CLINICAL INVESTIGATIONS

ANNUAL PROGRESS REPORT
30 JUNE 1972

CLINICAL RESEARCH SERVICE

MADIGAN GENERAL HOSPITAL
TACOMA, WASHINGTON 98431

RESEARCH AND TECHNOLOGY WORK UNIT SUMMARY

1. AGENCY ACCESSION*	2. DATE OF SUMMARY*	REPORT CONTROL SYMBOL
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3. DATE PREV SUM'RY	4. KIND OF SUMMARY	5. SUMMARY SCTY*	6. WORK SECURITY*	7. REGRADING*	8a. DISS'N INSTR'N	8b. SPECIFIC DATA-CONTRACTOR ACCESS	9. LEVEL OF SUM
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ADDRESS:* Tacoma, Washington 98431

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20. PERFORMING ORGANIZATION

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Madigan General Hospital
ADDRESS:* Tacoma, Washington 98431

PRINCIPAL INVESTIGATOR (Furnish SSAN if U.S. Academic Institution)
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TELEPHONE:
SOCIAL SECURITY ACCOUNT NUMBER:

ASSOCIATE INVESTIGATORS
NAME:
NAME:

21. GENERAL USE

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22. KEYWORDS (Precede EACH with Security Classification Code) Medicine; Preventive Medicine; General Medicine, Endocrine; Hematology; Pediatrics; Surgery; Radiology; OB GYN; Nursing, Psychology, Otolaryngology; Ophthalmology; Cardiology, Orthopedic, Endodontic

23. TECHNICAL OBJECTIVE,* 24. APPROACH, 25. PROGRESS (Furnish individual paragraphs identified by number. Precede text of each with Security Classification Code.)

(U) Technical Objectives. To provide the facilities and environment to stimulate an interest in clinical and basic investigations within Madigan General Hospital

(U) Approach: The Clinical Research Service has actively supported clinical investigators by providing the facilities and technical knowledge for the performance of clinical investigations Colonies of animals are provided as required, maintained according to the principles of the American Association for Accreditation of Laboratory Animal Care

(U) Progress. For the FY 72, 85 projects were ongoing At the end of the fiscal year 50 protocols were active with 16 completed and 9 terminated There were 24 publications and 6 presentations at National Meetings reporting work performed at Madigan General Hospital under the sponsorship of the Clinical Research Service

*Available on microfiche upon originator's approval

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13. ABSTRACT

A report of progress on clinical investigations at Clinical Research Service, Madigan General Hospital, Tacoma, Washington, for fiscal year 1972.

This research is devoted to providing facilities and environment to stimulate an interest in clinical and basic investigations within Madigan General Hospital.

DD FORM 1 NOV 65 1473 REPLACES DD FORM 1473, 1 JAN 64, WHICH IS OBSOLETE FOR ARMY USE.

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ANNUAL PROGRESS REPORT

30 JUNE 1972

CLINICAL RESEARCH SERVICE

MADIGAN GENERAL HOSPITAL

TACOMA, WASHINGTON 98431

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ANNUAL PROGRESS REPORT

30 JUNE 1972

Project Number 3A062110A825 00 Oral & Maxillofacial Sciences

Project Number 3A062110A826 00 Clinical Investigations

CLINICAL RESEARCH SERVICE
MADIGAN GENERAL HOSPITAL
TACOMA, WASHINGTON 98431

In conducting the research described in this report, the investigators adhered to the "Guide for Laboratory Animal Facilities and Care" as promulgated by the Committee on the Guide for Laboratory Animal Resources, National Academy of Sciences-National Research Council.

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.

Approved for public release: Distribution unlimited.

FOREWORD

This report identifies those individuals who are conducting research protocols at Madigan General Hospital, Tacoma, Washington. An abstract of each protocol giving abbreviated technical objectives, methods, and progress is presented. Each reader of this report is reminded that many of these abstracts are preliminary and are not to be construed as the final report or necessarily the end result which will be obtainable at the conclusion of the investigation.

The staff at Clinical Research Service would like to express their gratitude to those principal investigators who responded promptly with their abstracts. We would also like to express our appreciation to the many people who have given Clinical Research Service support in the past fiscal year, making it possible to conduct investigative procedures in many areas. In our opinion, the past fiscal year has been a very productive year with publications submitted and accepted by National medical journals and presentations at reputable meetings. I personally would like to express my gratitude to Mrs. Edith M. Hoyt for her assistance in compiling, typing, and proof reading this annual report.

Bruce L. Fariss

BRUCE L. FARISS, M.D.
LTC, MC
Chief, Clinical Research Service

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62110A 3A062110A826 00

TITLE: Caustic Effect of Sulfuric Acid on the Esophagus and Stomach of Cats.

WORK UNIT NO: 72/305

PRINCIPAL INVESTIGATOR: Ronald W. Brenz, MAJ, MC

TECHNICAL OBJECTIVES

To determine the immediate and short term delayed effects of various concentrations of sulfuric acid on the esophagus and stomach of kittens. This model was selected since the cat's esophagus responds most nearly to that of humans to the caustic effects of strong alkali and acids.

METHOD

Kittens from 6-10 weeks of age will be used throughout the study. One ml of sulfuric acid in concentrations of 50%, 10%, 5%, and 2% will be instilled in the esophagi of anesthetized kittens. A control group will be used. Thirty minutes after exposure, the first five animals will be sacrificed with anesthesia, and the esophagi and stomachs examined for evidence of corrosion, burn, and hyperemia. If hyperemia or corrosion is noted at the 2% concentration then a solution of 1% or less will be used. A second group of animals will be treated as the first and sacrificed. At six hours they will be examined. A third, fourth, and fifth group will be given concentrations of sulfuric acid as in the first group and survivors sacrificed at 24, 48, and 72 hours, and the esophagi, stomachs examined grossly and microscopically for evidence of injury. Color photographs and slides of the esophagi and stomachs in each group will be made to document injury patterns.

PROGRESS

(72 05 - 72 06) - The minimal concentration of sulfuric acid which induces mucosal implant injury is being determined.

STATUS: Ongoing.

62110A 3A062110A826 00

TITLE: The Effect of a Nursing Experimental Teaching Program on the Post-operative Pulmonary Function of Upper Abdominal Surgical Patients.

WORK UNIT NO: 72/397

PRINCIPAL INVESTIGATOR: Virginia K. Carrieri, R.N.

TECHNICAL OBJECTIVES

To investigate the differences in postoperative pulmonary function between upper abdominal surgical patients who had completed a preoperative teaching program with postoperative follow up and those patients who did not participate in this program.

METHOD

The sample consisted of 22 patients between the ages of 17 and 58 undergoing an elective upper abdominal surgical procedure. After a random start patients meeting the criteria for inclusion were alternately assigned to experimental and control groups. It was not possible to control for smoking history and IPPB treatments by selection, however, there were no significant differences in these variables or preoperative lung function measures between the two groups.

Experimental patients participated in a teaching program which included an exploratory period for patient concerns about their surgical experience, a discussion of the importance of the pulmonary system, and nurse modeling of deep breathing, coughing, and turning with patient demonstration and reinforcement. These patients met individually with the investigator for half hour sessions the day before surgery and three consecutive days post-operatively. In an attempt to control for the "Hawthorne Effect", the control group met with the investigator at these same times, however, discussion was limited to the topics unrelated to the pulmonary system.

Pulmonary function was measured by forced vital capacity (FVC), forced expiratory volume in one second expressed as a percentage of the forced vital capacity ($FEV_1\%$), maximal mid-expiratory flow rate (MMFR), pulmonary shunt (A-a P_{O2}), and partial pressures of arterial oxygen (Pa_{O2}) and carbon dioxide (Pa_{CO2}). Baseline values of the selected pulmonary function tests were measured preoperatively. Postoperatively, the spirometry was measured on three consecutive days, the pulmonary shunt only on the first day, and the remaining blood gas values on the second and third days.

Spirometry was performed in the sitting position. Arterial blood gas samples were drawn in the supine position using the usual techniques to prevent contamination by air. Samples for the determination of amount of right-to-left pulmonary shunt were drawn after the patient had breathed 100% oxygen for 15 minutes through a mouthpiece attached to a non-rebreathing Rudolph valve. The tests were conducted by the investigator unless a technician was available.

PROGRESS

(71 09 - 72 05) - Final analysis of the data and conclusions have not been completed at this time. Preliminary analysis has been started to determine where significance may lie. Since equal correlations or covariances cannot be assumed, the Wilcoxen Rank Sum test, a small sample non-parametric test having the efficiency of the t-test, has been used for preliminary analysis.

As found in previous studies in the literature, all patients had a reduction in forced vital capacity and arterial oxygen tension for three postoperative days with an increase in the percentage of right-to-left pulmonary shunt on the first postoperative day. Flow rates, arterial carbon dioxide and pH were not altered significantly.

Although the preliminary analysis shows some differences in the postoperative measurements between the two groups apparently due to the teaching program, none of these differences reach the .05 level of significance with a two-tailed test. The confounding variables of sex, age, smoking, and IPPB treatments between and within groups had no significant effect on post-operative ventilatory function in the preliminary analysis of the data.

STATUS: Ongoing.

62110A 3A062110A826 00

TITLE: Hormonal Modification of Protein Metabolism by Mouse Liver Lysosomes.

WORK UNIT NO: 71 '70

PRINCIPAL INVESTI' .TOR: Bruce S. Chertow, MAJ, MC

TECHNICAL OBJECTIVES

With slight modification of a model developed by Mego and McQueen, an investigation is to be made into the effect of cortisone acetate, glucagon, insulin, and thyroxine on lysosomal protein metabolism.

METHODS

Iodinated (^{125}I) human serum albumin (IHSA), 10 mg/ml in .45 % saline and bicarbonate buffer, pH 7-8.5, having a specific activity of 10.2 microcuries per mg will be obtained from Mallinchrodt Nuclear. The IHSA will be diluted 1:10 with and denatured in 4% formaldehyde, and then dialyzed in 0.1 M saline as described by Mego and McQueen.

Control and Hormone pretreated mice will be fasted for 18 hours with free access to water. Two-tenths ml of the above prepared IHSA will be injected by tail vein one hour prior to sacrifice in all experiments. All animals will be sacrificed by decapitation; livers will be quickly removed, rinsed in ice cold .25 M sucrose, blotted dry, weighed, and finely minced. Tissues were prepared in a glass Potter-Elvehjem homogenizer with a motor driven Teflon pestle. Large granule fractions will be prepared for studying the uptake and release of IHSA.

PROGRESS

(70 09 - 72 03) - The effect of cortisone acetate (CA) on hepatic lysosomal protein metabolism and its relation to stabilization of the lysosomal membrane has been studied in mice. Denatured Iodinated ^{125}Human Serum Albumin (IHSA) was injected by tail vein, and large granule fractions containing lysosomes were isola' .. and incubated at pH 7 and 37° for one hour in room air. The uptake o' IHSA was determined by measuring the total counts present in the lysosom' fractions after sacrifice, and degradation was determined by measuring the TCA-soluble counts present after sacrifice and released during incubation. Mice pretreated with a single injection of CA, 5 mg I.P., two

prior to sacrifice showed no significant change in uptake or degradation of IHSA. Mice pretreated with CA, 5 mg I.P. in three equally spaced injections the day before and two hours prior to sacrifice showed a 32% increase in degradation in vitro. Mice pretreated with CA, 5 mg I.P. daily for four days showed a 23% increase in degradation in vitro, 29% increase in degradation in vivo, and 73% increase in IHSA uptake. Although vitamin A, a lysosomal labilizing agent, decreased IHSA degradation, CA did not antagonize the effect of vitamin A. Hydrocortisone, 3.6×10^{-3}M in vitro, did not increase IHSA breakdown. CA did not decrease the nonsedimentable catheptic activity determined immediately after sacrifice. Thus, a catabolic effect of CA on mouse liver protein metabolism is mediated through the lysosome but, contrary to a generally held view, is not associated with membrane stabilization, although the integrity of the lysosomal membrane is necessary for optimal lysosomal catheptic activity.

STATUS: Completed.

62110A 3A062110A826 00

TITLE: Effect of Phenobarbital on Vitamin D Metabolism and Toxicity.

WORK UNIT NO: 72/399

PRINCIPAL INVESTIGATOR: Bruce S. Chertow, MAJ, MC

TECHNICAL OBJECTIVES

To determine if phenobarbital may alter the metabolism of Vitamin D and have a therapeutic role in Vitamin D intoxication and if pharmacologic doses of Vitamin D used in therapy may be altered because of coincidental phenobarbital administration

METHOD

Vitamin D_2 intoxication will be produced in 200-250 gram female Sprague rats fed ad lib with laboratory chow. Vitamin D_2 - 20,000 to 40,000 IU in 1 ml of olive oil will be administered via stomach tube daily. An experimental group of rats will be pretreated with phenobarbital, 100 mg/kg IP daily for four days prior and during Vitamin D administration. Observations will be made as to body weight, length of survival, and pathologic changes in the kidney and aorta. Calcium and phosphorus will also be determined serially.

PROGRESS

(71 08 - 72 04) - Three groups of rats have been studied. Serum calcium determination in female and male, and control groups were treated with phenobarbital 20 mg/kg three times a day, and 40,000 units of Vitamin D daily, revealed no difference between the groups after a week of treatment. Another group of rats was treated with 20,000 units of Vitamin D and the same dose of phenobarbital. Again, there was no difference in calciums noted; however, the evidence of toxicity from Vitamin D was less dramatic and the dose of 20,000 units appeared to be preferrable. A group of rats is now being treated with Dilantin, 100 mg p.o. twice a day, along with 20,000 units of Vitamin D daily.

STATUS: Ongoing.

62110A 3A062110A826 00

TITLE: Catheptic Activity and Insulin Secretion.

WORK UNIT NO: 72/400

PRINCIPAL INVESTIGATOR: Bruce S. Chertow, MAJ, MC

TECHNICAL OBJECTIVES

To develop a model in which catheptic activity can be correlated with insulin secretion. It is possible that defects in catheptic activity may be related to decreased insulin secretion in diabetes mellitus and diseases associated with glucose intolerance.

METHOD

The measurement of catheptic activity will be performed by measuring the uptake and release of IHSA by rat pancreas in isolated perfusion system used by Grodsky, et al. In this system insulin release can be measured simultaneously. The method of catheptic activity measurement originally developed by Mego and McQueen, is currently in use in another study. In this study denatured IHSA will be infused into the pancreas and pancreatic perfusage IHSA breakdown products will be determined by measuring TCA soluble iodinated aminoacids. Insulin will be assayed by the radioimmunoassay of Yallow and Berson in the Clinical Research Service laboratory.

PROGRESS

(71 08 - 71 12) - Study terminated.

STATUS: Terminated.

62110A 3A062110A826 00

TITLE: Evaluation of Exercise Effect on CPK Levels in Hypothyroidism.

WORK UNIT NO: 72/445

PRINCIPAL INVESTIGATOR: Bruce S Chertow, MAJ, MC

TECHNICAL OBJECTIVES

CPK levels have been found to be elevated in hypothyroidism. Exercise and hypoxia have been found to elevate the CPK in humans and animals. The object of this study will be to determine the effect of exercise on the level of CPK in hypothyroid patients

METHOD

Patients will have the diagnosis of hypothyroidism confirmed by the following thyroid function tests. PBI or other measure of circulating thyroxine as the competitive protein binding assay or thyroxine by column, RAIU and Scan, and serum cholesterol EMG and photomotograms and serial measurements of the CPK, SGOT, and LDH will also be performed.

After the diagnosis of hypothyroidism is established, patients will be exercised using a multistage treadmill test with submaximal exercise testing, 1 7 MPH 10% grade, and 2 5 MPH at 12% grade, walking a total of 6 minutes, 3 minutes at each exercise grade Heart rate will be monitored during exercise.

CPK, SGOT, and LDH will be measured prior to exercise and immediately after exercise, 15 minutes, one hour, four hours, and twenty-four hours. After patients have achieved the euthyroid state with treatment, repeat studies will be performed

PROGRESS

(71 08 - 72 04) - Ten patients with hypothyroidism were studied before and after treatment and SMA 12 and CPK s were obtained SGOT and LDH values were borderline high normal and returned to lower levels after treatment CPK levels were elevated with return to normal after treatment. Exercise tolerance tests revealed no difference between enzyme rises in hypothyroids and euthyroids. No further patients will be studied Results are now being tabulated.

STATUS. Ongoing

62110A 3A062110A826 00

TITLE: Cooperative Study for the Analysis of Risk Factors in Young Coronary Patients.

WORK UNIT NO: 72/454

PRINCIPAL INVESTIGATOR. Everett B. Cooper, COL, MC

TECHNICAL OBJECTIVES

A unique opportunity exists in the Army to study a large group of young coronary patients by pooling together the case material of all the Class II hospitals.

It is the purpose of this study to investigate these patients in comparison to age matched controls for the following.

a. obesity
b. hypertension
c. family history of coronary disease
d. plasma lipid classification
e. smoking history
f. carbohydrate intolerance
g. insulin response to glucose load

In the study of these parameters in young coronary patients those factors of major importance in the development of coronary disease should be detected because they have caused the disease to manifest at a young age.

METHOD

All patients who develop proven coronary heart disease under the age of 40 who are patients at any of the Class II Army hospitals are subjects for the study. Age matched individuals without coronary disease from the same institution as the patient will serve as controls.

Patients and controls will be studied for the following parameters:

a. family history of coronary disease
b family history of diabetes
c. smoking history

d. presence or absence of obesity
e. presence or absence of hypertension
f. family history of hypertension
g. serum cholesterol, triglyceride, and lipoprotein electrophoresis
h. glucose tolerance test with concominant serum insulins

These parameters in the patients will be compared to the same age matched healthy controls.

PROGRESS

(71 10 - 72 04) - The study has been formulated and sent out to the seven Class II Chiefs of Cardiology for final comment and/or approval. To date, all have not replied. A meeting of all the Cardiology Chiefs will be held at Madigan General Hospital 18-20 May 1972 at which time it is hoped that finalization can be achieved

STATUS: Ongoing.

62110A 3A062110A826 00

TITLE: Presence of Resistance Transfer Factors in Clinical Isolates of Enterobacteriaceae

WORK UNIT NO: 72/450

PRINCIPAL INVESTIGATOR: Martin H. Crumrine, CPT, MSC

TECHNICAL OBJECTIVES

To determine the number of clinical isolates of Enterobacteriaceae carrying Resistance Transfer Factors (RTF's), and to determine if those organisms not carrying RTF's can act as recipients of RTF's from donors.

METHODS

Phase I: Enterobacteriaceae isolated from the Madigan General Hospital Bacteriology laboratory will be screened for the RTF. The resistance spectrum of each organism will be reported. The presence of an RTF will be confirmed by incubating a resistant organism with a susceptible recipient E. coli K12. The E. coli will be recovered from the mixture and the presence of an antibiotic resistance acquired from the donor will be determined by plating on media containing antibiotics

Phase II: The ability of those organisms not carrying RTF's to act as recipients of R factors will be determined. Organisms carrying R factors will be incubated with RTF negative organisms to determine if transfer will occur between clinical isolates

PROGRESS

(71 10 - 72 04) - Clinical isolates of Enterobacteriaceae resistant to two or more antibiotics by the disc method were tested with the agar dilution method to further determine their sensitivities Most frequently observed multiple resistance patterns included Am, Te, Str; Te, C, G; Am, Te, C, G, Str. Organisms tested E. coli, Shigella sp., Salmonella sp., Klebsiella and Enterobacter sp., Providencia sp and Proteus sp Transferable resistance has been observed in approximately 25% of the cultures isolated. Multiply resistant E. coli transferred their resistance determinants to the E. coli K12 recipient strain with a higher frequency than the other species. A Sh coneii culture transferred its resistance determinants to the E. coli K12 recipient strain approximately the same frequency as the E. coli to E. coli transfer. Attempts to transfer R-factors from various clinical isolates to sensitive E coli isolates other than the E coli K12 recipient have been unsuccessful.

STATUS: Ongoing

62110A 3A062110A826 00

TITLE: An Adaptation of the Microtiter Technique for the Detection of Antibodies to Brucella canis.

WORK UNIT NO: 72/451

PRINCIPAL INVESTIGATOR: Suzanne Y. Damp, Medical Technologist

TECHNICAL OBJECTIVES

The microtiter system, since its inception ten years ago, has proven itself to be an efficient as well as a conservative means of accomplishing numerous serological tests. With a minimal amount of equipment and time, a particular test, i.e., agglutination, hemagglutination or complement fixation, can be performed as effectively as with the macro method.

Up to this time in the study of the serology of Brucella canis in this laboratory, only the macro agglutination (tube test) method for titers has been utilized. It is hoped that the microtiter system can be used in lieu of this more costly (time, glassware, mls of sera and antigen) method.

METHOD

Most of the microtiter equipment is available in the laboratory at the present time. Plates, 96 wells each, will be set up weekly in conjunction with the present macrotiter routine now in progress and comparisons will be made.

The same reagents - phosphate buffered saline (h. 15 and pH 7.2), antigen (Coleman Spectrophotometer O.D. 19- 20), and serum from infected dogs will be utilized.

Such parameters as temperature of incubation, elapsed time before reading, amounts of PBS and antigen, dilution of serum in the first well, and conditions for reading will be varied until an optimal test has been devised.

The test is set up as follows: PBS 25 μl is added to each well then 25 μl of undiluted serum is picked up in the diluter and carried through 8 or 12 wells depending on the desired number of dilutions. Antigen, 50 μl, is added to each well. The plate is covered with a pre-cut sealer and incubated at 50° in a moist atmosphere, but not a water bath. The samples were at 24 hours, part of the time for clarity, and all were read at 48 hours, with a microtiter mirror and bright lamp in a dark room. They were recorded as positive if a mat shape, possibly with folded-over edges, was present. A negative appeared

cloudy throughout the well or settled out into a button depending on the antigen. Both human and canine serum were run with negative controls made up of PBS and antigen. The macrotiter results served as a positive control.

PROGRESS

(71 10 - 72 05) - Since the project's beginning, 476 tests have been set up. Approximately 70 of these sera were repeats because of not being readable the first time.

Of those samples which were read at both 24 and 48 hours, the following results were obtained.

	24 hours	48 hours
No difference between macro and micro	44%	33%
Plus or minus one dilution	33%	24%
No correlation	23%	43%

It appears that at 24 hours, the reaction has essentially occurred. In the higher titers, however, 48 hours was necessary for the complete agglutination to take place. From the work accomplished, it seems that the microtiter test is a valid one as a screening device. Negatives are clearly defined when compared with positives. The macrotiter test could then be used to confirm a titer.

STATUS: Completed.

62110A 3A062110A826 00

TITLE: Evaluation of Treatment Regimens for Impetigo

WORK UNIT NO: 72/448

PRINCIPAL INVESTIGATOR: Leland J. Davis, MAJ, MC

TECHNICAL OBJECTIVES

To evaluate in a double blind method on an outpatient population the effect of penicillin and topical therapy, alone and in combination, in the treatment of bacterial skin infection (impetigo)

METHOD

The study population would consist of patients presenting to the Pediatric Outpatient Clinic with impetigo Initial patient evaluation would include physical examination and completion of a diagnostic form with a system for grading severity. Cultures would be made from the skin lesions and the experiment would be explained to the parents. With informed consent patients would be assigned to one of six treatment groups.

Parents will rate progress daily at home on a special form which will be provided. They will return to the clinic for follow-up examinations at 3, 6, and 9 days at which time a physician will score their progress on the initial physical evaluation sheet The effect of various regimens will be evaluated on the basis of (1) appearance of new lesions after initiation of therapy and (2) time required for resolution of those lesions present at time of diagnosis

PROGRESS

(71 08 - 71 12) - Further investigation of literature revealed this protocol would duplicate previous studies

STATUS: Terminated.

62110A 3A062110A826 00

TITLE: Response to Iron Supplemented Formula in the Neonate.

WORK UNIT NO: 71/372

PRINCIPAL INVESTIGATOR: Edmund A. Egan, MAJ, MC

TECHNICAL OBJECTIVES

This prospective study was designed to determine if iron supplemented formulas provided greater iron intake in the first year of life and yielded a lower incidence of iron deficiency anemia at one year of life.

METHOD

The characteristics of the population at Madigan General Hospital which urged us to begin the study were the birth rate of 16/1000 population and the prematurity rate of 5.8%. These are very close to the national average, and we feel are critical numbers which define the social-economic status of a population which are medically important.

Initially 1000 infants were enrolled in the study. It was estimated that about 50% would stay under our care for the entire year. Cutbacks in Army manpower in late 1971 and early 1972 lowered this prediction. Thus, only about 1.5% completed an entire year in the study and the value of the study will be less than projected.

PROGRESS

(71 03 - 72 05) - Monthly weights, head circumference, heights, and hematocrits; daily caloric and iron intakes on about 700 children for the first six months of life have been obtained. This information is prospective and involves five separate sets of information on each of the 700 infants. Full utilization of this information will necessitate computerization of the data.

Approximately 150 infants of the 700 were followed for the full year. The original aim of the study will only be valid for this group.

Fifty random patients were selected from the group of 700 for whom we have data for the first six months of life and preliminary evaluation of some of the information is presented In addition, diet information only

was gathered from 100 study infants and 73 additional patients from the same population, but not entered into the study. This limited diet information was gathered at one year of life. Data on the incidence of iron deficiency anemia of the 100 patients selected who completed one year in the study has been obtained, but the correlation of the anemia with diet has not been completed at this time.

Total iron intake for the first six months of life - 50 prospectively studied infants. Source of iron not specified - approximately 50% on iron formulas. The percentage of 2 mg/kg/day or more and the percentage on less than 2 mg/kg/day will equal 100%.

	less than 1 mg/kg/day	less than 2 mg/kg/day	2 mg/kg/day or more
0-1 month	12%	40%	60%
1-2 months	2%	22%	78%
2-3 months	2%	24%	76%
3-4 months	2%	22%	78%
4-6 months	4%	34%	66%

Incidence of iron deficiency anemia. All infants with hematocrits less than 33 received three weeks of ferrous sulfate in a dose of 6 mg of Fe/kg/day and had a rise in hematocrit to normal by the end of therapy. N=100 infants followed prospectively for one year.

Hematocrit 33 or less - 3%

Hematocrit 33-5 - 15%

Hematocrit 36 or higher - 82%

STATUS: Ongoing.

62110A 3A062110A826 00

TITLE: Determination of Radiation Reduction to the Lens During Polytomography of the Internal Ear.

WORK UNIT NO: 72/380

PRINCIPAL INVESTIGATOR: Robert A. Ellwood, MAJ, MC

TECHNICAL OBJECTIVES

To determine the radiation dose received by the ocular lens during routine polytomography of the internal ear, with and without orbital shields.

METHOD

"RANDO" (a tissue equivalent - man used to determine isodose curves in radiotherapy) will serve as our subject. With ionization chambers placed in the appropriate anatomic areas such as the lens, we plan to simulate a routine series of the internal ear using the polytome. A total of ten trials will be attempted with consistent radiographic factors. Subsequent trials will then be performed using two other factors commonly used in the procedure. The average lenticular dose will then be calculated by the radiophysicist, per factor series. Using the same factors, the experiment will be repeated employing ocular lead shields. Dosage calculations will then be compared to determine the percentage of reduction via the lead shields.

PROGRESS

(72 01 - 72 03) - Subject protocol has progressed as follows:
a. Preparation of the subject for the placement of ionization capsules.
b. Standardization of radiographic techniques for the study.
c. Development of ocular protective lens coverings.
d. Several rough dosage calculations on the subject, showing approximate four fold dosage reduction to the ocular lens

STATUS: Ongoing

62110A 3A062110A826 00

TITLE: Adrenal Venography in the Canine as an Experimental Model.

WORK UNIT NO: 71/394

PRINCIPAL INVESTIGATOR: Bruce L Fariss, LTC, MC

TECHNICAL OBJECTIVES

An attempt will be made to perform adrenal venography in canines. There are no reported instances of this procedure in canines, however, it is performed in human subjects with complications of adrenal hemorrhage and intravenous thrombosis.

METHOD

A total of ten dogs will be utilized. Each dog will be given 40 units of ACTH gel intramuscularly daily for a total of three months. Two months following the institution of the ACTH gel, the thoraco-abdominal veins will be occluded with silver clips placed distally to the adrenal glands. Following recovery from the surgical procedure and removal of all sutures, each dog will have adrenal venography performed through the left or right femoral veins, using the Seldinger technique. The procedure will be performed under intravenous anesthesia. Following injection of a small bolus of contrast material, an attempt will be made to collect blood samples from the adrenal veins. Two animals will be euthanized at weekly intervals and histological studies made of the adrenal glands. Two animals will not have adrenal venography performed to act as controls for the histopathology. Each animal will continue to receive ACTH up to the date of euthanization.

PROGRESS

(71 06 - 72 03) - Percutaneous adrenal venography was performed utilizing the Seldinger technique on normal dogs and dogs with adrenal hyperplasia. The procedure was found simple to perform. The glands were studied for pathological changes at intervals following catheterization including some glands purposefully extravasated. No significant pathological changes were found. To our knowledge, this procedure has not been previously reported with the canine and it may prove to be a useful tool.

STATUS: Ongoing.

62110A 3A062110A826 00

TITLE: Diphenylhydantoin-Induced Hyperglycemia and Impaired Insulin Release: Effect of Dosage.

WORK UNIT NO: 71/389

PRINCIPAL INVESTIGATOR: Bruce L. Fariss, LTC, MC

TECHNICAL OBJECTIVES

A patient at Madigan General Hospital has been found to have elevated blood sugars following the administration of diphenylhydantoin (Dilantin). It is proposed to evaluate this patient's insulin release and glucose response to standard testing methods.

METHOD

Insulin and glucose levels will be determined following the oral administration of 100 grams of glucose while the patient is receiving no diphenylhydantoin and 100, 200, 300, and 400 mg a day by mouth. These tests will be performed at two week time intervals at each dose level of diphenylhydantoin.

The patient's insulin and glucose response to the intravenous administration of 25 grams of glucose will be determined while receiving no diphenylhydantoin and while receiving 400 mg of diphenylhydantoin.

The patient's insulin and blood glucose will be measured while receiving no diphenylhydantoin and 400 mg of diphenylhydantoin following the administration of one gram of tolbutamide intravenously.

The oral and intravenous glucose tolerance tests will be performed in the customary manner. The dose of tolbutamide is the usual diagnostic test dose.

Blood levels of diphenylhydantoin will be performed by Bio-Science.

PROGRESS

(71 04 - 71 09) - Elevated postprandial blood sugar levels were found in a forty-two year old Negro woman taking 400 mg of diphenylhydantoin a day.

After discontinuance of diphenylhydantoin, blood glucose levels and insulin responses were normal when oral and intravenous glucose tolerance tests and an intravenous tolbutamide test were performed. After taking 400 mg diphenylhydantoin daily for two weeks the patient had decreased oral and intravenous glucose tolerance and an abnormal intravenous tolbutamide test with marked reduction in insulin response in all three tests. Oral glucose tolerance tests were within the limits of normal while the patient was receiving 300, 200, and 100 mg diphenylhydantoin by mouth; however, the insulin response was decreased when the patient received 300 and 200 mg diphenylhydantoin.

STATUS: Completed. Published in Diabetes 20:177-181, March 1971.

62110A 3A062110A826 00

TITLE: The Incidence of Diabetes Mellitus and Renal [illegible]

WORK UNIT NO: 70/097

PRINCIPAL INVESTIGATOR: Bruce [illegible] Farriss, LTC, MC

TECHNICAL OBJECTIVES

To identify diabetics and individuals with renal glycosuria following the administration of 75 to 100 grams of glucose by mouth

METHOD

The first week of orientation recruits will be brought to the examining station without ingestion of food A urine sample will be collected from each individual and he will be given 100 grams of glucose by mouth Two hours later a blood specimen will be withdrawn from the anticubital vein into a vacutainer. He will be asked to void a urine specimen Both urine specimens will be checked for sugar by using test tapes The blood specimen will be returned to the Clinical Research Service laboratory where it will be analyzed for sugar using the Technicon Autoanalyzer ferricyanide method

Those individuals found to have elevated two hour sugars or sugar in their urine will be given a standard glucose tolerance The incidence of diabetes will be determined using the standardization of the oral glucose tolerance test as described by the Report of the Committee on Statistics of The American Diabetes Association, June 14, 1968

PROGRESS

(71 03 - 72 04) - There were 4,931 recruits studied on this protocol. It was found that 19.2% of these individuals had 1 to 4+ glycosuria two hours after the ingestion of 100 grams of glucose It was noted that 24.5% of these individuals had a 2-hour post-glucose load blood sugar of less than 60 mg% performed by the alkaline ferricyanide reduction method Glucose tolerances were performed on those individuals with blood sugars greater than 100 mg% with six being diagnosed as having chemical diabetes mellitus and one individual with overt diabetes mellitus requiring insulin.

STATUS: Ongoing

62110A 3A062110A826 00

TITLE: Renal Glycosuria: Evaluation of Renal Function, Carbohydrate Metabolism and Possible Development of Diabetes Mellitus

WORK UNIT NO: 69/307

PRINCIPAL INVESTIGATOR Bruce L Fariss, LTC, MC

TECHNICAL OBJECTIVES

To study patients with renal glycosuria in an attempt to further classify these patients More importantly, we shall attempt to distinguish those patients who may develop diabetes mellitus by studying responses to oral glucose and intravenous glucose and tolbutamide with measurement of blood and urine glucose and insulin levels The renal transport of glucose, insulin, H^+, HCO_3, NH_4, protein, amino acids, and additional renal tubule defect

The patients will be reevaluated at yearly intervals up to five years to determine the incidence of diabetes mellitus

METHOD

Twenty patients who are found to have flat or normal oral glucose tolerance tests with renal glycosuria shall be admitted to the hospital.

Day 1: History, physical examination, routine CBC, Chest X-ray, STS, regular hospital diet (300 gm CHO)

Day 2: Twenty-four hour urine for Na, K, Ca, Creatinine, sugar, titratable acid, ammonia excretion, proteins, amino acids and osmolitary. Serum electrolytes (Na, K, CO_2, Cl_2, Ca, P), SGOT, alkaline phosphatase, BUN, creatinine, uric acid and serum electrophoresis. Urinary pH measured at each voiding.

Day 3: Oral glucose tolerance-blood and urine glucose and plasma insulin levels.

Day 4: Intravenous glucose tolerance test, (25 gm), blood and urine glucose and plasma insulin.

Day 5: Infusion of glucose, intravenous to calculate the splay (renal tubular reabsorption as a function of load presented to the tubule) Inulin and endogenous creatinine clearances to be done in conjunction with the glucose infusion

Day 6: Day of rest.

Day 7: Tolbutamide tolerance test (1 0 gm I V) specimens for glucose and insulin at 0, 2, 5, 15, 30, 45, 60, 90, 120, 150 and 180 minutes.

Day 8, 9, and 10: NH_4Cl loading p o with measurement of hydrogen secretory capacity, net acidification ar ' NH_3 production each day

Day 11: Discharge

PROGRESS

(71 03 - 72 04) - To date 37 individuals have been studied with renal glycosuria with oral and intravenous glucose tolerance tests and intravenous tolbutamide. Individuals with diabetic glucose tolerance tests were rejected from the study.

Subdivisions of the study group can be made on the basis of the oral glucose tolerance test Four members of the group have flat glucose tolerance tests with the remainder having normal glucose tolerance tests. The range of glycosuria during the oral glucose tolerance test was 0 1 to 4 grams of glucose. Insulin response was extremely high in many of these subjects

STATUS: Ongoing

62110A 3A062110A826 00

TITLE: A Retrospective Study of the Preoperative Electrocardiogram in the Adult Surgical Patient.

WORK UNIT NO: 72/398

PRINCIPAL INVESTIGATOR: Kevin J Farrell, CPT, MC

TECHNICAL OBJECTIVES

To conduct a retrospective study of multiple clinical aspects of a large number of general surgical patients who have had a preoperative electrocardiogram. A thorough indepth review of the literature regarding the preoperative electrocardiogram and related topics will be made. An attempt will be made to correlate the results of this study with the prior literature.

METHOD

A large number of charts, initially 1000 and hopefully 5000, of general surgical patients who have had preoperative electrocardiogram will be reviewed. They will be selected on the basis of specific operations over a given time interval, i e , all cholecystectomies done in the past year, and so forth.

Multiple aspects of the clinical data will be recorded on a data form. A pilot study of 20 charts as an aid to designing this data form has been made. For purposes of the postoperative complications only the time interval of the hospitalization, up to one month, in which the operation occurred will be considered The data will be subjected to computer analysis.

PROGRESS

(71 08 - 72 05) - In an attempt to better determine the significance of the preoperative electrocardiogram in the adult general surgery patient, a retrospective study has been undertaken To date no conclusions can be drawn

STATUS: Ongoing

62110A 3A062110A826 00

TITLE: Reevaluation of Blood Culture Technique.

WORK UNIT NO: 72/455

PRINCIPAL INVESTIGATOR: Gerald W. Fischer, CPT, MC

TECHNICAL OBJECTIVES

One to two ml of intravenous blood is currently deemed necessary in evaluating sepsis in the newborn. Oftentimes intravenous blood is difficult to obtain and this amount of blood may be detrimental to the child. 0.2 ml of blood from a 2-3 Kg baby on a dilutional basis is the same as 4 ml in a 70 Kg man. There have been no heel sticks as a blood culture method.

METHOD

PHASE I - Adult rabbits will be used. A central venous catheter will be placed via the femoral vein to the area of approximately the inferior vena cava. The femoral artery will also be cannulated for the measurement of blood pressure, specifically to monitor the possibility of gram-negative sepsis. Approximately 10^6 organisms will be infused via a bolus into the central venous catheter and at varying intervals, 8 samples over the next two hours will be drawn from the central venous catheter for quantitative blood cultures on a pour plate and for injection into a blood culture bottle. One cc will be used on the pour plate and 2 cc will be injected into one blood culture bottle while .2 cc will be injected into the other blood culture bottle. This will be done at intervals of immediately after the injection of the bolus, at 10 minutes, 20 minutes, 30 minutes, 45 minutes, 1 hour, 1 1/2 hours and 2 hours after the injection of the organisms. The bottles and pour plates will be randomly numbered and will be read at intervals after drawing of 12 hours, 24 hours, 36 hours, and 48 hours. At 48 hours each blood culture bottle will be sub-cultured and then read at 24 and 48 hours. Either general anesthesia via inhalation or pentobarbital will be used. Strict aseptic technique will be followed at all times and a constant infusion pump will be used to insure a steady low flow into the animal. Approximately 28 cc of blood total will be removed and approximately 16 cc of saline will be replaced at the rate of 8 cc per hour, making a net volume of approximately zero.

PHASE II - Purpose will be to see if 0.2 cc of blood from a peripheral stick is as accurate and sensitive as 2 cc of I.V. drawn blood.

Phase I and II to be run simultaneously.

PROGRESS

(71 11 - 72 05) - The preliminary data suggests that rabbits will be a good model for quantitating *E. coli* in blood culturing. Organisms are rapidly removed from the circulation producing a steady decrease in *E. coli* per cubic centimeter of blood.

E. coli 10^8 per cubic centimeter (2 cc) are injected into a rabbit. Pour plates with 1 cc of blood added to Maconkey's media show no growth within 30 minutes. More animals need to be tested to establish the validity of this data and to ensure its reproducibility.

STATUS: Ongoing.

62110A 3A062110A826 00

TITLE: Detection of Subclinical Emphysema

WORK UNIT NO 72/306

PRINCIPAL INVESTIGATOR: Arthur F Gelb, MAJ, MC

TECHNICAL OBJECTIVES

The present study is designed to diagnose subclinical emphysema. This is important for both clinical and epidemiological reasons. Since specific clinical and radiological hallmarks do not exist early in the disease, the diagnosis will have to be made on physiologic tests To date, previous studies have only been able to detect moderately advanced disease when symptoms are obvious and disease irreversible

METHOD

All patients scheduled for thoracotomy will undergo routine pulmonary function studies including maximum expiratory flow volume curve and diffusing capacity. Lobes and/or lung removed at time of surgery will be sent to Department of Pathology for routine studies Following this, lobes and/or lungs will be air inflated and analyzed for extent of emphysema. Correlation will be made between preoperative pulmonary function studies and anatomy obtained. Furthermore, extensive preoperative evaluation will better aid the surgeons as to identify those patients with serious underlying disease, preoperative subclinical diagnosis of emphysema; one developed extensive complications after a pneumonectomy

PROGRESS

(72 04 - 72 05) - None

STATUS: Ongoing

62110A 3A062110A826 00

TITLE: Non-Invasive, Simple Technique for Detection of Peripheral Airway Disease.

WORK UNIT NO: 72/312

PRINCIPAL INVESTIGATOR: Arthur F. Gelb, MAJ, MC

TECHNICAL OBJECTIVES

It has recently been demonstrated that the major site of obstruction in chronic obstructive lung disease occurs in peripheral or small airways (2 mm in diameter or less). Conventional tests of lung mechanics may be normal because these airways contribute less than 30% of total airway resistance. Therefore, diseases of small airways may present as "dypsnea" but physiologically are silent on routine pulmonary function studies. The tests that are utilized to diagnose peripheral airway disease are frequency dependence of compliance, and tests that measure efficiency of gas exchange. These tests are technically difficult, require esophageal balloons, indwelling catheter and do not lend themselves for screening purposes. The object of this study is to develop simple accurate tests to detect small airways disease.

METHOD

Patients with complaints of dyspnea and/or wheezing and/or bronchitis will undergo routine pulmonary function studies when indicated. In some patients the only abnormality will be in "small airways" that will only be detected by frequency dependence of compliance and/or studies of gas exchange. These patients will be studied by two simple, non-invasive, single breath tests, i e , maximum expiratory flow volume curve and closing volume to see if these tests can detect the abnormality Also, work so far in our laboratory indicated that these two tests are able to distinguish patients with small airways disease

PROGRESS

(72 04 - 72 05) - None

STATUS: Ongoing

62110A 3A062110A826 00

TITLE: Controlled Study in Assessing the Efficacy of Phenobarbital in Decreasing Morbidity of Hepatitis

WORK UNIT NO: 71/371

PRINCIPAL INVESTIGATOR. David I Grayer, MAJ, MC

TECHNICAL OBJECTIVES

To test the ability of phenobarbital at two-dose ranges to decrease the morbidity of viral hepatitis

METHOD

Patients admitted to the study will be from the Hepatitis Ward, Madigan General Hospital The following criteria must be fulfilled before being entered into the study (1) Increased bilirubin and transaminase; (2) Onset of symptoms within 14 days of hospitalization; (3) Not asymptomatic for more than 4 days before admission; (4) Negative mononucleosis screen; (5) Prothrombin time less than 3 seconds off control; and (6) Be willing to enter the study Routine history and physical will pay special attention to prior blood transfusion or parenteral administration of drugs under non-sterile conditions; absence of viral type gastroenteritis in the week before jaundice noticed; and existence of other cases of hepatitis in the family members or barrack mates.

Patients will then randomly be placed in one of three groups unknown to the physician Each patient will receive 3 pills/day as follows. Group I - Placebo (lactose); Group II - Phenobarbital 15 mg; and Group III - Phenobarbital 32 mg Patients will all have blood drawn for serum Australian antigen as well as routine chemistry upon admission Patients will all be seen twice/weekly and evaluated for the morbidity of their disease. This evaluation will check for the presence of fever, malaise, anemia, emesis, diarrhea, and liver pain Liver chemistries and prothrombin time will be checked also twice weekly BSP retention will be done on all patients after jaundice has disappeared. Patients will be hospitalized until the SGOT is below 100 and they are non-jaundiced Activity for patients will be modified bed rest.

Results will be analyzed to determine if one group did better than another and if the type of hepatitis (I versus II) affected the outcome. Twenty-five patients will be entered into the study

PROGRESS

(71 03 - 72 05) - There was no difference between the treated and non-treated groups as far as speed of recovery from hepatitis However, those patients with serum Australian antigen possibly had a longer convalescence

STATUS Completed

62110A 3A062110A826 00

TITLE: Evaluation of Minocycline in Prevention of Meningococcal Disease in U S. Army Recruits

WORK UNIT NO. 71/378

PRINCIPAL INVESTIGATOR: Richard B Guttler, CPT, MC

TECHNICAL OBJECTIVES

To determine if Minocycline can abort an outbreak of meningococcal meningitis that is expected at Fort Lewis during the winter months.

METHOD

It is proposed to observe the case rate of meningococcal disease and when two cases/week have occurred, treat all recruits at Fort Lewis with Minocycline, 100 mg every 12 hours for four days.

The use of URI Wards for observation for early signs of meningitis and the excellent techniques of diagnosis (buffy coat cultures) make it possible to verify the existence of meningococcal meningitis

Three hundred and fifty cultures/month will be done by the Sixth US Army Laboratory as part of the routine surveillance of nasopharyngeal carriers in the sixth week of basic training

PROGRESS

(71 01 - 71 12) - Minocycline has an effect on meningococcal carriage which is similar to that of sulfadiazine, but its value in preventing meningococcal disease has not been studied When five cases of meningococcal meningitis occurred within two weeks among recruits at Fort Lewis, Washington, 8,721 men were given 100 mg of minocycline every 12 hours for five days. No new cases of meningococcal disease occurred for almost five weeks. Subsequently, six additional cases occurred among recruits who had entered training after the initial course of minocycline and who had not received the drug. Minocycline was given to all 6,130 of these men, and again, occurrence of new cases was halted abruptly. One week later, group C polysaccaride vaccine was administered to all recruits in the first six weeks of training and subsequently to all new entering

trainees No new cases of meningococcal disease occurred in the next three months Surveys showed that minocycline significantly lowered the meningococcal carrier rate for 4 to 5 weeks No strains of N. meningitidis, among 344 isolated after minocycline treatment, were resistant to the drug. Prophylaxis with minocycline clearly interrupted the course of this meningococcal outbreak, and the drug appears to be capable of preventing disease due to sulfa-resistant meningococci Although immunization is the preferred method of prophylaxis, minocycline may be useful until a suitable polyvalent vaccine is available

STATUS. Completed Publication - J Infect Dis 124 199, 1971.

62110A 3A062110A826 00

TITLE: 5-Fluorouracil in Adenocarcinoma of Colon and Rectum

WORK UNIT NO: 71/377

PRINCIPAL INVESTIGATOR: Daniel C. Hadlock, MAJ, MC

TECHNICAL OBJECTIVE

To prolong survival and/or improve quality of life in patients with residual adenocarcinoma of the colon and rectum.

METHOD

Selection of Patients - All patients must meet the following criteria: Histologic proof of adenocarcinoma of the colon or rectum. All patients with histologically proven unresectable disease at surgery, or evidence of metastases are all eligible for chemotherapy. Those patients with what was thought at surgery to be resectable disease but who showed on histological examination evidence of (1) external serosal involvement; (2) lymph node involvement; (3) blood vessel involvement, will be acceptable for treatment but therapy will be randomized between a control group and those receiving 5-FU.

Study Parameters - Record all parameters - Physical, hemotologic, biochemical on Oncology Clinic Flow Sheet.

Mechanics of Study - Patient must be classified as "good" or "poor" risk in order to determine dose schedule. "Poor risk" patient will receive the lower dose.

Evaluation of Response - Course of treatment will not be considered adequate until at least four months' therapy has been given.

Duration of Therapy - Patients without measurable disease at the onset should be kept on the protocol for a minimum of two years and, tentatively, no more than five years. Patients with measurable disease should be kept on protocol as long as there is objective evidence of a therapeutic response. 5-FU may be discontinued after no less than two years of a Category I-C response (complete relief of symptoms, if any, and regression of all manifestations resulting from active disease for one month or more); no patient should receive more than five years therapy, tentatively.

PROGRESS

(70 07 - 72 03) - Entered two patients, one with metastatic liver disease which appeared several years after an A-P resection for rectal adenocarcinoma, the other was started on weekly 5-FU prophylactically because she had positive lymph nodes found on A-P resection for rectal adenocarcinoma.

Results:

Tumor - The patient with disease present has been on therapy for 12 months. During this time her liver metastases have increased steadily in size, albeit very slowly, and she has developed positive (presumably) in her left axilla and left cervical area.

The patient who was started on prophylactic 5-FU continues to show no gross evidence of tumor after 8 months of therapy.

Toxicity - Both patients have developed marked hyperpigmentation and slight alopecia. However, these signs have improved by the third month despite continuing therapy.

Also, loss of eye lashes has been bothersome and both patients have commented on some dryness of the eyes. This has been controlled by methylcellulose drops in the one patient who has required continued 5-FU because of progressing tumor In the second case, signs and symptoms resolved when the 5-FU was given every second week.

No marrow suppression or GI toxicity seen.

Conclusions - Not enough data to date.

STATUS. Ongoing.

62110A 3A062110A826 00

TITLE: Combination Chemotherapy of Metastatic Breast Cancer.

WORK UNIT NO. 71,376

PRINCIPAL INVESTIGATOR Daniel C Hadlock, MAJ, MC

TECHNICAL OBJECTIVES

To prolong survival and/or improve quality of life in patients who have proven refractory to standard surgical radiotherapeutical and hormonal treatment for breast cancer at Madigan General Hospital

METHOD

Selection of Patients - All patients with biopsy proven primary breast carcinoma of any type should be considered when they can be shown to have recurrent and/or resistant tumor after standard therapy including (1) surgical removal of the primary, (2) irradiation of the primary site and adjacent areas either prior to or following surgery, (3) hormonal therapy, either additive (medications) or ablative (surgical removal of ovaries, adrenals, pituitary)

Study Parameters - All parameters, hematologic, biochemical, and tumor measurements, are to be recorded on Flow Sheets.

Mechanics of Study - Drugs will be given on an outpatient basis. Patients will be admitted to the hospital only when there are definite clinical situations requiring it

Evaluation of Response - The effect of therapy will be evaluated according to the following categories with an opinion being recorded in the progress notes after each month of treatment

Category 0	No clinically useful effect on the course of disease.
0-0	Disease progresses, no subjective benefit
0-A	Tumor progression objectively with subjective improvement.
0-B	Tumor shrinks - 50% or response lasts less than one month. No subjective improvement

Duration of Therapy - Induction will not be considered adequate until eight weeks of therapy have been given

Termination of Therapy - The only absolute criteria for discontinuing all drugs will be: (1) Active tissue infection. (2) Evidence of extreme bone marrow hypoplasia as manifested by WBC less than 2000 and/oo platelets less than 75,000

PROGRESS

(70 07 - 72 03) - Entered four patients with widespread metastatic breast carcinoma which has recurred following initial mastectomy, with or without post-operative irradiation, and not been controlled with repeat irradiation and/or oophorectomy

Extent of Tumor: at onset of RX	Hilum	Lung	Liver	Abdomen	Bone	Marrow
IM	+	+	+	+	+	-
OP	-	-	-	+	-	-
LB	+	+	-	-	-	+
MJ	+	+	-	+	+	+

Results.

Tumor - one patient (MJ) showed no response and died within three months of starting treatment. This treatment was limited in that it was interrupted while she received a month of radiotherapy to an involved weight-bearing joint.

One patient (IM) has showed no progression of disease over a 12 month period with symptomatic improvement. She has been living an essentially normal life at home.

Two patients (OP & LB) show no evidence of disease at 8 and 10 months respectively. They are being continued on treatment.

Toxicity - Drug doses have been modified in all patients because of bone marrow suppression. All patients have developed reversible but moderately severe peripheral neuropathy requiring cessation of vincristine. Two patients (IM & LB) have developed severe colonic dilatation requiring colostomy under complex circumstances; one clearly related to the presence of tumor in the abdomen, one unexplained. All patients have developed some hyperpigmentation and alopecia. No patients have developed any GI symptoms.

Conclusions - This is an extremely effective regimen for the control of breast cancer which has not been controlled by surgery, irradiation and hormone management.

Use of this protocol requires careful follow-up for the management of side-effects, primarily myelosuppression, and adjustment of drug dosages. Fifty percent incidence of colonic dilatation is disturbing; cannot be clearly related to the use of vincristine (in neither instance had it been given for two weeks) but nonetheless, since the other manifestations of vincristine toxicity have been significant, the dosage of this drug should probably be reduced to 0.15 mcg/kg per dose.

STATUS: Ongoing.

62110A 3A062110A826 00

TITLE The Use of Prednisone in Treatment of Infectious Mononucleosis: A Double-Blind Study

WORK UNIT NO. 69,100

PRINCIPAL INVESTIGATOR. Richard J Hannah, MAJ, MC

TECHNICAL OBJECTIVES

To determine if Prednisone, administered in tapering doses over a ten day course can affect the duration of fever, pharyngitis, malaise, necessity for hospital care, and overall time away from duty in patients with proven infectious mononucleosis

METHOD

Patients to be considered for the study are all patients, male and female, seen or admitted to Madigan General Hospital with infectious mononucleosis. Diagnosis to be made only in patients who show the clinical characteristics, hematologic picture, and serologic studies of infectious mononucleosis as outlined by Hoagland and others

Patients with proven infectious mononucleosis who have (1) oral temperature of 101 0 degrees or more on or after the seventh day of the clinical illness; (2) disabling pharyngitis on or after the fourth day of the clinical illness (difficulty eating, swallowing, or talking); (3) extreme malaise on or after the fourteenth day of the clinical illness such that the patient is unable to join in ward activities, sit up to eat, watch television, play cards, and so forth; and (4) SGOT over 100 or bilirubin greater than 2.0 at any time in the illness will be entered into the study group

Treatment schedule. When the patient meets any one of the four sets of criteria listed above, therapy will begin

Patients will be evaluated at three weeks and six weeks post-discharge from the hospital and blood studies will be repeated They will be followed until they are asymptomatic and at full duty File cards on each patient will contain pertinent clinical and laboratory data

The treatment schedule will be determined by random number assignment by the secretary, Hematology Service, and drug choice will not be known to attending physicians, nurses, patient or study physicians. Code will be broken only when a number of patients have completed the study

PROGRESS

(71 05 - 72 05) - A total of 44 patients have been entered into the study and completed the protocol without untoward effects. Because of the forthcoming separation from the Army of the principal investigator, no more patients will be studied. The code will be broken and statistical analysis applied to several parameters, such as length of fever, lymphadenopathy, and length of disability, to see if there is a difference between Prednisone and placebo groups.

STATUS Ongoing

62110A 3A062110A826 00

TITLE: Autoradiographic Tracing of a Specific Behavior-Inducing Brain Peptide.

WORK UNIT NO: 72/373

PRINCIPAL INVESTIGATOR: Keith R Haushahn, GS7, Psychology Asst.

TECHNICAL OBJECTIVES

To test the report that a specific peptide may be responsible for transfer of dark-avoidance behavior (Ungar, Desiderio, and Parr, In Press). An additional parameter is whether there are behavioral differences between subjects injected with a synthetic peptide or with the bio-synthesized material in dark avoidance behavior, latency, running time, or emotional responses. The determination of the pathway this material may take on its way to various loci in the brain is a final possibility to be examined using autoradiographic techniques

METHOD

Four hundred naive rats were trained to avoid a dark box in a one way avoidance apparatus using an improved variation of the conditioning paradigm of Ungar, Galvan, Clark (1968) Each subject received six trials daily for eight days with an ITI of 60 seconds

After training the donor rats were decapitated, their brains removed, and the active peptide extracted using the technique of Ungar, et al (In Press). Control extracts were prepared in a similar manner from untrained brains.

A synthetic peptide with the same sequence as the biosynthesized material was prepared and all three extracts were labeled for autoradiographic tracing One hundred twenty recipient mice were divided into each of the three treatment conditions and randomly assigned to one of 10 post-injection intervals for testing of the transfer effect At each post-injection interval, one subject from each treatment group was sacrificed and histologically prepared for autoradiography

PROGRESS

(72 01 - 72 04) - Donor rats were procured in four groups of 100 animals each Two hundred rats have been trained in the manner described in Method,

decapitated, their brains removed, and frozen in dry ice. They are now being stored at -20°C until the remainder of the sample has been trained.

Control donors have been sacrificed and their brains prepared in the manner as described in Method.

STATUS: Ongoing.

62110A 3A062110A826 00

TITLE: Evaluation of a Tracheopharyngeal Shunt

WORK UNIT NO: 70/313

PRINCIPAL INVESTIGATOR: Leonard L. Hays, LTC, MC

TECHNICAL OBJECTIVES

To design and evaluate an artificial tracheopharyngeal shunt on laryngectomized animals.

METHOD

The Silastic tracheopharyngeal tube can be fashioned each from two Silastic tracheostomy tubes. The tubing can be connected with Silastic medical adhesive. Simple laryngectomies will be performed on several dogs, although it may be advisable to perform this first on one or two cats in order to anticipate any problems. Adequate time will be left for complete healing of these animals and to insure long-term viability After the wounds have been completely healed, a simple pharyngotomy will be performed by a simple puncture through to the pharynx. The Silastic tube will then be inserted into the trachea and pharynx The animals will be evaluated for aspiration and leakage. The air flow from the tracheal end of the shunt will be compared to that at the pharynx The design of the tubes will be varied according to the amount of aspiration, leakage and volume of air that can be recovered at the pharynx with the tracheal opening covered. The pharyngeal end of the Silastic tube will contain a simple flutter valve which will eliminate aspiration and leakage This will also be evaluated and changed according to the results of the preliminary investigations

PROGRESS

(70 04 - 72 03) - It was found that the side-arm tubes were well tolerated by the animal if they were placed in a fistula below the cricopharyngeus muscle. However, if placed above, the strong muscular contractions of the pharynx and base of the tongue caused the dogs to try to continually reject them.

No significant difference in reactivity was found between the esophagotomies made by a stab incision or by actual mucocutaneous anastomosis except for the lengthened healing time for the stab incisions An esophagostomy performed

at the time of the laryngectomy, however, eliminated the necessity for a second surgical procedure and esophagostomy was used for tube feedings during the immediate post-operative period.

The fistula could be maintained tightly against the side-arm tube if it were removed for eight hours daily. This allowed for slight closure of the fistula. If the tubing was left in place continuously, breakdown of tissue and gross leakage of saliva were noted on the 10th day. With daily removal of the tube, gross tissue reaction remained minimal until termination of the experiment three months later The dogs tolerated the indwelling side-arm tubes well and were able to eat and drink without difficulty. They maintained their weight after an initial drop that occurred during the immediate post-laryngectomy period Tissue tolerance of Silastic tubing has been reported to be good and hence, Silastic tubing was used in this experimental study.

Valve Type I was chosen for the final design of the apparatus because it was of simplest construction, produced the least resistance and functioned equally as well as the other types in preventing aspiration into the side arm tube. Airflow measurements were similar with Types I and IV valves, revealing that the deflective qualities of the Type IV valve were not advantageous.

Airflow measurements also revealed the esophagus to fill rapidly when air was introduced into the side-arm tube. A linear increase of recovered air was recorded with increased flow into the esophagus until a level was reached in each dog where the gastrointestinal system began to fill with air. Pressure measurements obtained on Valve Type I deviated from the linear characteristics expected of a straight tube without a valve only at low airflows. Negative intraesophageal pressures with respiration could be recorded with the valve in place indicating that only a small pressure gradient was necessary to open the valve. Airflow rates were also comparable to the egress rate noted in the human esophageal speaker.

STATUS: Completed

62110A 3A062110A826 00

TITLE: Experimental Correction of Laryngeal Webs.

WORK UNIT NO: 71/375

PRINCIPAL INVESTIGATOR: Leonard L. Hays, LTC, MC

TECHNICAL OBJECTIVES

To prevent the regrowth of laryngeal webs and/or glottic stenosis by suturing to one vocal cord a sleeve of thin silastic sheething.

METHOD

Under general anesthesia and using the Jako-Pilling operating laryngoscope under magnification of the Zeiss operating microscope using microlaryngeal instruments, bare edges on vocal cords by thorough stripping will be produced. With the silastic sleeves sutured to one of the exposed cords, re-epithelialization and healing will be followed. The silastic sleeves will be removed and results determined by histology, function, photography, and long term follow up.

PROGRESS

(71 05 - 72 05) - It has been demonstrated that webs can be prevented in canine larynxes using silastic sleeves. The animals tolerated the procedure well and without apparent difficulty in barking, swallowing, and breathing.

STATUS: Ongoing

62110A 3A062110A826 00

TITLE: Clomiphene Citrate - Double Blind Evaluation.

WORK UNIT NO: 71/393

PRINCIPAL INVESTIGATOR. Paul A. Hensleigh, MAJ, MC

TECHNICAL OBJECTIVES

To utilize clomiphene citrate in a double blind administration regimen as primary treatment for a group of selected anovulatory, eugonadal patients in whom concommitant infertility factors have been excluded. Evaluation of side effects, complications of treatment, and progression of ensuing pregnancies will also be obtained.

METHOD

Study group. Patients to be included in the study will be evaluated initially to establish an anovulatory dysfunction. Patients with cyclic menstruation will not be evaluated prior to 18 months exposure without conception. Anovulation will be established by recording of basal body temperature for at least 3 cycles and endometrial biopsies in the latter half of at least 2 cycles Initial evaluation will include a battery of laboratory tests

Patients with amenorrhea or oligomenorrhea (interval greater than 45 days) in addition to the initial screening tests will also have skull films and visual fields evaluations, vaginal smears for estrogenic effect, acute progesterone treatment to establish a withdrawal flow and if indicated, determination of urinary ketosteroids, hydroxycorticosteroids, and FSH excretion Patients showing no evidence of pituitary tumor, nor end organ failure (ovarian or uterine) will be included in the study groups with the above cyclic patients and further evaluation

Cervical factors including infections, stenosis, polyps or abnormal Pap smears will be evaluated and adequately treated before including the patient in the study groups Uterine configuration will be evaluated by X-ray hysterosalpingography in patients with histories or examinations suggesting congenital anomalies, uterine myomata or incompetent cervices. All patients in the study will have tubal patency established by the performance of a Rubin's test and in patients with histories of remote pelvic inflammatory disease, hysterosalpingograph will be obtained to confirm patency of the fallopian tubes and lack of significant pelvic adhesions Any patient who has non-remedial infertility factors of the cervix, uterus or fallopian tubes will be excluded

from the study. Thus, the patients included in this study will be only anovulatory patients who have no evidence of pituitary or ovarian failure and no recognized secondary infertility factor of the genital tract. Only patients who will be available for treatment and evaluation for at least 6 months will be studied

Treatment schedule: Clomiphene citrate (Clomid(R)) will be supplied by the William S. Merrell Company as will placebo tablets which are indistinguishable. Patients will be randomly selected to begin treatment with either clomiphene citrate or placebo. After the initial selection the patients will remain in the same treatment group for 3 months whereupon they will be switched to either clomiphene citrate or placebo for an additional 3 month period. In this manner each patient will serve as her own control with half of the patients receiving placebo medication during the first 3 months and clomiphene citrate during the second 3 months and vice versa.

All patients will be instructed that they are candidates for treatment with a fertility medication, will be given counselling regarding the side effects and potential complications of clomiphene citrate and will be given the option of receiving the drug. Furthermore, the use of placebo medication during part of the study will not be discussed nor will the exact drug to be used be mentioned. The desirability of continuous basal temperature records and endometrial biopsies in the early post ovulatory period will be stressed.

The treatment schedule and patient choice outlined conforms with the manufacturers approved labeling. It is hoped that 100 patients can be included in this study in order to obtain statistically significant data. A minimum of three years is anticipated to attain this number of qualified candidates for treatment

PROGRESS

(71 05 - 72 05) - Anovulatory patients who have no demonstrable pathology and 18 months of infertility are being studied with clomiphene citrate and placebo using double blind technique to evaluate Clomid (R) as to its effectiveness in inducing ovulation Each patient serves as her own control by receiving 3 months of the placebo and 3 months of Clomid(R) in double blind technique. Since spontaneous abortions would appear to be more frequent in Clomid(R)-induced pregnancies than in pregnancies occurring after spontaneous ovulation, plasma progesterone and 17-hydroxyprogesterone levels will be determined between the 20-25th days of ovulatory cycles, then weekly for 7 weeks for patients who conceive on therapy It is expected that 100 patients will be studied. As yet data is insufficient for making any conclusions Nine patients have thus far been included in the study

STATUS: Ongoing.

62110A 3A062110A826 00

TITLE: In vitro Demonstration of Homocytotropic Antibody for the Schultz-Dale Method.

WORK UNIT NO: 71/386

PRINCIPAL INVESTIGATOR: Leonard S. Hoffman, MAJ, MC

TECHNICAL OBJECTIVES

To develop and perfect in vitro methods to demonstrate immune reactions contributing to clinical illness.

METHOD

Fresh monkey ileum will be obtained from the Regional Primate Center at the University of Washington. The tissues will be incubated with selected patient's sera, then tested in the Schultz-Dale system with dilutions of suspected antigens.

A similar evaluation will be done using guinea pig ileum, plus the additional procedure of passively transferring the patient's antibodies intravenously prior to sacrifice of the guinea pigs.

The patients to be studied are those with suspected allergic diseases but with negative or equivocal skin tests, such as weak tests or delayed tests Twenty mls of whole blood will be removed via venapuncture with the serum removed and frozen until tested

PROGRESS

(71 03 - 71 10) - This study has been terminated due to ETS of principal investigator.

STATUS: Terminated.

62110A 3A062110A825 00

TITLE: Gingival Hyperplasia Caused by Sodium Dilantin.

WORK UNIT NO: 70/311

PRINCIPAL INVESTIGATOR: Dennis E Holt, CPT, DC

TECHNICAL OBJECTIVES

Gingival hyperplasia is an undesirable side effect of the use of Sodium Dilantin in the control of seizures. The literature reveals that Sodium Dilantin gingival hyperplasia has been produced experimentally in only two animal species, female ferrets and cats. There have been no reports of any attempt to produce the condition in monkeys An attempt will be made to produce gingival hyperplasia in monkeys which, if successful, would provide an additional experimental model.

METHOD

Ten Macaca nemestrina monkeys are to be used in this investigation. Preoperative study casts will be made of each monkey along with color, intraoral photographs of the anterias labial and right and left buccal surfaces. Knotches will be cut on the facial surfaces of the crowns of the maxillary right second premolar, maxillary left central incisor, maxillary left first molar, mandibular left second premolar, mandibular right central incisor and mandibular right first molar. Measurements will be made on the mesial facial, mid-facial and distal facial areas of these teeth from the marks to the gingival crests, and from the gingival crests to the depths of the gingival crevices. Due to the death of one monkey during quarantine, only nine monkeys will be used in this investigation. Four monkeys will be used as controls and five will be placed on a daily regimen of orally administered diphenylhydantoin sodium 25 mg b.i d. for eighteen months. The monkeys will be coded to allow for a double-blind study At the end of that time, identical examinations to those preoperatively will be made with the additional procedure of biopsies taken of the interproximal gingiva between the upper left central and lateral incisors of each monkey. This will enable us to evaluate histologically any evidence of epithelium and/or collagen hyperplasia in addition to clinical observations

PROGRESS

(71 09 - 72 05) - To date, all final examinations have been made and biopsies taken The data is in the process of analysis A paper will be written when all data has been compiled and analyzed

STATUS: Ongoing

62110A 3A062110A826 00

TITLE: Production of Monospecific Leukocyte Typing Antisera by Selective Immunization and Immunosuppression

WORK UNIT NO: 71/390

PRINCIPAL INVESTIGATOR: Paul B. Jennings, MAJ, VC

TECHNICAL OBJECTIVES

This project is designed to produce a monospecific lymphocyte typing serum in mice utilizing the initial stimulus of pregnancy selective immunization and immunosuppression.

METHOD

C57BL/6J$^{(H\text{-}2^b)}$ male mice will be mated to virgin C57BR/cdJ$^{(H\text{-}2^k)}$ female mice. One fertilized ovum will be transferred to each of several pseudo-pregnant virgin C57BR/cdJ female mice. It is hoped that this stimulus of one pregnancy will produce a low level of anti ($H\text{-}2^b$) antibody in the C57BR females. These females will then be immunized (skin grafts, lymphocyte injections) with cells or skin from hybrid mice containing H-2 antigens, b,d,k, simultaneously with a tolerance producing dose of cyclophosphamide. It is hoped that this immunological "trick" will produce a high titered anti ($H\text{-}2^b$) serum only in the C57BR/cdJ mice.

PROGRESS

(71 10 - 72 05) - Techniques have been developed for sedation of mice for skin grafting, and splenectomy for lymphocyte collection using a fentanyl-droperidol combination. A new tail skin grafting technique has also been developed. Mice were able to tolerate a single dose of 200 mg/kg of cyclophosphamide, injected intraperitoneally, for induction of tolerance.

The inbred strains of mice were ordered and the breeding program was begun in October 1971. However, because of the variable winter weather and lack of availability of a temperature-controlled environment, the entire colony succumbed to several overnight episodes of low temperature. Therefore, the project is temporarily suspended until improvements in facilities can be arranged.

STATUS Ongoing

62110A 3A062110A826 00

TITLE: Investigations of the Etiology and Pathogenesis of Acute Glossitis of Military Dogs in Southeast Asia.

WORK UNIT NO: 71/392

PRINCIPAL INVESTIGATOR: Paul B. Jennings, MAJ, VC

TECHNICAL OBJECTIVES

To determine the etiology and pathogenesis of Acute Glossitis (Red Tongue), a recently described condition of military dogs in the Republic of Vietnam.

METHOD

The lesions of Red Tongue are loss of lingual papillae, epithelial vacuolization, and mononuclear cell infiltration of the lamina propria. The natural condition appears to be related directly to sunlight exposure and other unknown factors. An attempt will be made to reproduce and study the natural condition in a laboratory environment.

PROGRESS

(71 04 - 72 04) - A radiation chamber has been constructed which will provide a constant, hot, humid environment with 8-12 hours of artificial sunlight. German Shepherd dogs have been exposed to the sunlight plus several potential photosensitizing agents An acute lesion similar to the natural condition has been produced by exposure to artificial sunlight Preliminary studies with the photosensitizing agents tetracycline and iodine have not produced a more severe lesions. Studies are presently underway to define the more chronic form of Red Tongue and produce a mononuclear cell infiltrate.

STATUS: Ongoing

62110A 3A062110A826 00

TITLE: Antigenic Specificity of Leukocyte Antibodies Formed During the First Pregnancy.

WORK UNIT NO. 71/391

PRINCIPAL INVESTIGATOR. Paul B Jennings, MAJ, VC

TECHNICAL OBJECTIVES

This study is intended to determine what percentage of primiparous and multiparous females in an American hospital setting contain isoantibodies against lymphocyte antigens In women where such antibodies are demonstrable, the specificity of such antisera will be tested to see whether primipara produce more useful lymphocyte typing reagents, i.e., sera recognizing only one lymphocyte antigen. Using a heteroantibody technique an attempt will be made to increase the sensitivity of the lymphocytotoxicity testing system. Finally, a lymphocyte typing capability will be developed for human clinical and experimental use at Madigan General Hospital.

METHOD

The lymphocytotoxicity test will be developed according to the methods of Terasaki. Primiparous and multiparous sera will be collected from women at the Madigan General Hospital Obstetrical Service at their six-week postpartum examination. Standard human lymphocyte typing sera will be acquired from the National Institutes of Health

PROGRESS

(71 10 - 72 05) - To date, sera have been collected from 126 multiparous women, and 53 primipara Of the first 60 multipara tested, 40% had detectable lymphocytotoxic antibodies Sera from a few of these women on initial testing seem to be monospecific Studies are in progress to test the specificity of the primiparous sera.

NIH has provided 53 lymphocyte typing sera and the laboratory of E D Thomas at the University of Washington has provided 35 typing sera for the Madigan program.

A heteroantibody system is being tested to see whether augmentation of the lymphocytotoxicity test will allow detection of previously undetectable antibody.

The lymphocytotoxicity test is working well and typing of some hospital patients has been possible. Two military families where renal transplantation is a distinct possibility have been typed in conjunction with the Department of Medicine, Madigan General Hospital. Screening of hospital patients with neoplastic and autoimmune disease has been initiated to see if correlation exists between disease and specific HL-A antigens.

STATUS: Ongoing.

62110A 3A062110A826 00

TITLE: HL-A Antigens in Human Autoimmune and Neoplastic Disease.

WORK UNIT NO: 72/311

PRINCIPAL INVESTIGATOR: Paul B. Jennings, MAJ, VC

TECHNICAL OBJECTIVES

To determine the frequency of occurrence of the various HL-A antigens in a large population of human patients with autoimmune and neoplastic disease

METHOD

A large population of autoimmune disease patients (150+) is available from the University of Oregon Medical School Arrangements have been made with the University of Oregon Medical School to obtain blood samples from these patients. Special blood transport bags will be provided so the University may send the blood to the Clinical Research Service for lymphocyte typing. Samples will be provided from the autoimmune disease patient population as well as from a control population for that area. Initially, typing will be performed without prior knowledge of the patients condition (to prevent bias) After completion of the typing procedures, results will be compared with the patient diagnosis and statistical analyses will be performed.

Simultaneously, lymphocyte typing of patients with various neoplastic diseases will be performed using the Madigan General Hospital population A large control population will also be included

PROGRESS

(72 04 - 72 05) - None

STATUS: Ongoing.

62110A 3A062110A826 00

TITLE: An Evaluation of the Uses of Diagnostic Ultrasound in Obstetrics and Gynecology

WORK UNIT NO: 71/388

PRINCIPAL INVESTIGATOR: Peter R. Kesling, CPT, MC

TECHNICAL OBJECTIVES

The rationale of ultrasonic diagnostic procedures is well established. Several proven techniques have been derived. The place of diagnostic ultrasound in Obstetrics and Gynecology, however, has yet to be fully delineated. The ultrasound research effort will be directed in three areas.

METHOD

The three ultrasound research efforts are: 1. The study of fetal development and obstetric pathology. 2. Ultrasonography in gynecology. 3. Basic investigational ultrasonography.

This study will establish a diagnostic ultrasound section within the Department of Obstetrics and Gynecology, Madigan General Hospital. The patients will be referred to this service for the following indications: (1) All patients pregnant in a high risk category; (2) Patients with a history of or question of intrauterine growth retardation; (3) All patients for elective cesarean section for the evaluation of fetal maturity; (4) All patients with question of multiple pregnancy; (5) All patients for amniocentesis or amniography to determine placental location; (6) All patients with suspected gestational trophoblastic disease; (7) Patients with pelvic masses requiring follow-up; (8) All patients with pelvic masses, uterine or adnexal, prior to surgery; (9) Those patients under treatment with radiotherapy or chemotherapy for pelvic malignancy.

All patients evaluated in the diagnostic ultrasonography section will be recorded on duplicate study sheets; one copy of which will be placed in the patient's hospital chart, and the other copy preserved in a study file. Experience in diagnostic ultrasonography will be reviewed frequently and an OB GYN ultrasonography procedure book developed from our experience.

PROGRESS

(71 04 - 72 04) - No progress to report to date as the ultrasound equipment is not yet available due to lack of funds

STATUS. Ongoing

62110A 3A062110A826 00

TITLE. Treatment of Herpetic Keratitis by Photodynamic Inactivation (PDI) of Herpes Virus

WORK UNIT NO: 72/387

PRINCIPAL INVESTIGATOR. Steven G Kramer, MAJ, MC

TECHNICAL OBJECTIVES

Herpetic keratitis is a leading cause of disability attributable to acute infectious ocular disease The purpose of the proposed project is investigation of a new type of therapy for this disease. Favorable results have been reported using a similar treatment for Herpetic dermatitis; relief was unusually rapid in a large proportion of cases, and the incidence of recurrence was significantly reduced

METHOD

Herpetic keratitis is presently treated by IDU therapy and/or corneal epithelial scraping and cautery. These modes of therapy are known to be effective, but at least 30% of cases are therapeutic failures, the course is frequently prolonged,and recurrences are frequent.

To date, photodynamic inactivation (PDI), using neutral red dye applications followed by irradiation with visible light, has been used for dermatitis but has not been tried for keratitis The present study uses herpetic keratitis in rabbits as the experimental model. Thirty rabbits are divided into three groups of 10 animals each, and Herpetic keratitis is induced in both eyes of all rabbits. One eye of each rabbit is then treated with neutral red dye followed by light exposure; the other eye is not treated in 10 animals, treated with IDU in 10, and treated with corneal scraping in 0. All eyes are evaluated and photographed daily

It is hoped that effectiveness of a new treatment for Herpetic keratitis may be shown by this study.

PROGRESS

(72 03 - 72 05) - The onset of this study has been delayed

STATUS Ongoing

62110A 3A062110A826 00

TITLE: The Pathogenesis of Brucella canis in the Guinea Pig and the Rabbit.

WORK UNIT NO. 71/384

PRINCIPAL INVESTIGATOR: George E Lewis, Jr., CPT, VC

TECHNICAL OBJECTIVE

PART I - Guinea Pigs

The gestation period of the guinea pig and the dog are similar. The guinea pig is susceptible to other Brucella, therefore, the guinea pig will be evaluated as a suitable biological model for studying Brucella canis.

METHOD

Eight guinea pigs (6 female, 2 male) will be serologically and culturally tested for Brucella canis. Two females will be serviced by one male and then orally inoculated with a culture suspension of Brucella canis. Two other females will be serviced by one male and 20 days following service will be orally inoculated with a culture suspension of Brucella canis. The two remaining females will be orally inoculated but not serviced.

Serological and cultural examinations will be performed on the three groups of females at routine intervals A histopathological study of the tissues of the six females will be made.

PROGRESS

(71 05 - 72 04) - Eight guinea pigs were inoculated with large numbers of viable Brucella canis organisms Six of eight guinea pigs developed significant serum titers but only two of these six were hemoculture positive for Br. canis. Two of the pregnant females late aborted or early welped Feti were organ tissue positive for Br. canis Adult female to adult male transmission of of the organism in question was not detected

TECHNICAL OBJECTIVE

PART II - Rabbits

The pathogenesis of Brucella canis has not been well studied in the rabbit. Due to a short gestation period and a year-round breeding season, the rabbit

will be evaluated as a suitable biological model for study of pathogenesis of Brucella canis.

METHOD

Fourteen rabbits (12 females and 2 males) will be serologically tested for the presence of Brucella canis. The blood of these rabbits will be cultured for Brucella canis. Four females will be serviced by the two male rabbits. After servicing, the females will be orally inoculated with a suspension of Brucella canis. At this time four non-serviced females will also be orally inoculated with suspension of Brucella canis. Serological and cultural examinations will be performed on both groups of four rabbits at routine intervals after oral inoculation.

PROGRESS

(71 05 - 72 04) - All inoculated rabbits were experimentally infected with Brucella canis as demonstrated by positive hemocultures and the presence of significantly high serum titers to Br. canis. Titers ranged from 1:100 to 1:3300. Few gross lesions were noted at postmortem examination of the sacrificed rabbits. Microscopic tissue pathology is presently being evaluated.

STATUS: Ongoing.

62110A 3A062110A826 00

TITLE. A Transmission Study of Brucella canis in the Canine.

WORK UNIT NO: 71/383

PRINCIPAL INVESTIGATOR: George E. Lewis, Jr., CPT, VC

TECHNICAL OBJECTIVES

To investigate the transmission of Brucella canis from infected male dogs to culturally and serologically clean female dogs. Investigate the transmission of the Brucella organism by infected female dogs to culturally and serologically clean male dogs By serological and cultural techniques, follow the development and recession of the disease in the affected dogs. To make a histopathological study of the sampled tissues. Compile needed research data on the pathogenesis of the organism in the canine.

METHOD

Ten dogs were inoculated by various routes with Brucella canis. Weekly blood samples were examined for the presence to Brucella canis organisms and agglutinins The animals were sacrificed at various intervals and samples of all tissues were collected for cultural and histopathological examination.

PROGRESS

(71 11 - 72 05) - Ten beagles, 5 male and 5 female, were inoculated by various routes (oral, preputial, vaginal) with live suspensions of Brucella canis. Serological and hemo culture responses were monitored weekly for 12 to 14 months post inoculation All females inoculated were subsequently bred by clean males and aborted during the last quarter of gestation. The time and maximum extent of titer appearance, peak, and recession was easily predictable as was the time of abortion

Preliminary data indicates a low frequency of natural contraction of Br. canis infection by genital contact of infected female and clean male dogs. The possibility of female to female transmission of Br canis via a genital-oral route seems more likely in a kennel environment Bone marrow culture, tissue culture and microscopic examination results are presently being evaluated.

STATUS: Ongoing.

62110A 3A062110A826 00

TITLE. A Survey of a Segment of the Human Population for the Presence of Detectable Brucella canis Antibodies.

WORK UNIT NO. 71/382

PRINCIPAL INVESTIGATOR: George E Lewis, Jr , CPT, VC

TECHNICAL OBJECTIVE

To serologically survey the serum of approximately 2,500 to 3,000 male Army recruits for the presence of detectable Brucella canis antibodies.

METHOD

Excess serum previously collected, as well as similar collections in the future, for a renal glycosuria study will serve as the source of human serum.

Standard tube agglutination tests will be performed on the serum samples for the presence of detectable Brucella canis antibodies.

PROGRESS

(72 01 - 72 05) - A serological survey of 1,208 male military recruits, ages 18-26 was made to detect titers to Brucella canis, a known canine and occasional human pathogen The agglutination test procedure used proved reliable in the detection of Br. canis antibodies. A titer of 1:100 or greater was considered "positive" and of significance

Two specimens demonstrated 1.100 titers and two demonstrated 1:200 titers for Br. canis. One sample was positive at a 1:400 dilution for Br. canis. Twelve hundred and three of the sera tested were negative for Br. canis agglutins

Although the incidence of significant titers reported is low, the mere fact of their detection may be of epidemiological importance.

A manuscript reporting findings has been accepted for publication by the American Journal of Public Health

STATUS: Completed

62110A 3A062110A826 00

TITLE. Penicillin Treatment of Gonorrhea in Active Duty Male Personnel at Fort Lewis

WORK UNIT NO 72/456

PRINCIPAL INVESTIGATOR: Timothy O Lipman, CPT, MC

TECHNICAL OBJECTIVES

To determine the optimal dose of parenteral penicillin to use in the treatment of gonorrhea This was done with the understanding that the Center of Disease Control (C D C), Atlanta, Georgia, was changing its recommendations for treatment of gonorrhea.

METHOD

All soldiers seen in the Venereal Disease Clinic with a positive history of urethritis will have a brief history taken, then have a gram strain and a culture plated. All soldiers with positive gram stains will be divided into three treatment groups based upon serial number. Individuals allergic to penicillin will be eliminated from these groups There will be three treatment schedules of penicillin All cultures will be positively identified for N gonorrhoeae, subcultured, and stored in special horse serum at 70°C. One week post-treatment (3 days for RVN returnees) each soldier will have repeat examinations with intermittent history and repeat gram stain, if necessary. All soldiers will have repeat urethral cultures All pre- and post-treatment urethral cultures will be analyzed for minimal-inhibitory concentration of penicillin, i e , testing for penicillin sensitivity before and after treatment All patients who are treatment failures with regimen 1 or regimen 2 will be given regimen 3 All treatment failures with regimen 3 will be given a different antibiotic Definitive cure will be taken as a negative culture

PROGRESS

(72 01 - 72 05) - This study is currently in abeyance because (1) the C.D.C. has recently revised its recommendations for treatment of gonorrhea, and (2) decreased enlisted strength working for the Preventive Medicine Service has necessitated curtailment in activities of the Venereal Disease Clinic

STATUS: Ongoing.

62110A 3A062110A826 00

TITLE: Asymptomatic Gonorrhea in Vietnam Returnees

WORK UNIT NO: 72/459

PRINCIPAL INVESTIGATOR: Timothy O. Lipman, CPT, MC

TECHNICAL OBJECTIVES

To study the prevalence of asymptomatic gonorrhea in a young adult male population

METHOD

Over a 3-month period, as part of the ETS physical examination, a urethral culture and sexual history will be obtained from active duty personnel who have just returned from Vietnam or Korea.

PROGRESS

(71 12 - 72 05) - Total Cultured: 1655. Number Admitting Sexual Relations Overseas ("at risk" population): 1314

	NUMBER	PER CENT OF TOTAL POPULATION	PER CENT OF POPULATION "AT RISK"
Total number positive N gonorrhoeae cultures	33	1.98	2.51
Asymptomatic	12	0.75	0.92
Asymptomatic plus aniatrotropic(urethral discharge without being aware of it)	18	1.08	1.37

In order to determine whether these data were unique only to soldiers returning from overseas, a group of domestic, active duty personnel underwent a similar examination Results are as follows:

TOTAL CULTURED. 493

	NUMBER	PER CENT OF TOTAL
Total positive N gonorrhoeae	9	1.82
Number asymptomatic	7	1 42

	NUMBER	PER CENT OF TOTAL
Number antiatrotropic (discharge without knowing it)	2	0.41
Number symptomatic	0	----

Results are being prepared for publication.

STATUS. Ongoing

62110A 3A062110A826 00

TITLE: Comparison of Fetal Acid-Base Status in Normal and Pitocin Induced Labor.

WORK UNIT NO: 71/369

PRINCIPAL INVESTIGATOR: Thomas O. McCann, MAJ, MC

PRINCIPAL OBJECTIVES

To compare fetal acid-base balance in normal spontaneous labor and Pitocin-induced labor

METHOD

Fifty primigravida patients undergoing pitocin induction of labor for premature rupture of membranes will comprise the study group. Only patients with normal antepartum course and at term will be included. In addition, 50 normal primigravida patients undergoing spontaneous labor at term will be studied as controls.

Each patient will have maternal and fetal blood sample taken at 5-6 cm dilatation This will be repeated at full dilatation and a cord segment will be clamped at delivery and acid base determinations done on umbilical artery and umbilical vein blood Each labor will be monitored so that comparisons of intensity, frequency and duration of contractions can be assured. This data will be correlated with acid base status and fetal outcome as determined by Apgar score

Anesthesia management will depend upon the individual case and would be expected to be comparable in the two groups

PROGRESS

(70 09 - 71 12) - Terminated due to the ETS of the principal investigator.

STATUS: Terminated.

62110A 3A062110A826 00

TITLE: Comparison of Mono-Vacc Tuberculin Test and Tuberculin Tine Test using Mantoux as Standard

WORK UNIT NO: 70/368

PRINCIPAL INVESTIGATOR: William P. Morgan, LTC, MC

TECHNICAL OBJECTIVES

To compare the Mono-Vacc tuberculin test with the tuberculin tine test utilizing the Mantoux (PPD-5TU) as the standard. Factors such as percentage of false positives, percentage of false negatives, ease of administration and interpretation will be compared.

METHOD

Subjects for this study will be approximately 2500 individuals entering active duty at U.S. Army Reception Station, Fort Lewis from 15 August to 15 September 1970. On day number one of processing week each individual entering active duty on above dates will receive the Mono-Vacc test, Mantoux, and Tuberculin Tine test The Mono-Vacc test will be applied to the right mid-forearm, the Tuberculin Tine test to the lower right forearm and the Mantoux to the upper left forearm

All tests will be read 72 hours after administration. The Mono-Vacc and Tuberculin Tine test will be read and recorded before the Mantoux site is bared to avoid prejudice. The reactions will be recorded in terms of millimeters of induration measured in the transverse direction. The Mantoux test will be considered positive if a reaction of 10 mm or greater of induration is present The Mono-Vacc test will be considered positive if any degree of induration is present The Tuberculin Tine test will be considered positive if 2 mm or more induration is present at any of the four tine contact points Data will then be compiled to interpretation between Mono-Vacc Tuberculin test and Tuberculin Tine test

PROGRESS

(70 07 - 71 12) - Mono-Vacc and TTT compared very closely in all areas. However, the proportion of false positives which are generated by the

Mono-Vacc test is slightly greater and the number of individuals which fall into the weakly reactive group requiring retesting appears to be greater using the Mono-Vacc test also. Therefore, Mono-Vacc does not have any clear-cut advantages over the TTT as an initial screening procedure at least as far as our purposes are concerned. In fact, one of our problems is the large number of false positives and weakly positive reactions with the Tine test. The data indicates that this situation would not be improved by adopting the Mono-Vacc as the primary screening test

STATUS: Completed.

62110A 3A062110A825 00

TITLE: Effects of Iontophoresis on Secondary Dentin Formation in Rat Molars.

WORK UNIT NO: 71/313

PRINCIPAL INVESTIGATOR: Donald H. Newell, LTC, DC

TECHNICAL OBJECTIVES

That electric current stimulates the formation of secondary dentin has been presented as one theory of the mechanism of desensitization of hypersensitive dentin with iontophoresis. To date no study has accurately documented this statistically. The purpose of this investigation will be to measure with a calibrated micrometer any histologic changes in secondary dentin in rat molars treated by iontophoresis. The effects of variations in the number of treatments, and in time intervals following single treatments will be studied.

METHOD

Forty female, albino rats between the ages of 110 and 120 days will be divided into two groups of twenty rats each. Random selection will be utilized. The animals in Group I will be treated as follows: Three quadrants each will receive one iontophoresis treatment at the first operation while the fourth will be left untreated as a control. One week later two of the previously treated quadrants will receive a second treatment, and one week later, one of the previously treated quadrants will receive a third treatment. The rats will be sacrificed one month after the last treatment. Over a six week period each animal will serve as its own control plus experimental teeth with one, two, and three treatments with iontophoresis. Utilizing random selection, the animals in Group II will be treated as follows: Three quadrants in each animal will receive only one iontophoresis treatment spaced at intervals of one month and two weeks apart, while the fourth quadrant will be left untreated as a control. Each animal will be sacrificed two weeks following the last treatment. Each rat will serve as its own control, two weeks, one month, and two months postoperative specimen. The sections will be coded for a double-blind study; the first molars serially sectioned in a buccal-lingual plane, and stained with hematoxylin and eosin and Mallary's connective tissue stain. The zones of secondary dentin will be measured with a calibrated micrometer.

PROGRESS

(70 11 - 72 05) - To date all animals have been operated. Results are inconclusive and several technical difficulties make it impossible to give a valid interpretation.

STATUS: Ongoing.

62110A 3A062110A825 00

TITLE: Secondary Dentin Formation in Rat Molars and Incisors Treated with Iontophoresis.

WORK UNIT NO: 72/314

PRINCIPAL INVESTIGATOR. Donald H. Newell, LTC, DC

TECHNICAL OBJECTIVES

A histologic evaluation of the pulps of rat molars will be instigated utilizing calibrated measurements to confirm or refute previous visual but unmeasured observations of increased secondary dentin formation in rat molars and incisors treated with iontophoresis Secondary dentin formation is a suspected, but unproven, mechanism by which iontophoresis accomplishes desensitization of hypersensitive root surfaces of teeth

METHOD

Thirty rats will be used for the study. They will receive a specified dosage of tetracycline to mark a reference point in the dentin of the teeth; one administered at start of the project and a second administered at the termination. Iontophoretic treatment will be administered to the facila surfaces of the incisors and first molars In each rat, one quadrant will serve as control, one will receive an application of current with a 1.4% solution of sodium fluoride, one will receive an application of current with normal saline, and the last quadrant will receive the sodium fluoride with no current. The animals will be sacrificed at two week and four week intervals. The incisor and first molar from each quadrant will be dissected from the jaws and their surrounding hard and soft tissues. Histologic sections of the teeth will be viewed under ultraviolet light and the zones of secondary dentin measured with a calibrated micrometer

PROGRESS

(71 08 - 72 05) - To date, all animals have been operated and measurements recorded. The inclusion of incisors in the experiment was dropped due to the continued eruption of these teeth with rapid, continuous physiologic formation of secondary dentin, and the close proximitry of the right and left incisors to each other rendering isolation of specific treatments more difficult Statistical evaluation of the results remains to be accomplished before the final writing

STATUS: Ongoing

62110A 3A062110A826 00

TITLE: A Comparison of Colposcopic-Directed Biopsies versus Cone Biopsies in Diagnosis of Carcinoma of the Uterine Cervix.

WORK UNIT NO: 70/308

PRINCIPAL INVESTIGATOR: George P. Pettit, CPT, MC

TECHNICAL OBJECTIVES

Primary - Comparison of colposcopic directed biopsies to cone biopsies of the cervix regarding their accuracy in diagnosing carcinoma in situ and invasive carcinoma of the uterine cervix. Relation of colposcopic findings to cytologic and histopathologic findings in cervical disease. Development of a method whereby colposcopic directed biopsies may be substituted in many instances for cone biopsy of the cervix.

Secondary - Resident education in newer diagnostic procedures in cervical neoplasia. Evaluation of possibility of reducing outpatient and operating room time in accurate evaluation of patients with cervical neoplasia by use of the colposcope. Evaluation of the possibility of eliminating cervical conization in appropriately selected patients.

METHOD

Patients with suspicious or positive for malignancy cervical vaginal smears will be given a special clinic appointment at which time colposcopic evaluation of the cervix-uteri will be performed. A clinical colposcopic impression will be given. Colposcopic-directed biopsies will be obtained from abnormal areas. If there is any question regarding the colposcopic findings, or if colposcopy is unsatisfactory in delineating the lesion, the patient will undergo cone biopsy of the cervix. The findings from the colposcopic-directed biopsies will be compared with the findings at cone biopsy to determine whether colposcopic-directed or cone biopsy are more accurate in pinpointing and determining the extent of carcinoma of the cervix-uteri.

Colposcopic-directed biopsies that are negative for severe dysplasia will be followed up by Pap smears at three month intervals. If any of these smears show dysplasia the patient will be returned for a colposcopy re-evaluation and possible cone biopsy of the cervix in cases of severe dysplasia.

PROGRESS

(70 04 - 72 03) - Colposcopic evaluation was suitable in 85% of the patients examined. In none of these patients was the conization histopathology more than one grade more severe than the directed biopsy histopathology.

At each colposcopic examination, a judgment was made whether or not the colposcopic examination was satisfactory, i.e., (1) was the lesion entirely seen without extension up the canal, and (2) was the lesion less than 25% of the cervical surface. These criteria were suggested to eliminate sampling errors.

All histologic material was classified by the chief pathologist without clinical history or knowledge of which biopsies correlated with which conization.

Fifty-two patients were examined in the study. In eight patients (15.4%), the colposcopic examination was judged to be unsatisfactory by the above criteria. However, in one of these patients, the biopsy showed invasive squamous cell carcinoma, thereby eliminating the need for conization. In the seven remaining patients the conization specimen revealed significantly greater histopathology in four patients, demonstrating the importance of adhering to the criteria for a satisfactory colposcopic examination.

In seven patients a diagnosis of invasive squamous cell carcinoma was made. In the routine evaluation of the submitted biopsy material, the pathologist suggested invasive cancer in two patients but felt he could not unequivocally diagnose invasion. The chief pathologist in reviewing this material under the above protocol did diagnose invasive cancer in both biopsy specimens. No patients had minimal stromal invasion during this study period.

Twelve patients had carcinoma in situ and twelve had severe dysplasia. We believe that it is proper to consider these two subgroups as one for handling of this data. Five of these patients were classified as colposcopically unsatisfactory. In the remaining patients with diagnoses of severe dysplasia and carcinoma in situ the directed biopsy diagnosed the worst lesion in all cases except one in whom the directed biopsy was moderate dysplasia and the conization specimen was severe dysplasia. We do not feel that this diagnostic discrepancy is significant.

Reviewing the compared histologic interpretations of the remaining patients showed that the conization was never more than one histologic grade more severe than the directed biopsy histopathology.

Publication by previous investigators - Donohue, L.R., and W. Meriwether. Amer J Obstet Gynec 113:107-110, May 1972.

STATUS: Ongoing.

62110A 3A062110A826 00

TITLE: Evaluation of Droperidol in Pregnant Patients in Labor.

WORK UNIT NO: 71/379

PRINCIPAL INVESTIGATOR: George P. Pettit, CPT, MC

TECHNICAL OBJECTIVES

The purpose of this double-blind study is to compare the use of Droperidol 5 mg with Phenergan 50 mg with regard to their sedative effect on normal patients in labor.

METHOD

Physicians will select patients on admission and write on the order sheet "STUDY GROUP," which will number 300.

Medication will be ordered as follows:

a. Tranquilizer order will be written "STUDY" tranquilizer, 2 cc I.M.

b. Demerol order will be written "Demerol 50 mg I.M." and repeated as necessary.

c. "a" and "b" may be combined for a single I.M. administration.

d. Tranquilizer order will not be repeated sooner than five hours (repeat by "straight" Phenergan).

Study tranquilizer selection will be by consecutively numbered prepared syringes.

Excluded Patients - Patients with a medical disease, i.e., diabetes, hypertension, or complication of pregnancy, i.e., toxemia, will be excluded. Patients receiving caudal anesthesia will be excluded.

The patients responses will be evaluated by questionnaire and record review. The attending physician will complete one set of questions and the patient will complete another set on the first postpartum day.

The infants will be evaluated by the Nursery staff. At birth and at one hour of age, blood gases will be obtained. There is no test available to detect droperidol in the maternal or fetal blood.

PROGRESS

(71 12 - 72 04) - Currently more than 100 patients have been studied and the observations recorded on these patients have been submitted for computer analysis. Upon receipt of analysis, findings will be compiled.

STATUS: Ongoing.

62110A 3A062110GA826 00

TITLE: Effect of Intramuscular Medication on Serum Enzymes.

WORK UNIT NO. 69/098

PRINCIPAL INVESTIGATOR. Frank S Pettyjohn, LTC, MC

TECHNICAL OBJECTIVES

To determine the effect of intramuscular medication in usual dosage and by commonly used needle size on serum elevations of CPK, SGOT, SGPT, Aldolase, and LDH

METHOD

A total of 50 patients were evaluated for serum enzyme response to include CPK, SGOT, SGPT, LDH, and Aldolase Various needle sizes and medications as well as normal saline were evaluated and serial collections were made Laboratory values were obtained utilizing the C F Boehringer and Soehne test system Values obtained were not statistically applicable to determine an accurate trend

Attempts to apply this enzyme determination system to other clinical situations, i e , pregnancy rate, post-surgery, documented the lack of adequate range for statistical application

PROGRESS

(71 03 - 71 12) - Conclusions Effects of intramuscular medication in fifty patients utilizing various needle sizes, saline and various medications produced limited change in enzymes by the Boehringer and Soenne test system. No definite trends in enzymes were established

STATUS. Completed

62110A 3A062110A826 00

TITLE: Surveillance Study of Mycoplasma and Other Microorganisms in Hospitalized Pneumonia Patients.

WORK UNIT NO. 70/353

PRINCIPAL INVESTIGATOR. Frank S. Pettyjohn, LTC, MC

TECHNICAL OBJECTIVES

To determine the incidence of M. pneumoniae infections of hospitalized pneumoniae patients in a military general hospital and to provide surveillance of viral agents present in pneumonia patients to include Adenovirus, Influenza A and B, and respiratory syncitial virus.

METHOD

Each admission to the Pneumonia Ward with a diagnosis of pneumonia by clinical symptoms and/or X-ray findings will be evaluated within 24-48 hours of admission.

The following specimens will be obtained: Throat culture in special viral/M. pneumoniae media; admission acute serum; and a follow-up "convalescent serum specimen" will be obtained at 12 to 21 days or at time of discharge.

The primary ward routine history, physical and laboratory studies will remain as dictated by the Pulmonary and Infectious Disease Service. Clinical data will be obtained from the "routine" hospital chart.

Serum specimens will be stored at -20°C; throat specimen will be stored at -70°C. All specimens will be transported to the University of Washington Mycoplasma and Viral Laboratories weekly by the principal investigator. All data will be collected and stored on standard computor data cards and continually analyzed during course of study.

PROGRESS

(71 03 - 72 05) - The study was performed from December 1969 to May 1971 Paired sera and throat cultures were collected on patients hospitalized with

a primary diagnosis of pneumonia. Mycoplasma pneumonia was present in 5 to 20% of the cases with an average of 8%. There was either serological or cultural evidence of mycoplasma pneumonia infection every month of the 18 months of this study, therefore, it would appear that mycoplasma pneumonia is endemic in the recruit population at Fort Lewis, Washington, with a peak incidence in the winter months.

Adenovirus infection was present in most of the months of the study. The overall number of serological rises was substantially less in the winter of 1971 than in December 1969 and January 1970. Only a few sera showed antibody rises in the influenza A or B in the winter of 1971.

CONCLUSIONS: 1. M. pneumonia is endemic in hospitalized pneumoniae patients ranging from 5-20% in a recruit population with an average of 8%.

2 Peak number of M pneumoniae cases occur in the winter months.

STATUS: Completed.

62110A 3A062110A826 00

TITLE. A New Diagnostic Malaria Blood Smear Technique.

WORK UNIT NO: 69/311

PRINCIPAL INVESTIGATOR. Frank S Pettyjohn, LTC, MC

TECHNICAL OBJECTIVES

To compare diagnostic significance of routine thin malaria smears with a new technique of thin smear utilizing the red blood cell layer immediately subjacent to the buffy coat of a centrifuged hematocrit tube.

METHOD

All patients admitted to the Infectious Disease and Pulmonary Service with the diagnosis of malaria suspected or proven, and fever of unknown origin, will be studied. A minimum of twenty patients with Plasmodium Vivax and, if available, twenty patients with Plasmodium Falciparum will be studied. Capillary blood will be obtained by sterile lancet from the finger. Venous blood will be obtained by vacutainer. The heparinized micro hematocrit tubes will be centrifuged for two to three minutes to provide adequate buffy coat layer. The vacutainer will be centrifuged for three to five minutes to provide adequate buffy coat layer. A pipette will be utilized to obtain the desired level of red cell for the smear. Giemsa stain will be utilized on all slides. Interpretation of the smears will be made by the following personnel and scoring recorded on form: Clinical Pathologists, Random ward physicians, and laboratory technicians both skilled and semi-skilled.

PROGRESS

(71 03 - 72 04) - Thirty-five complete sets of four slides each have been reviewed as unknown by separate skilled laboratory technicians.

In thirty sets of vivax smears, a venous buffy coat smear from the vacutainer collection was selected as best in 60%. In five sets of Falciparum smears again 60% were selected from the vacutainer prepared smears but the number is limited. The hematocrit prepared smear was selected in only 23%. Of five control sets, no false positives were obtained. CONCLUSION: A standard vacutainer containing EDTA centrifuged for two minutes and a smear made of red cell layer immediately subjacent to the buffy coat was selected in 60% of the cases studied. This would appear to be of benefit to the active ward physician who desires to draw blow rapidly and prepare a slide later in a proper laboratory facility. Additionally, it would be of benefit to have an unskilled nurse or technician obtain a vacutainer sample as opposed to the skill required to make a satisfactory thin blood smear for malaria.

STATUS. Ongoing

62110A 3A062110A826 00

TITLE. Effect of Propranolol on Electrocardiogram Changes Due to Central Nervous System Disease.

WORK UNIT NO: 72/395

PRINCIPAL INVESTIGATOR: Frank S. Pettyjohn, LTC, MC

TECHNICAL OBJECTIVES

To determine the effect of propranolol, a Beta adrenergic blocking agent, on the electrocardiogram change of central nervous system disease, primarily subarachnoid hemorrhage.

METHOD

A total of five patients were given intravenous propranolol. In three patients with subarachnoid hemorrhage, no changes in ST-T were noted after propranolol injection. In two patients with a tachycardia, one with occasional nodal beats, propranolol slowed the rate and decreased the frequency of arrhythmia. Two additional patients, one with brain stem contusion, and one with a cerebral hemorrhage, minor ST-T changes were noted

PROGRESS

(71 08 - 72 04) - Conclusions A total of five patients with ST-T changes possibly related to central nervous system disease received varying doses of intravenous propranolol as a diagnostic measure No definitive conclusions can be reached The limited number of patients and the time delay from initial injury to time of trial may be critical

STATUS: Completed.

62110A 3A062110A826 00

TITLE: Platelet Kinetics in Vivax Malaria

WORK UNIT NO. 70/100

PRINCIPAL INVESTIGATOR. H Irving Pierce, MAJ, MC

TECHNICAL OBJECTIVES

A prospective evaluation of coagulation kinetics in Vivax malaria will be instituted with the Division of Hematology, University of Washington School of Medicine, Seattle, Washington This study has been prompted by reports of a possible consumptive coagulopathy and the high incidence of thrombocytopenia noted in these patients.

METHOD

According to the protocol, any patient admitted to Madigan General Hospital in whom a diagnosis of Vivax malaria is established by blood smear, and following voluntary consent, will be transferred to the Clinical Research Center, University of Washington School of Medicine Initial drug therapy will be withheld, the patient's condition permitting, and studies including coagulation screens, assays for factors II, V, VII, and VIII, serial platelet counts, chromium platelet survivals, I^{125}-Fibrinogen and -Plasminogen turnovers, and bone marrow aspirate for megakaryocyte quantitation will be performed.

PROGRESS

(71 03 - 72 05) - To date, two patients have been thoroughly evaluated. Data can be summarized as follows The initial thrombocytopenia may spontaneously clear, despite no anti-malarial therapy In both patients, one of whom had normal platelet counts during the study period and both being symptomatically well, platelet survivals were markedly shortened (5 days and 2 days), and fibrinogen survivals were 1/2 normal, with increased turnover rates Coagulation screens were normal Repeat survival studies during low-dose Heparin therapy demonstrated a normalization of the fibrinogen and plasminogen survivals but not of the platelet survival All abnormalities were corrected following institution of anti-malarial therapy Preliminary evaluation of the data indicates that a consumptive process is present in Vivax malaria that may be corrected by Heparin therapy even in the asymptomatic individual with mild parasitemia Further patient material will have to be studied before final conclusions can be made

STATUS: Ongoing

62110A 3A062110A826 00

TITLE Immunoassay of 3 5' Cyclic Adenosine Monophosphate in Hyperparathyroidism.

WORK UNIT NO: 72/360

PRINCIPAL INVESTIGATOR: Stephen R Plymate, MAJ, MC

TECHNICAL OBJECTIVES

To develop an immunoassay for 3'5' cyclic adenosine monophosphate and evaluate its usefulness in diagnosing hyperparathyroidism, and to evaluate the success of surgery for hyperparathyroidism.

METHOD

Develop an immunoassay for 3'5 c AMP by using the modification of the method of Steiner et al with anti 3'5'c AMP antibody obtained from collaborative research

Obtain pre- and post-surgical urine samples from patients with hyperparathyroidism and measure 3'5'c AMP in these samples.

Obtain urine samples from patient with hypercalcemia from causes other than excess PTH and measure them for 3 5 AMP

PROGRESS

(72 01 - 72 04) - Preoperative and postoperative urines have been obtained on seven patients with parathyroid adenomas All parathyroid adenomas have been confirmed by surgery The radioimmunoassay using I^{125} labelled cyclic AMP and commercial ant body obtained from collaborative research as well as antibody prepared locally in rabbits is in the process of being developed. The estimated date of completion of this study is July 1972

STATUS Ongoing

62110A 3A062110A826 00

TITLE: The Use of Azathioprine in Medical Diseases.

WORK UNIT NO: 71/374

PRINCIPAL INVESTIGATOR. Robert H Reid, MAJ, MC

TECHNICAL OBJECTIVES

The purpose of this study is to monitor the immunological response in patients being treated with azathioprine

METHOD

Patients with alleged immunologically mediated medical diseases will be utilized The selection of patients for this study will be determined by clinical indications, following clinical evaluation by the primary care physician; however, for a given patient to enter this study, approval must be given by the principal investigator

The dosage of azathioprine will be between 2 and 2 5 mg/k body weight orally daily

The patients will be followed for both clinical response and possible drug toxicity at weekly intervals for one month, then at two week intervals for one month, at three week intervals for six weeks, and then at monthly intervals until taken off azathioprine The patients will be followed by this investigator either directly or indirectly through a primary care physician

The serum levels of immunoglobulin and C-3 complement will be monitored.

Humoral primary immunity will be monitored by immunizing and following the Anti-Keyhole Limpet Hemocyanin (KLH) and Anti-typhoid O and H titers. Humoral secondary immunity will be monitored by following the Anti-A and/or Anti-B isoagglutinin titers

Cellular primary immunity will be monitored by immunizing and challenging with 2,4-dinitrochlorobenzene (DNCB) and KLH Cellular secondary immunity will be monitored by following the intradermal skin tests with trichophytin candida and mumps antigens Also, the secondary cellular immunity will be monitored with the use of the Rebuck window technique

PROGRESS

(70 12 - 72 04) - This protocol has not been active for several reasons:

(1) the principal investigator was reassigned as a permanent change of station,
(2) azathioprine was not used except for the several patients begun previous to the activation of this protocol

It is anticipated that this protocol will become more active since the original principal investigator has been recently reassigned back to this installation.

STATUS: Ongoing.

62110A 3A062110A826 00

TITLE. Immunological Evaluation and Treatment of Impaired Cellular Immunity in Chronic Mucocutaneous Candidiasis

WORK UNIT NO. 72385

PRINCIPAL INVESTIGATOR. Robert H Reid, MAJ, MC

TECHNICAL OBJECTIVES

Immunological evaluation and treatment of impaired cellular immunity in chronic mucocutaneous candidiasis

METHOD

The patient's mother, who has a strong cellular immunity to candida, will donate 500 cc s of whole blood, to be collected in a sterile evacuation bottle with heparin added The plasma with leukocytes will be separated from the red cells and the polymorphonuclear leukocytes removed by passage through non-absorbent cotton The lymphocytes then will be concentrated into a volume of 5 mls of enriched media All these manipulations will be done under sterile conditions The lymphocytes are then frozen and thawed 10 times and incubated with DNA At that time the lysed cellular material will be dialyzed against distilled water for four days The dialysate is then lyophilized and stored at 20 C until it is to be given to the patient at which time it will be reconstituted into 2 mls of the distilled water and resterilized by passage through a millipore filter One cc of the sterile material will be injected subcutaneously into the patient

The patient will be followed clinically by Dr Reid After eight weeks, the patient s cellular immune system will be reevaluated in vitro by lymphocyte stimulation assay and migration inhibition factor assay to avoid the possibility of immunizing her with skin tests; after the in vitro evaluation, the patient will be followed by skin testing in addition to the clinical response

PROGRESS

(71 10 - 72 04) - A 23 year old, Caucasian female, was evaluated and found to have no cellular immunity to candidiasis both in skin testing and in vitro testing Transfer factor was prepared from the patient s mother who did demonstrate cellular immunity to candidiasis on skin testing and in vitro testing This transfer factor was administered to the patient with conversion of her skin test to positive The skin test subsequently reverted to negative; however, there was no reexacerbation of her mucocutaneous candidiasis

STATUS Ongoing

62110A 3A062110A826 00

TITLE: Lymphocyte Culture Assay for Demonstration of Tumor Immunity in Man.

WORK UNIT NO. 72/371

PRINCIPAL INVESTIGATOR: Robert H. Reid, MAJ, MC

TECHNICAL OBJECTIVES

To determine if the lymphocyte culture assay, a more rapid immunological approach, will produce the same information as the colony inhibition technique provides.

METHOD

Tumor tissue will be obtained at the time of resection in the operating room. The tumor tissue will be carried to the pathologist, who will decide that a tissue specimen can be spared for the study The tumor will be put into a cell suspension, with cell division blocked by a treatment with Mitomycin C, and placed into culture tubes with peripheral lymphocytes from the patient. The collection and isolation of lymphocytes requires approximately 25 ml of whole blood taken by venipuncture. After three days in culture, the lymphocyte DNA is tagged with tritiated thymidine; and 18 to 20 hours later, the cultures are stopped, precipitated with trichloracetic acid, solubolized, and placed into counting vials The samples are then counted in a Beta-Scintillation counter Also, the ability of the patient's serum to block the lymphocyte response will be determined

The importance of this study is two fold. Firstly, the clinical prognosis of the patient with a malignant tumor might be determined within a seven-day period; and secondly, the patient's immunological response to his/her tumor might well be taken into consideration in regards to future cancer chemotherapy or possible immunotherapy.

PROGRESS

(72 04 - 72 06) - This study has been reactivated due to the reassignment of the principal investigator to this installation

STATUS: Ongoing

62110A 3A062110A826 00

TITLE. Natural History of Acute Pneumonias in a Military Population

WORK UNIT NO 70/360

PRINCIPAL INVESTIGATOR. Mark E Reinecke, MAJ, MC

TECHNICAL OBJECTIVES

To define the etiology of an acute pneumonic process Additionally, there is a need to better define as well as determine the incidence of hypoxemia in association with an acute pneumonic process

METHOD

One hundred twenty five pneumonias admitted to the Pulmonary disease Service will be evaluated in a prospective manner The definition of the etiologic agent will be attempted in the following manner' Sequential blood cultures, sputum cultures; gram stain of sputum specimen These will be reviewed by the investigators as well as an independent observer and an attempt will be made to correlate this with the final bacteriologic results. Acute and convalescent sera for Mycoplasma pneumoniae, Adenovirus, Respiratory syncitial virus; influenza virus, A & B, Hemophilus influenzae; Pneumococci; and ASO titer will be obtained with the acute taken within the first 24 hours admission and the convalescent 21 days thereafter A questionnaire will be completed by each participant

PROGRESS

(71 03 71 03) This study has been terminated due to ETS of the principal investigator

STATUS Terminated

62110A 3A026110A826 00

TITLE The Role of Intermediate Antitrypsin Levels in the Etiology of Emphysema.

WORK UNIT NO 70305

PRINCIPAL INVESTIGATOR Mark E Reinecke, MAJ, MC

TECHNICAL OBJECTIVES

To correlate alpha-1 protein on electrophoretic determinations with trypsin inhibitory capacity to the incidence, severity, and type of pulmonary disease.

METHOD

Serum will be drawn and frozen in duplicate specimen on a large number of normal persons Serum samples will also be drawn and frozen on the Chest Clinic population at Madigan General Hospital Normal sera will be sent to the University of Oklahoma Medical Center where the amount of alpha-I antitrypsin activity will be determined by an immunophoretic technique. Serum from the Chest Clinic population will also be assayed in the same manner. Serum from the Chest Clinic population will be assayed in addition by a routine serum electrophoresis for purposes of determining the amount of alpha-I protein The technique of acid starch gel electrophoresis for the separation of pre-albumen, allowing accurate determination of the normal intermediate and homozygote state of antitrypsin deficiency, has been perfected

PROGRESS

(71 03 - 71 12) Routine electrophoresis with serum protein was performed on approximately 120 serum specimens from the Chest Clinic searching for cases of homozygous deficiency The anticipated number of cases in this population was approximately one case, no cases were found

STATUS. Completed

62110A 3A062110A826 00

TITLE. The Evaluation of Post-Episiotomy Pain

WORK UNIT NO. 72/457

PRINCIPAL INVESTIGATOR Robert E Rogers, COL, MC

TECHNICAL OBJECTIVES

This study investigates possible differences in post-episiotomy pain in two groups of patients, (1) patients whose episiotomies have been repaired with 3-0 chromic catgut, (2) patients repaired with 3-0 Dexon (polyglycolic acid) suture

METHOD

Subjects for this study will be patients delivered at Madigan General Hospital. Sutures supplied to operators will be chosen in a random method by opening envelopes containing either polyglycolic acid suture or 3-0 chromic catgut The type of suture used will be recorded on the study sheet but not on the hospital record Other than the random assignment of suture, the patient will receive routine obstetric care, providing her with standard anesthesia and analgesia

In the postpartum period, the patient will be given analgesia slips for the purpose of requesting analgesic medication and documenting the site and degree of pain Analgesia slips will be imprinted with the patient's name. There will be provisions for listing the site of discomfort and the degree of discomfort on a scale of 1 to 4 All patients delivered will be given analgesia slips regardless of whether they had an episiotomy or not

The study will be terminated after 1,000 patients with episiotomies have been evaluated For the ease of evaluation we would anticipate 500 patients in each suture group The non-episiotomy patient analgesia slips will be evaluated to provide "non episiotomy controls"

PROGRESS

(71 11 - 72 04) - The first groups of patients were studied shortly after the first of March 1972 Approximately a hundred patients have been studied to date The data are being evaluated No trend has been noted to date

STATUS. Ongoing

62110A 3A062110A826 00

TITLE: Placental Alkaline Phosphatase and Oxytocinase.

WORK UNIT NO: 71381

PRINCIPAL INVESTIGATOR. Francis R. Sacco, MAJ, MC

TECHNICAL OBJECTIVES

Objective methods of assessment of the fetus and placenta have become increasingly important in modern obstetrics especially in the high-risk pregnancy. At present, estimation of urinary estriol is the most generally used and reliable test of feto-placental function. Estriol assay is, however, complicated by frustrating collections for the patient as well as difficult and expensive methods for the laboratory. In an effort to discover a more simple and reliable indicator, two placental enzymes have been evaluated in maternal sera.

METHOD

Heat stable alkaline phosphatase and oxytocinase were serially measured in fifty-five controls and in groups of patients in various high risk categories (including diabetes, toxemia, chronic hypertension, and apparent poor intrauterine growth) over a fourteen month period.

PROGRESS

(71 05 - 72 05) - Control sera generally showed a predictable rise in values from 32 weeks to term. There was a considerable spread in the values of individual patients especially close to term. Several patients also showed unpredictable and unexplained variation in values from week to week.

In the high risk groups, there was no consistent pattern differentiating the abnormal patients from the normal controls. There was also no consistent predictability at the onset of complications. Isolated patients, in some cases, showed abnormal patterns.

Although a statistical analysis has not been completed at this point, we feel that following heat-stable alkaline phosphatase and oxytocinase activity on a weekly basis has shown little merit in predicting or managing a high risk pregnancy.

STATUS: Ongoing.

62110A 3A062110A826 00

TITLE: Clinical Study on the Usefulness of Isosorbide for the Continued Reduction of Intracranial Hypertension.

WORK UNIT NO: 69/308

PRINCIPAL INVESTIGATOR: Robert G. Scherz, COL, MC

TECHNICAL OBJECTIVES

Isosorbide, an effective, nontoxic, oral, osmotic diuretic in man, has been demonstrated to reduce intracranial pressure in animals and man. This project is a clinical study of the usefulness of isosorbide for the continued reduction of intracranial hypertension.

METHOD

All cases of hydrocephalus, myelodysplasia, or children with increased intracranial pressure (whether from fluid accumulation or from cerebral edema secondary to infection, trauma, etc) referred will be accepted. Neurosurgical evaluation will be required and provided to rule out potentially surgically correctable lesions such as brain cyst, benign brain tumor, hydrocephalus with a pressure in excess of 200 mm og VCSFP, and so forth. Complete physical examination with appropriate special studies will be utilized to establish as accurately as possible the extent of central and peripheral neurological damage and an accurate diagnosis. In the absence of obvious danger (central nervous system infection, open infected myelodysplastic lesions, cerebral edema, etc), air contrast studies will be obtained to define architecture of the central nervous system. Cases will be matched as nearly as possible for diagnosis, degree of progression of hydrocephalus, level of VSCFP, degree of CSF leakage, secondary complications, age, sex, social situation, and unassociated organic complications.

PROGRESS

(71 07 - 72 05) - During the reporting period there have been no suitable patients admitted to the hospital for inclusion in the study. In July 1972, the initial principal investigator will return to take over the study.

STATUS. Ongoing.

62110A 3A062110A826 00

TITLE: Evaluation of Child-Resistant Containers for the Prevention of Accidental Poisoning.

WORK UNIT NO: 69/095

PRINCIPAL INVESTIGATOR. Robert G. Scherz, COL, MC

TECHNICAL OBJECTIVES

The estimated number of childhood poisonings in the United States each year approaches 4,000,000. Most of these poisonings (80-90%) occur among children under the age of 5 years The estimated annual number of poisonings among the 3,000,000 child dependents of military sponsors of all three military services ranges between 60,000 and 240,000. No exact figures are available since childhood poisonings are not reportable. When one examines the containers commonly used to package the toxic products ingested, they are found to be poor barriers to the active, inquisitive, naive child who is at greatest risk. It is the purpose of this study to evaluate the effectiveness of child-resistant containers.

METHOD

The military and dependent population in the Madigan and McChord area will be the source of a mixed sampling We will study the effectiveness of various child-resistant containers, "failure" of the test container, attachment of the test container to proprietary medications sold in the Post Exchange system, the effect of long term use of child-resistant containers on childhood poisoning rates due to prescription tablets and capsules, and a search for a suitable child-resistant container for liquids.

PROGRESS

(71 05 - 72 04) . This project has been very active during the last 12 months. In Phase I studies (screening and formal studies of special packaging with panels of normal children and adults), 20 screening studies have been done and 9 formal studies have been completed The screening and formal studies have been useful to the Bureau of Product Safety in H.E.W., in evaluating and confirming the usefulness of our protocol as a method for determining what is or is not a safe child resistant package. These studies have also been of value to industry in establishing standards and developing improvements to make their packages more effective The formal studies will be useful in the future for comparison with Phase II, or clinical experiences.

CLINICAL STUDIES:

1. Children's aspirin sold in local post exchanges and commissaries in special packaging. This has been a successful project. There continues to be a very low incidence of children's aspirin poisoning reported from aspirin sold in local post exchanges and commissaries. Only two were identified from that source compared to 12 in the preceding 12 months. Also, there was a decrease in poisoning from flavored aspirin from all sources to 10 compared to 49 the previous year. This was attributed to the general use of effective safety packaging for aspirin sold in civilian stores during the last 12 months.

2. Safety packaging of prescription tablets and capsules. During the reporting period there have been only 5 childhood poisonings treated at Madigan General Hospital from prescriptions dispensed in safety packaging, involving four containers. In each instance, the poisoning occurred because of failure of the parent to use the container properly. There were no hospitalizations or deaths from prescription poisonings dispensed in safety containers. During the reporting period approximately 230,000 containers were used to dispense drugs from the Madigan, McChord, and Fort Lewis pharmacies.

Madigan General Hospital now has a five-year experience with safety packaging of prescription drugs. During this period, over 75,000,000 safety packages have been purchased for use throughout the Federal pharmacy systems. At Madigan General Hospital, the expected number of poisonings prevented are approximately 200 per each 1,000,000 containers used. By extrapolation, the total number of childhood poisonings from prescriptions prevented directly with the use of safety packaging by the Federal Government during the last five years has been approximately 15,000.

The five-year summary will be prepared for publication and presentation at the annual meeting of the American Association of Poison Control Centers, New York, 16 October 1972.

STATUS: Ongoing.

62110A 3A062110A826 00

TITLE: Chromosome Analyses of Children with Multiple Congenital Malformations.

WORK UNIT NO: 69/312

PRINCIPAL INVESTIGATOR: Robert G. Scherz, COL, MC

TECHNICAL OBJECTIVES

To evaluate infants and children with multiple congenital abnormalities and to correlate phenotypic expression with gross chromosome abnormalities.

METHOD

Chromosome preparations were made from peripheral blood cultures of lymphocytes. Karyograms were prepared by laboratory technicians and cytogenetic analyses performed by the investigator.

PROGRESS

(69 05 - 72 01) - During the reporting period, 18 children have been studied with a variety of congenital anomalies. No new, not previously reported, chromosomal abnormalities have been found. The studies have been most useful in genetic counseling of parents who have infants and children with Down's syndrome. Since the Department of Pathology is now able to provide an adequate service for the preparation of chromosomes from peripheral blood, and karyograms of a quality useful for screening, there is no need at this time for continuation of this project. There have been no new patients introduced into this study for the last 16 months. We do not anticipate adding additional patients in the foreseeable future. The karyograms of the final three patients studied with abnormal karyograms, listed below, are typical of the types of chromosomal abnormalities reported.

1. Laurie DeCarlo, 45 chromosomes, XO - a typical "Turner's" syndrome.

2. Maria Compton, 45 chromosomes, XO - "Turner's" syndrome.

3. Infant DeJournett, XY and XX, trisomy 21, 47 chromosomes - a mosiac XX, XY with a trisomy 21, is an unusual finding; however, it has been presented previously.

STATUS: Completed.

62110A 3A062110A826 00

TITLE: Child Restraint Systems for Prevention of Motor Vehicle Injuries and Death.

WORK UNIT NO: 71/367

PRINCIPAL INVESTIGATOR: Robert G. Scherz, COL, MC

TECHNICAL OBJECTIVES

To determine whether or not techniques for instructing parents and children in a Well Child Clinic will increase compliance with recommendations to purchase and use child restraint systems in motor vehicles.

METHOD

The population for study will include the infants and children of parents who attend the Well Child Clinic. To be selected for study, the parent and child will be expected to be in the Fort Lewis-McChord area for at least six months. In the pilot study, 500 infants and children will be studied (100 children in each of five groups).

Group 1. Display of approved restraint systems for infants from birth through the age of 10 years.

Group 2 Display as above with a handout that lists (a) ages of infants and children; (b) appropriate restraint for age where (specifically) the restraint can be purchased; and (c) approximate cost of restraint

Group 3. Display and handout - with the handout given to parent by the secretary when making an appointment for next visit.

Group 4. Display and handout - with the handout given by the Well Child Clinic nurse during her normal patient visit - accompanied by a brief question period, safety message and specific recommendation (estimate not more than 2 minutes).

Group 5. Display and handout - with the handout given by the Well Child Clinic physician during the normal patient visit - accompanied by a brief question period, safety message, and specific recommendation (estimate not more than 2 minutes).

Follow-up correspondence in the form of a letter survey, with telephone confirmation when appropriate, will be done at one month and two months following entrance into the study.

PROGRESS

(71 05 - 72 04) - The most effective time to influence young parents to purchase safe systems for young infants, is before the birth of the infant, not after. However, in late infancy, after 6-8 months of age, parents can be effectively stimulated by displays, literature, and conversations with either the Nurse Clinician or Pediatrician in the Well Child Clinic to obtain child restraint systems that are effective, 65-70% of those studied. In all groups, there is a consistent 20-30% who, despite efforts so far expended, see little reason for altering their unsafe practices for transporting infants and children in the family automobile. We are awaiting an educational film produced by the Department of Transportation for use in our Outpatient and Well Child Clinics, to see whetner it will influence parental compliance.

STATUS: Ongoing.

62110A 3A062110A826 00

TITLE: Prolonged Pregnancy - Diagnosis by Amniocentesis.

WORK UNIT NO: 70/364

PRINCIPAL INVESTIGATOR. Robert K. Smith, MAJ, MC

TECHNICAL OBJECTIVES

To pursue the analysis of the amniotic fluid in an effort to establish and correlate laboratory and clinical criteria for the diagnosis of prolonged pregnancy and/or postmaturity. It is hoped that this would help spotlight those potential cases of postmaturity from the "normal" prolonged pregnancies.

METHOD

Patients with recorded gestation of 41 weeks + will be seen for evaluation by a member of the study group Chart review with effort to determine validity of dates, abdominal and pelvic examination to determine fetal life, attitude, condition of cervix, amnioscopy if possible, depending on state of cervix, amniocentesis on all patients, will be performed routinely. If meconium is present patient will be admitted for induction of labor with intrapartum fetal monitoring, if no meconium, manage expectantly. Induction of labor will be done only if meconium is present or other evidence suggests postmaturity, i.e., scant fluid, no fluid, uterine size decrease If gestational age of 43+ weeks is reached, biweekly follow-up with amnioscope and amniocentesis will be done. Total estrogens will be followed biweekly on a selected group when the technique becomes available to us Pregnancies of 42 weeks duration plus would have amnioscopy where possible and amniocentesis performed for the following tests: Nile blue sulfate stain, creatinine, protein, and character of amniotic fluid on gross examination D&C when done on the SMA-12 will give the fringe benefit of ten other tests. The amnioscopy and amniocentesis will be repeated biweekly until delivery and a sample of fluid during labor will also be analyzed. Note: Normal values at other states of pregnancy are being established for Madigan General Hospital by amniocentesis done for Rh incompatibility establishing fetal maturity prior to cesarean, and diagnosis of third trimester bleeding.

PROGRESS

(72 01 - 72 05) - Of 89 patients studied from September 1970 through August 1971, eight were induced for what was felt to be post maturity. This diagnosis was made by combined amnioscopy and amniocentesis on all patients after 42 weeks gestation. Positive findings were meconium staining of the amniotic fluid. Amnioscopy was falsely negative or impossible in five of the eight. Amnioscopy was thus felt to be unreliable as a sole means of evaluation.

STATUS: Completed

62110A 3A062110A826 00

TITLE: A Study of Production and Prevention of Stress Fractures with Emphasis on Shock Absorbing Pads.

WORK UNIT NO: 70/362

PRINCIPAL INVESTIGATOR: Donald H. Tilson, LTC, MC

TECHNICAL OBJECTIVES

To give a numerical profile of the average inductee; to give a numerical profile of the inductee who has stress fractures; to study the effects, if any, of a shock absorbing heel pad on the incidence of stress fractures; to study the effects of weight gain or weight change on stress fractures; and to study racial difference in stress fracture formation. The above mentioned numerical index would include height, weight, age, physical activity ratio.

METHOD

The method will include standardization of training procedures; gather information at the Reception Center, X-ray unit, dispensary and control information center. There will then be a conclusion and discussion of information gathered.

PROGRESS

(71 03 - 71 12) - No progress to report. Study terminated.

STATUS: Terminated.

62110A 3A062110A826 00

TITLE: Measurement of Renal Clearance of Isoniazid at Varying Urine Flow Rates.

WORK UNIT NO: 72/446

PRINCIPAL INVESTIGATOR: John M Olivia, MAJ, MC

TECHNICAL OBJECTIVES

The studies of isoniazid metabolism indicate renal excretion is the major factor in its elimination, however, the degree to which its excretion can be affected by urine flow rates has not been analyzed. The literature would indicate that in cases of poisoning due to isoniazid, dialysis should be performed, yet it might be possible to eliminate the drug very effectively by forced diuresis Also, the degree to which the dosage of the drug should be altered in the presence of renal disease needs to be clarified

METHOD

Patients with normal renal and liver function who are receiving isoniazid for PPD conversion or in the therapy of tuberculosis will be studied. These patients may be studied as outpatients

They will take 300 mg INH at bedtime and 300 mg upon arising. They will then report to the ward fasting at 0900

At time zero the patient voids and blood is drawn for creatinine, urea nitrogen, uric acid and isoniazid

At one hour the patient voids and urine volume measured and aliquot analyzed for creatinine, urea nitrogen, uric acid and isoniazid. Another blood sample is drawn The patient then ingests 15 ml/kg tap water

At 90 minutes and 2 hours urine is collected and blood drawn for similar analysis

This data will allow calculation of clearances of creatinine, urea, uric acid and isoniazid The clearances can then be correlated with urine flow rate

PROGRESS

(71 08 - 72 04) - Two patients have been studied for the effects of urine flow rates on excretion of INH with the following results:

	INH Clearance (cc/min)	Urine Flow (cc/min)
Patient A	4.3	0.67
	4.6	0.67
	20.50	2.50
Patient B	47.4	1.58
	29.75	3.40
	33.4	11.60

No conclusions can be drawn from the data at this time.

STATUS: Ongoing.

62110A 3A062110A826 00

TITLE. Evaluation of a Simple Screening Technique for the Detection of Lipid Abnormalities.

WORK UNIT NO: 72/458

PRINCIPAL INVESTIGATOR: Angel M. Vazquez, COL, MC

TECHNICAL OBJECTIVES

To set up a simple screening procedure for the detection of lipid abnormalities. The proposed method is a modification of the procedure of Burnstein and others. It is based on the fact that beta and pre-beta lipoproteins are precipitated from serum by the combination of heparin and some of the divalent metal ions.

METHOD

The analysis is carried out on serum specimens. The blood specimens may be obtained in the fasting or postprandial state as food ingestion does not significantly alter the PLP number. The blood should be allowed to clot then should be promptly centrifuged and separated. The sera may be stored at refrigerator temperature (not frozen) for as long as 7 days without change in PLP number

The PLP number is obtained by quantitating the change in suspension concentration following the precipitation of beta and pre-beta lipoprotein from a calcium chloride solution with heparin Therefore, a serum blank and serum test solution are used They are handled in an identical fashion except that heparin is added to the test solution

Two large test tubes containing 50 cc each of 0.025 M $CaCl_2$ are prepared. One cc of the heparinized test solution is added to one test tube, while 1 cc of the serum blank solution is added to the other. Both are inverted three times. The nephelometer is zeroed against the $CaCl_2$ solution. The serum blank and the serum sample are then read

The PLP number is determined by subtracting the nephelometric reading of the serum blank solution from the serum test solution. The method is highly reproducible with less than 2% variation on multiple repeat readings of the same specimen

PROGRESS

(71 11 - 72 04) - Employing the nephelometric technique, we are evaluating a simple screening method for the detection of lipid abnormalities. This method consists of the determination of the serum PLP number. The PLP number for serum is obtained by quantitating the change in suspension concentration following the precipitation of beta and pre-beta lipoprotein from a calcium chloride solution with heparin We have started to collect data from the adolescent population seen at the Pediatric Adolescent Clinic

STATUS: Ongoing

62110A 3A062110A825 00

TITLE: Endodontic Therapy with Delayed Canal Obliteration.

WORK UNIT NO: 72/315

PRINCIPAL INVESTIGATOR: Christian Vikari, MAJ, DC

TECHNICAL OBJECTIVES

The primary objective of this study is to establish a simple treatment procedure to save periapically involved teeth from extraction prior to a soldier's departure to an overseas theater. The second objective is to avoid liability to the United States Government for tooth replacement in case of extraction in the Armed Forces, even beyond separation. The third objective is to show if periapical healing can be expected under conditions as outlined in the study

METHOD

All restorable endodontically involved teeth will be restored to establish good physiologic contour, relationship and seal. These teeth then will be treated endodontically by vigorous chemomechanical canal preparation The teeth will be medicated and sealed with appropriate materials. Final obliteration of the canals will be accomplished not earlier than one year from the date of initial therapy. Pre- and postoperative roentgenograms will be taken, as well as films at regular intervals during that year to monitor periapical response. Each patient will also be monitored with an oral examination at the time of the radiographic examinations for symptomatic conditions.

This study is to be conducted (a) on selected permanent party individuals projected to remain at Fort Lewis for the next 1-2 years and (b) on individuals who can be followed up during the study even though they transfer from this post.

PROGRESS

(72 01 - 72 03) - No progress to date.

STATUS: Ongoing.

62:10A 3A062110A825 00

TITLE. Interceptive Endodontics

WORK UNIT NO. 72,389

PRINCIPAL INVESTIGATOR Christian Vikari, MAJ, DC

TECHNICAL OBJECTIVES

To show the advantages of preservation of teeth previously extracted under the heading "non-restorable Caries". Advantages include saving of chair time for dentist, saving of lost duty time for patients, decrease of post-operative complications; increased patient protection due to decreased requirement for the use of drugs; duty availability of patient immediately after treatment; decrease in U S Government liability for tooth replacement; and improved image of U S Army Dental Corps

METHOD

Civilian Routine:

I Examination and Triage
- A Classification of Conditions
  - 1 Asymptomatic
    - a Referral to oral hygiene instruction and plaque control, prophylaxis.
    - b Controlled patient referral for definitive treatment.
  - 2 Symptomatic
    - a Non-endodontic
    - b Endodontic
      - (1) Dentinal pain
      - (2) Pulpitis (vital, non-vital)
      - (3) Swelling.

II Endodontic Therapy
- A Dentinal pain - large carious lesions
  - 1 Excavate - removal of infected dentin
  - 2 Indirect pulp cap
  - 3 IRM
- B Pulpitis
  - 1 Reversible
    - a Excavate
    - b Indirect pulp cap
    - c IRM (intermediate restorative material).
  - 2 Irreversible
    - Begin Endodontic Treatment.
- C Swelling
  - 1 O&D, begin endodontic treatment
  - 2 I&D

III Oral hygiene and plaque control, prophylaxis after patients are comfortable (asymptomatic).

IV Routine definitive care after control.

V Recall for clinical and radiographic follow-up.

A 8 weeks
B 6 months
C 12 months

PROGRESS

(72 03 - 72 04) - No progress to date.

STATUS: Ongoing.

62110A 3A062110A826 00

TITLE: Lymphocyte Stimulation in Intrinsic Asthma.

WORK UNIT NO: 72,396

PRINCIPAL INVESTIGATOR: Clarence M. Virtue, LTC, MC

TECHNICAL OBJECTIVES

The etiology of intrinsic asthma is not completely understood. The cellular immune response of these patients has not been fully explored. It has been postulated by several investigators that intrinsic asthma may be an autoimmune phenomenon. If so, these patients may exhibit an abnormal response of their cellular immune system when challenged with extracts of their own tissue.

METHOD

This experimental project was designed to explore the *in vitro* response of lymphocytes from patients with intrinsic asthma when challenged with smooth muscle extract. The lymphocyte stimulation is carried out in vitro using a modification of the Bach technique. The reaction tubes are pulsed at day 6 with 2 uc of tritiated thymidine. The reaction tubes are harvested on day 7 using TCA precipitation followed by NCS solubilization and assay is subsequently performed by liquid scintillation counting.

PROGRESS

(7108 - 7204). The first phase of the experimental protocol was a screening of *in vitro* lymphocyte response upon challenge with a crude smooth muscle extract. Thirteen patients with intrinsic asthma and 13 normal controls have been examined to date by the in vitro Lymphocyte Stimulation Assay challenge using crude smooth muscle extract. The data has been analyzed by setting up ratio responses and statistically comparing the ratio response of the control with that of the responses from patient specimens. To date, the ratio response of the control reaction tubes has been 1.27, whereas, that of the patient responses has been an average ratio of 1.7, overall. While there does appear to be a slight increase of responsiveness in the patient section, the order of significance is low. Therefore, it would appear that there is not a marked significant difference in the reaction of patients when compared to controls upon *in vitro* lymphocyte challenge with crude smooth muscle extract. The second phase of the experimental design is to purify the smooth muscle extract by selective centrifugation to isolate the cell wall and lysosomal fractions and to challenge *in vitro* with this fraction of the smooth muscle. This phase of of the experimental protocol is now being processed.

STATUS: Ongoing

62110A 3A062110A826 00

TITLE: The Effect of Freezing, Thawing, and Frozen Storage on the Serum Proteins of the Canine.

WORK UNIT NO: 72/452

PRINCIPAL INVESTIGATOR: Elaine R. Wedral, Ph.D.

TECHNICAL OBJECTIVES

To quantitatively determine the effect of freezing on the serum proteins of the canine. This will be determined by (1) the amount of protein fragmentation; (2) the alteration of electrophoretic protein separations; (3) the quantitative changes in the albumin and Alpha 1, Alpha 2, Beta 1, Beta 2, and gamma globulins; and (4) the quantitative changes that occur in immunoglobulin G.

METHOD

Fifteen control dogs, 8 males, 7 females, will be studied. Two blood samples (A&B) will be drawn from each dog. After serum separation, all serum will be tested for total protein; electrophoretic separation and quantitation of albumin; Alpha 1; Alpha 2; Beta 1; Beta 2; and gamma globulin; quantity of immunoglobulin G; and quantity of fragmentation.

All samples (A&B) will then be stored at -10°C, one set (A) will be removed from the freezer each month for four months, allowed to warm to room temperature (23 ± 2°C), and electrophoretic separation and quantitation of albumin, Alpha 1, Alpha 2, Beta 1, Beta 2, and gamma globulin determined. At the end of the four month period, both sample groups (A&B) will be removed from the freezer, allowed to equilibrate to 23 ± 2°C and tested as follows. (1) Total protein as determined by 260 and 280 mm ratios and the folin-ciocalteu procedure. (2) Albumin and globulin quantitation through sodium sulfate precipitation and protein determinations as described above. (3) Quantitation of albumin, Alpha 1, Alpha 2, Beta 1, Beta 2, and gamma globulin using a Beckman microzone 161 system, cellulose acetate strips, and veronal buffer. (4) Quantitation of immunoglobulin G will be performed by immunodiffusion plates. (5) Quantity of fragmentation will be determined on G-200 Sephadex eluted with 0.01 M Phosphate Buffer pH 7.4 at room temperatures.

PROGRESS

(71 10 72 04) - It was demonstrated that freezing and thawing diminishes total protein as measured by the biuret, 280, 260 ratios and electrophoretic pattern. It was also demonstrated that the ratio of albumin to globulin increased, which may be due to protein fragmentation. The immunoglobulin G was lowered following freezing.

STATUS. Ongoing

62110A 3A062110A826 00

TITLE: Factors in Raw Oysters that Prevent Botulinum Toxin.

WORK UNIT NO: 72/447

PRINCIPAL INVESTIGATOR: Elaine R. Wedral, Ph.D.

TECHNICAL OBJECTIVES

Many times when a new food product or method of preservation is developed, the potential dangers from Clostridium botulinum and its production preclude immediate military or industrial application. There has been no investigation of the chemical properties of the oyster which might prevent C. botulinum toxin production

METHOD

Oysters will be homogenized and protein separations performed. Study the effect of the active fraction on the growth kinetics and metabolism of Clostridium and other organisms through supplementation of synthetic media with the fraction. Use commercially prepared protein of similar nature to attempt to induce a similar suppressive response. Ultimate protein fragment identification through mobility rates, denaturation patterns and amino acid sequence determination.

PROGRESS

(71 08 - 72 01) - Arrangements were made with the Microbiology Section, Department of Fisheries, Seattle, Washington, to perform all toxin assays at their facility. Oysters to be grown in non-polluted environment in tanks and will be harvested, irradiated, and homogenized.

Work unit not started due to the departure of the principal investigator.

STATUS: Terminated.

62110A 3A062110A826 00

TITLE. Comparison of Feto-Maternal Hemorrhage in Suction and Sharp Curettage in Termination of Pregnancy.

WORK UNIT NO: 71/387

PRINCIPAL INVESTIGATOR: Dennis A. Wight, MAJ, MC

TECHNICAL OBJECTIVES

Studies which have demonstrated an increased incidence of transplacental passage of fetal cells after curettage have all utilized traditional (sharp) methods. There has been no study of the percentage of fetal cells entering the maternal circulation after suction curettage. There has been no controlled study of the passage of fetal cells comparing suction to sharp curettage.

METHOD

Approved candidates for termination of pregnancy would be assigned to one of two groups, suction or sharp.

Maternal blood sample would be drawn and analyzed for fetal cells by the Kleihauer technique at the following times: Admission, immediately post-operative, four hours post-operative, and 24 hours post-operative. A total of 50 patients will be evaluated in each study group.

PROGRESS

(71 03 - 71 10) - It was necessary to terminate this study due to insufficient numbers of patients having voluntary terminations of pregnancies.

STATUS: Terminated

62110A 3A062110A826 00

TITLE: Intravenous Ethanol for the Treatment of Threatened Premature Labor

WORK UNIT NO: 70/365

PRINCIPAL INVESTIGATOR: Dennis A Wight, MAJ, MC

TECHNICAL OBJECTIVES

To determine what extent various factors as outlined in protocol play in the successful use of intravenous ethanol for treatment of premature labor

METHOD

Fuchs has shown in a series of experiments that ethanol inhibits the release of oxytocin He subsequently used intravenous alcohol to treat threatened premature labor in a number of patients and found that labor could be successfully stopped and pregnancy prolonged in 67% of treated patients In order to accurately determine the fact that the patients are in premature labor, and that the alcohol is stopping such, a Hewlett-Packard model 8020A OPT 003 cardiotocograph is necessary to monitor uterine contractions, the effect of intravenous ethanol on such, and the effect of the premature labor and alcohol on the fetal heart rate. Fuchs used a similar device and stated that it was the only way of proving the patients were in premature and not false labor

PROGRESS

(70 03 - 72 04) - Several recent articles in the literature have proven the efficacy of this study

STATUS: Terminated.

62110A 3A062110A826 00

TITLE: Evaluation of Low Dosage Combination Oral Contraceptive.

WORK UNIT NO: 72/097

PRINCIPAL INVESTIGATOR: William B. Wilson, Jr., LTC, MC

TECHNICAL OBJECTIVES

To study the efficacy, patient acceptance, and possible side effects of Norgestrel 0.30 mg, and 0.03 mg of Ethinyl Estradiol, administered cyclically as an oral contraceptive. This is a 10:1 formulation similar to Ovral but lower in milligram content (Ovral=norgestrel 0.5 mg +ethinyl estradiol 0.05 mg).

METHOD

Examinations: Initial - general history and physical examination including eye and CNS detailed gynecologic history, breast and pelvic. Patients must be seen for follow-up after the first, third, and every three month treatment cycle thereafter. All patients will be contacted by phone monthly during the study. Repeat general physical examinations will be conducted at six month intervals.

Laboratory studies: All patients will have CBC, urinalysis, and Pap smear performed in the pretreatment month and at six month intervals. In addition, 20% of the patients will have SGOT, bilirubin, serum alkaline phosphatase, BUN, FBS, performed in the pretreatment month and at six month intervals. (These patients must not have used oral contraceptives or other hormones for at least two months prior to initial laboratory determinations).

Follow-up visits: During the follow-up visit, the presence of character of menses, spotting, breakthrough bleeding, headache, abdominal pain, breast discomfort, dizziness, nausea, vomiting, weight gain or loss, edema, acne, mental depression, thrombophlebitis, change in libido, change in appetite, hirsutism, jaundice, eye symptoms, nervousness, amenorrhea, and missed pills, will be determined.

Medication: Medication will be supplied in 21 tablet calendar dispenser packages by Wyeth Laboratories. Clinical Stock Record sheets will be supplied by Wyeth in order that the investigator may keep a record of all medication dispensed. These records will be kept in duplicate; the original to be returned to Wyeth Laboratories and the copy retained on file by the investigator.

PROGRESS

(72 05 - 72 06) - None.

STATUS: Ongoing.

62110A 3A062110A826 00

TITLE: Breech Deliveries: A Five-Year Study.

WORK UNIT NO: 72/453

PRINCIPAL INVESTIGATOR: Dewey J. Yates, MAJ, MC

TECHNICAL OBJECTIVES

The place of Cesarean section in breech presentation is still an unresolved question in obstetrics. This study is a review of our experience and practice with breech deliveries at this installation as part of an attempt to resolve this problem of management.

METHOD

The study consists of a view of the inpatient records of the mothers with a breech presentation and the infants at Madigan General Hospital from 1 January 1965 to 31 December 1969. The information extracted on each patient will consist of: name, registration number, date of delivery, fetal presentation, method of delivery, infant's birth weight, pathology report (if stillborn or neonatal death), congenital abnormalities, length of labor in the first, second, and third stage, mother's postpartum course, infant's postpartum course, unusual medications taken during pregnancy, weeks of gestation at delivery, prenatal blood pressure, mother's family history, obstetric history, prenatal complications, type of anesthesia, type of analgesia for labor, type of episiotomy, mother's blood type and Rh, mother's age, infant's name and registration number.

In those patients delivered by Cesarean section, the following additional information will be obtained: type of section performed, time between initiation of anesthesia and delivery, estimated blood loss at delivery, reason for Cesarean section, and the results of pelvimetry.

Although all of the above information was initially obtained, a portion of the data was found to be not pertinent or useful.

PROGRESS

(71 10 - 72 03) - A five-year retrospective study of 311 breech deliveries is presented including 276 vaginal deliveries and 35 Cesarean sections. There

were seven stillbirths and nine neonatal deaths after eliminating twins, infants under 1000 grams and those with severe anomalies. The perinatal mortality rate was 58 per 1000 as compared to 17 per 1000 for cephalic presentation. All neonatal deaths occurred in infants under 2200 grams and most of these deaths were associated with pulmonary immaturity. Cesarean section in these small infants may not in actuality improve survival, but the high morbidity in the large infant of the primigravid mother may make a more liberal Cesarean section policy worthwhile. A combination of sodium pentothal, 50-50 nitrous oxide-oxigen and succinylcholine for patients undergoing Cesarean section provided healthy babies with high Apgar scores in difficult situations.

STATUS: Ongoing.

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