NO.: Terminated

INVESTIGATORS: LTC Geoffrey V. Davis, MC, Dept of Surgery

FUNDING: FY 79 - \$3000.; FY 80 - none

OBJECTIVES: (1) The evaluation of the incidence, extent, and significance of ocular problems encountered during decompression sickness.
(2) Evaluation of occult ocular problems encountered in divers.

TECHNICAL APPROACH: Any individual with decompression sickness will be given an ocular examination. This examination will include visual acuity, external examination, ocular pressure, ocular motility, and slit lamp examination. All symptomatic patients admitted to TAMC will undergo fluorescein angiography. Efforts will be made to examine all patients who undergo treatment at the Naval Decompression Chamber, regardless of whether their symptoms warrant admission to a hospital. These patients will not have angiography performed. Efforts will be made to notify the civilian medical community of our proposed study and solicit cases from that sector. Recent evidence, not reported in print, has shown that asymptomatic divers have occult ocular changes. Control subjects who have undergone normal, nondecompression dives and who are asymptomatic will be examined. Fluorescein angiography will be performed on selected cases.

PROGRESS: There has been an inadequate input to our study from referring physicians who have had patients with the bends. Because of difficulty in coordinating the staff, facilities, investigators and experimental animals, and because the principal investigator will be leaving Tripler Army Medical Center in the near future, the study is being terminated.

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TITLE: Experimental Closure of the Rat or Dog Bladder With Surgical Auto-Suture, Stainless Steel Staples for Closing Bladder Defects

PROJECT NO.: 21/79 - Ongoing

INVESTIGATORS: MAJ Basil D. Fossum, MC, Dept of Surgery
MAJ Bradford S. Goodwin, VC, Clin Invest Svc
CPT Carroll Ray Dotson, MSC, Clin Invest Svc

FUNDING: FY 79 - \$300.; FY 80 - \$300.

OBJECTIVES: To determine feasibility and safety of using Auto-Suture stainless steel staples for closing bladder defects.

TECHNICAL APPROACH: An anesthetized dog or rat undergoes incision of the lower abdomen with exposure of the bladder. The dome of the bladder is excised and the remaining bladder closed with a row of surgical staples using a TA-55 or TA-30 model suture device. The bladder is opened in periods of 3, 6, and 12 months and examined for calculi or other anatomic or microscopic defects.

PROGRESS: The bladders of ten rats and four dogs have been opened and surgically closed using surgical nonabsorbable metal staples. On reexamination of the bladders of the rats, two were found to contain calculi of a composition of magnesium ammonium phosphate which is associated with infection and/or foreign body. To date, bladders of the dogs have not been reexamined.

TITLE: Incidence of Injury to Recurrent Laryngeal Nerves during Thyroidectomy

PROJECT NO.: 18/78 - Ongoing

INVESTIGATORS: CPT Jeffrey Panosian, MC, Dept of Surgery
COL John E. Major, MC, Dept of Surgery

FUNDING: FY 79 - \$1000.; FY 80 - \$1000.

OBJECTIVES: Documentation of the incidence of injury to recurrent laryngeal nerves by pre and postoperative indirect laryngoscopy of all patients undergoing thyroidectomy.

TECHNICAL APPROACH: Preoperative indirect laryngoscopy of all patients undergoing thyroidectomy at Tripler Army Medical Center with fiberoptic laryngoscope. Postoperative indirect laryngoscopy within three days of the operation with fiberoptic laryngoscope. Follow-up examination at 7 days to 6 weeks of all patients showing evidence of nerve injury whether subclinical or associated with voice disturbances. Report incidence of nerves showing evidence of injury.

PROGRESS: Awaiting arrival of equipment.

TITLE: Retropatellar Pain Syndrome

PROJECT NO.: 14/79 - Ongoing

INVESTIGATORS: LTC Kent A. Reinker, MC, Dept of Surgery
MAJ Anna Chacko, MC, Dept of Radiology
CPT Daniel R. Johnson, MC, Dept of Surgery

FUNDING: FY 79 - none; FY 80 - \$1000.

OBJECTIVES: To determine the true nature and etiology of retro-patellar pain in active duty personnel.

TECHNICAL APPROACH: Initial history will be taken to include (1) presence or absence of trauma to the kneecap; (2) presence of absence of dislocation of the kneecap, locking episodes, or effusion; (3) any recent changes in activity status; (4) presence or absence of pain on sitting or standing long periods; (5) exacerbation of symptoms with activities; (6) current activity level; and (7) duration of symptoms. Full physical examination will be accomplished to include the measurement of patellofemoral Q-angle, presence or absence of apprehension test, presence or absence of thigh atrophy, and presence or absence of subluxability of the patella. Bone scanning will be done using technetium-labeled calcium pyrophosphate. Abnormalities on x-ray or bone scan will be followed at periodic intervals. All patients with symptoms lasting three months or longer following conservative treatment will be scheduled for arthroscopic evaluation of the knee joint. Patients will be followed for six months following arthroscopy or surgical treatment if indicated.

PROGRESS: Preliminary data has been collected on 36 patients, six of whom have satisfied all criteria as originally stated in the protocol. All 36 patients have had radionucleid scanning of the patella and clinical examination. Arrival of the Stryker small caliber arthroscope in July of 1979 will allow arthroscopic evaluation of the remaining patients on an outpatient basis.

An abstract of initial findings was submitted to the Society of Military Orthopedic Surgeons and has been accepted for presentation.

TITLE: Ambulatory Treatment of Ipsilateral Femoral and Tibial Fractures; Retrospective, Introspective, and Prospective Study

PROJECT NO.: 24/78 - Terminated.

INVESTIGATORS: MAJ Michael M. Roash, MC, Dept of Surgery
CPT B. Hudson Berney, MC, Dept of Surgery

FUNDING: FY 79 - none; FY 80 - none.

OBJECTIVES: To (1) review the Tripler experience with treatment of the ipsilateral femoral and tibial fracture and the efficacy of our treatment; (2) determine if principles of fracture management of either of these bones as isolated injuries has been modified or compromised as a result of the multiple injuries, and whether these principles may be better applied by modifying our mode of treatment; and (3) determine if the modified method of treating this fracture combination improves the end result or hastens time to healing.

TECHNICAL APPROACH: A retrospective study of charts and x-rays of patients with ipsilateral tibial-femoral fractures for the years 1972 to 1977 will be made to ascertain types and locations of fractures, methods of treatment, times to union, and anatomical and functional end results. A review of the literature will be made pointing out principles of fracture treatment and parameters that may be measured to ascertain functional stimulation of the casted limb.

A cadaver limb will be used in a knee-hinged cast brace to measure forces across fracture sites, pressures within compartments of the limb, and pressures between the cast and flesh with and without fractures of the tibia and femur; with and without a tibial pin incorporated in plaster; and with and without the sole of the foot encased in plaster.

The limbs of volunteers both normal and with acute fractures will be used to measure pressures in leg compartments and between cast and flesh in knee-hinged cast braces when weight bearing with and without tibial pins, with and without the sole of the foot encased in plaster.

Prospectively, patients will continue to be treated in an ambulatory fashion when indicated; however, the sole of the foot will not be encased in plaster, but allowed to contact the floor. The types and locations of the fractures will be noted, the time to union and anatomical and functional results recorded. These will be compared to the retrospective study.

PROGRESS: This project is terminated due to the departure of the principal investigator.

TITLE: T-cell Antigenicity of Canine Tunica Albuginea

PROJECT NO.: 36/78 - Ongoing

INVESTIGATORS: CPT Kenneth A. Rutledge, MC, Dept of Surgery
COL Edward M. Blight, Jr., MC, Dept of Surgery

FUNDING: FY 78 - \$1400.; FY 79 - \$1000.

OBJECTIVES: To determine by specific responses the T-cell antigenicity of canine tunica albuginea.

TECHNICAL APPROACH: The dog tunica albuginea will be surgically obtained along with skin specimens. The tunica albuginea will be cleaned. The tunica albuginea and skin will be sutured onto mice. The response to each sutured specimen will be judged as to their generated immune response. The sutured skin specimens will serve as controls. The amount of response to each specimen will be measured and compared to skin controls.

PROGRESS: Three dogs have been castrated with tunica specimens implanted in the rats along with comparison skin grafts. Grossly all reactions appeared to be quantitatively the same. Specimens were taken for microscopic analysis. These need to be reviewed.

TITLE: Tensile Strength of Tunica Albuginea

PROJECT NO.: 37/78 - Terminated

INVESTIGATORS: CPT Kenneth A. Rutledge, MC, Dept of Surgery
COL Edward M. Blight, Jr., MC, Dept of Surgery

FUNDING: FY 79 - \$1000.; FY 80 - none.

OBJECTIVES: To determine the tensile strength of tunica albuginea.

TECHNICAL APPROACH: Tunica albuginea will be surgically removed from mongrel dogs along with skin and fascia lata. A comparison of tunica albuginea, skin, and fascia lata tensile strength will be made. A determination of the amount of stretch per cross sectional area will also be made. From this, a conclusion and quantitation of the tensile strength of tunica albuginea will be made. Plethysmographic studies on the intact testis and internal pressure studies will be done.

PROGRESS: We have not been able to show that tunica albuginea has elasticity, making it difficult to quantitate the true tensile strength. We still do not have machinery to be able to adequately measure the true tensile strength. Grossly the tunica appears to be stronger than fascia lata. Because of the problems encountered and lack of time, the project is terminated.

TITLE: Management of Unilateral Pulmonary Insufficiency with a Double Lumen Endotracheal Tube

PROJECT NO.: 17/77 - Terminated

INVESTIGATORS: CPT Robert E. Schatz, MC, Dept of Surgery
LTC Peter J. Barcia, MC, Dept of Surgery
LTC Lee R. Joyner, MC, Dept of Medicine
MAJ Bradford S. Goodwin, VC, Clin Invest Svc
Mr. Gordon H. Bryant, Clin Invest Svc

FUNDING: FY 79 - none; FY 80 - none

OBJECTIVES: To create a unilateral pulmonary insufficiency model in dogs and pigs and evaluate the pulmonary mechanics and selective pulmonary flows of each lung independently under a variety of conditions. To compare the results of conventional intubation, ventilation, and positive end expiratory pressure (PEEP) with a double lumen endotracheal tube and independent ventilation and PEEP. Emphasis will be on oxygenation, shunt, and pulmonary flows in data acquisition.

TECHNICAL APPROACH: The animal will be anesthetized (but not paralyzed) and intubated by tracheostomy with the Carlens double lumen endotracheal tube. A thoracotomy will be performed and flow probes placed about the right and left pulmonary arteries while the animal is ventilated with an Ohio ventilator, specifically modified for this experiment. Cannulation of systemic and pulmonary arteries will be accomplished and on-line acquisition of pulmonary tidal volumes and pressures will be obtained. After baseline data acquisition, the right lung will be subjected to 0.1 normal hydrochloric acid to achieve a 50 percent shunt or greater while under conventional intubation and ventilation. Online data will then be obtained comparing this conventional system with a system that effectively treats each lung independently. Positive end expiratory pressure delivered by the conventional system is known to cause a deleterious increase of shunted blood through the injured lung, but when delivered by the double ventilation system to only the injured lung, a shunt of blood to the normal lung should occur. The animals will be sacrificed at the termination of each experiment and probes and lines recovered.

PROGRESS: The project has been terminated because of difficulties encountered in maintaining a viable preparation.

TITLE: Characteristic Impedances and Reflection Co-efficients of Graft-Artery Anastomoses

PROJECT NO.: 33/78 - Ongoing

INVESTIGATORS: COL Paul L. Shetler, MC, Dept of Surgery
CPT Robert E. Schatz, MC, Dept of Surgery

FUNDING: FY 79 - \$100; FY 80 - \$900.

OBJECTIVES: To measure reflection co-efficients at graft-artery anastomoses and determine the importance of characteristic impedances in causing these reflections.

TECHNICAL APPROACH: Following insertion of a graft in continuity into a divided artery, simultaneous measurements of pulsatile pressures at two points in the graft proximal to the distal anastomoses and in the artery just distal to the anastomoses are performed. Also, pulsatile flow is measured through the graft. Pressure measurements are repeated with the artery occluded distal to the anastomosis. The reflection co-efficient is derived from this data and compared to the theoretical reflection co-efficient derived from the characteristic impedances of the artery and graft.

PROGRESS: Three experiments have been completed and seven more will be performed during this next year to complete the project.

TITLE: Endocardial Oxygen Supply-Demand Ratio: The Reliability of Clinical Approximations in Prediction of Subendocardial Ischemia

PROJECT NO.: 11/79 - Ongoing

INVESTIGATORS: COL Paul L. Shetler, MC, Dept of Surgery
Gordon H. Bryant, Clin Invest Svc

FUNDING: FY 79 - none; FY 80 - \$2,500.

OBJECTIVES: To determine clinically useful hemodynamic factors reflecting acute subendocardial ischemia resulting from anemia-induced hypoxia.

TECHNICAL APPROACH: Experimental animals will be progressively exsanguinated while blood volume is replaced with dextran until a left ventricular endocardial electrode indicates ischemic changes. The endocardial viability ratio and modifications by oxygen delivery, arterial oxygen content, cardiac index, and left ventricular stroke work will be correlated with ratio of diastolic coronary blood flow and tension time index to assess the reliability of the hemodynamic factors in warning of impending subendocardial ischemia.

PROGRESS: Awaiting purchase of endocardial viability ratio monitor.

TITLE: Evaluation of the Immunologic Basis for Post-renal Transplant Hypertension

PROJECT NO.: 10/7T - Ongoing

INVESTIGATORS: LTC Douglas W. Soderdahl, MC, Dept of Surgery
LTC Edward N. Raleigh, MC, Dept of Pathology
MAJ Bradford S. Goodwin, VC, Clin Invest Svc
CPT Carroll Ray Dotson, MSC, Clin Invest Svc

FUNDING: FY 79 - \$1000.; FY 80 - \$1000.

OBJECTIVES: To study the renal arteries of dogs that have undergone transplantation and have developed hypertension that is not responsive to the usual therapy for immunologic rejection. Arteries will be studied via angiography and microscopy to determine what role the animal's immunologic response has played in the development of fixed hypertension.

TECHNICAL APPROACH: Dogs will undergo renal transplantation after unilateral nephrectomy. Immunosuppressive therapy will be given consisting of Imuran, 10 mg/kg for 2 days, 5 mg/kg for 4 days, and 2.5 mg/kg daily thereafter. Prednisone will be given in a dose of 30 mg daily. Drugs will be given orally. Blood pressure will be monitored on a daily basis and renal function, via BUN and creatinine, on an every-other-day basis. WBC will also be obtained to avoid excessive bone marrow suppression. Clinical or laboratory evidence of rejection will be treated by an increase of the steroid dose to 100 mg/day. Should hypertension develop, the first therapy will be as if rejection is occurring. Thus, prednisone will be increased to 100 mg/day. If renal function shows no further deterioration and hypertension persists, a transplant renal arteriogram will be performed to evaluate the presence of lesions of the major vessels. Should these be present, the graft will be removed, and the vasculature and parenchyma will be studied with routine microscopy, and immunofluorescent studies for the immunoglobulins, complement, fibrinogen, and albumin will be performed on the vessels. Similar studies will be performed in the dogs that die from other complications without hypertension or vigorously reject the graft without the development of hypertension, and from several dogs that appear to accept the graft normally.

PROGRESS: Transplants have been performed and removed from the dogs. Renal arteries are fixed and frozen. Appropriate stains are not available for immunofluorescent staining at this time. However, it is likely that the University of California Medical Center in Los Angeles will be able to supply us with the appropriate materials to complete this project.

TITLE: Stented Cutaneous Ureterostomy

PROJECT NO.: 15/79 - Terminated

INVESTIGATORS: LTC Michael Uechi, MC, Dept of Surgery
MAJ Basil Fossum, MC, USAF, Dept of Surgery
MAJ Bradford S. Goodwin, VC, Clin Invest Svc

FUNDING: FY 79 - none; FY 80 - none

OBJECTIVES: To see if utilizing ureteral stents will prevent ureterocutaneous stenosis.

TECHNICAL APPROACH: Eight to ten dogs will be utilized; one ureter will be stented, and one will be the control. An IVP will be done at three months and six months. The dogs will then be sacrificed, and ureters and kidneys will be examined for pathology. The IVP will provide sufficient data on the degree of obstruction of the control versus stented ureter. Pathologic evaluation will confirm the findings on IVP.

PROGRESS: Project has been terminated.

TITLE: Teflon Injection Indications

PROJECT NO.: 22/77 - Ongoing

INVESTIGATORS: LTC Thomas E. Van Sant, Jr., MC, Dept of Surgery
LTC Donald W. S. Yim, MC, Dept of Surgery

FUNDING: FY 79 - none; FY 80 - none

OBJECTIVES: To participate in expanded clinical trials of Ethicon Polytef Paste for Injection for the following clinical indications: the selected treatment of patients with velopharyngeal insufficiency and/or abnormally patent eustacian tubes.

TECHNICAL APPROACH: The protocol will follow the clinical study group proposals. Patients will originate in the ENT Clinic. Only patients who have not responded to conventional treatment modalities will be considered. The procedure with its possible risks will be explained to the patient, as well as its investigative nature. If the patient agrees to participate, the case history will be forwarded for consideration to the study group who will furnish the necessary material (Teflon). Patients will require hospitalization for approximately 1-3 days for the surgical procedure which will be done under appropriate anesthesia. Surgery time will be 30 minutes to one hour. The patients will continue to be followed on an outpatient basis for a minimum of 90 days as required by the protocol.

PROGRESS: No patients have yet been accepted for this protocol. It is anticipated that very few patients will be accepted under the strict criteria used for selection. It is doubtful that more than 3 or 4 patients will be accepted in a year's time.

TITLE: Strain Differences of Staphylococcus aureus based on lipid analysis

PROJECT NO.: 21/78 - Ongoing

FUNDING: FY 79 - \$1500.; FY 80 - \$1000.

INVESTIGATORS: LTC David K. Ohashi, MSC, HSC
CPT Carroll Ray Dotson, MSC, Clin Invest Svc

OBJECTIVE: To examine the feasibility of determining strain differences of Staphylococcus aureus by analysis of GLC (gas liquid chromatography) fatty acid profiles. If strain differences can be demonstrated, epidemiologic analysis can be simplified, and rapid laboratory analysis can be made without resorting to time-consuming phage typing.

TECHNICAL APPROACH: Strains of S. aureus will be collected and identified to species by the Microbiology Section, Department of Pathology, TAMC. Organisms will be prepared for gas chromatographic analysis using a modification of the method of Ohashi. Briefly, whole cells will be prepared for GLC analysis using tetramethylammonium hydroxide by a very simple procedure requiring less than two hours for the preparation of a dozen samples. The organisms will grow on several media formulations to determine which media will enhance lipid accumulation by the strains being examined. Gas chromatographic data will be subjected to pattern analysis and strain differences will be defined in terms of observed variations.

PROGRESS: A total of 15 strains of S. aureus were characterized using their lipid profiles. It was determined that a commonly used media, Mannitol Salt Agar, could be used to grow the strains used in the analysis. Digest of the basal media were prepared and chromatographed; no evidence was found that the medium contained a level of any component which was used in the analysis. The S. aureus digests yielded approximately 24 peaks which were used to characterize the strains. Most peaks were found in all chromatograms, but the absence of some components and differing levels of some components were used to characterize the strains. All data was normalized for comparative purposes. Using these approaches, three strains had unique and obviously different patterns. Over half the remaining strains possessed lipid profiles which were different from the rest; the remainder did not present sufficient differences to separate them from the rest.

In summary, the method used demonstrated this general method may have the potential to be used in the infrasubspecific identification of S. aureus. The ease of sample preparation, ability to use a commonly available media and the finding of a large number of parameters which may be used to characterize the strains suggest that refinements to the method may improve it. Several simple methodological changes are planned to improve the sensitivity.

TITLE: The Mechanism of Ovulation

PROJECT NO.: 23/79 - Ongoing

INVESTIGATORS: MAJ A. David Barnes, MC, US Army Health Clinic
Gordon H. Bryant, Clin Invest Svc
MAJ Bradford S. Goodwin, VC, Clin Invest Svc
Frederick Greenwood, Ph.D., Univ of Hawaii
Gillian D. Bryant-Greenwood, Ph.D., Univ of Hawaii

FUNDING: FY 79 - \$500.; FY 80 - \$5000.

OBJECTIVES: (1) To work with the University of Hawaii and Queen Elizabeth Hospital, Australia, to clarify the role of intrafollicular enzymes and ovarian hormones, particularly relaxin, in the mechanics of ovum release from the follicle. (2) To investigate the relationship between intrafollicular pressure and relaxin. (3) To assay total collagen in follicles of different sizes and relationship to intrafollicular pressure. (4) To determine the location of relaxin by fluorescein techniques. (5) To quantitate plasma relaxin levels in prepubital sows and the effect of HCG. (7) To confirm whether isolated ovarian follicles contract spontaneously.

TECHNICAL APPROACH: Ovulation will be induced by gonadotropins in prepubital pigs. Under general anesthesia, laparotomy will explore the supported ovary within the peritoneal cavity. Follicles will be pierced with 27-gauge needles, samples removed for determination by radioimmunoassay, and intrafollicular pressures recorded. In addition to steroid identification, we shall be looking for relaxin, relaxin receptors, collagen assay, and a correlation with pressure variance.

PROGRESS: This project will be assumed by MAJ David A. Kallenberger, MC, as Principal Investigator in FY 80.

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