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## Abstracts of Recent Publications of the Professional Staff of the Henry Ford Hospital and the Edsel B. Ford Institute for Medical Research

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## ABSTRACTS OF RECENT PUBLICATIONS OF THE PROFESSIONAL STAFF OF THE HENRY FORD HOSPITAL AND THE EDSEL B. FORD INSTITUTE FOR MEDICAL RESEARCH

STUDIES ON THE SITES OF METABOLISM, DISTRIBUTION AND TOLERANCE DEVELOPMENT TO CERTAIN THIOBARBITURATES. ANNETTA R. KELLY, Ph.D., D.Sc. University Press, Ann Arbor, Mich., 1954. xi 110 pp., 23 illus.

Prior to 1939, the assumption was made, both by clinicians and experimentalists, that the liver constituted the main site of detoxication for the short-acting thiobarbiturate, thiopental (Pentothal). Beginning in that year, contradictory views became increasingly prevalent in the literature, and, by 1945, several reports had appeared which agreed that the liver was *not* involved in the detoxication of this thiobarbiturate. Feeling that methods employed in a number of these investigations were questionable, in 1946, studies were initiated by the author in an attempt to resolve this controversy. Portions of the work on thiopental and several other thiobarbiturates were published in ten papers in the succeeding three-year period, some in collaboration with Dr. Frederick E. Shideman. This monograph deals primarily with unpublished data and includes a chronological survey of the significant advances in the field of thiobarbiturate metabolism up to the present time. In addition to evaluating the role of the liver in the metabolism of thiopental, Surital, Thioethamyl and B-10 (5-isopropyl-5-[2-methylpentenyl-2]-2-thiobarbituric acid), studies on the plasma and tissue distributions of these compounds, as well as tolerance development and potentiation, were reported.

In *Part I*, data obtained by the following methods (five *in vivo* and one *in vitro*) definitely implicated the liver as a major metabolic site for these thiobarbiturates in man and three animal species: (1) Production of liver dysfunction in the mouse by use of an hepatotoxic agent; (2) reduction of the amount of functioning liver tissue in the rat by subtotal hepatectomy; (3) reduction of blood flow through the liver by production of an Eck fistula in the rat and dog; (4) comparison in patients with normal and decreased hepatic function; (5) comparison of rates of disappearance from plasma in the dog heart-lung, heart-lung-liver, and heart-lung-kidney preparation; and (6) *in vitro* degradation of the drug by rat liver tissue. Significantly increased durations of action of the thiobarbiturates were demonstrated with liver dysfunction produced by methods (1-4) above. Eck fistula dogs (3), in addition, showed elevated plasma levels and slower rates of removal from plasma than normal. Disappearance rates of thiopental from plasma in the intact animal, dog heart-lung, heart-lung-kidney, and heart-lung-liver preparation (5) were 12.6, 1.2, 6.2 and 15.2 per cent per hour, respectively. *In vitro* degradation (6) of thiopental by rat liver slices and mice was demonstrated.

*Part II* deals with plasma and tissue distributions of the four thiobarbiturates. Plasma time-concentration curves and anesthetic durations were obtained in dogs following single equimolar doses of the thiobarbiturates and, despite differences in side-chain structure and durations of action, they were observed to dis-

appear at identical rates. As the anesthetic duration (potency) increased, the plasma level at the point of recovery declined. Potency ratings, calculated for the thiobarbiturates by both of these criteria, were compared.

Plasma disappearance curves for various doses of thiopental were parallel, but plasma levels at recovery increased with dosage.

Concentrations of thiopental in mouse plasma, liver and kidney were determined at intervals following intravenous injection. Ratios of liver and kidney concentrations to that of the blood indicated that equilibrium occurred within one minute after injection of the drug, the liver containing a concentration almost four times that of blood and kidney twice.

*Part III* is devoted to tolerance development and potentiation in relation to thiopental. Acute tolerance to the depressant action of the drug was demonstrated in the dog. After a large dose of thiopental, the plasma level of the anesthetic at awakening was found to be significantly higher than after a small dose. After several small doses (each administered after apparent recovery from the last) increasing durations of action were obtained, and plasma levels at awakening increased with each succeeding dose.

Administration of a single daily 20 mg./kg. dose for seven days showed no evidence of tolerance or cumulation in the dog. Two doses of this size per day demonstrated marked cumulation, but also recovery at significantly higher plasma levels. Development of central respiratory tolerance with this latter dose was investigated but could not be demonstrated.

A large number of malonic and thiobarbituric acid derivatives, which were theoretically possible thiobarbiturate degradation products, were screened for ability to potentiate these thiobarbiturates. Thiourea and thiobarbituric acid were each found to potentiate thiopental but only in amounts too large to be possible degradation products.

**TUBE FEEDING WITH LIQUEFIED WHOLE FOOD.** JAMES BARRON and LAURENCE S. FALLIS. *Surg. Forum* (1953) p. 519.

This article originally appeared in this journal, 1:13, June, 1953.

**\*GROWTH AND THE METABOLISM OF GLUTATHIONE.** PAUL D. BARTLETT. *Fed. Proc.* 13:179, 1954

Implication of glutathione in the biogenesis of peptides and proteins makes the study of the metabolism of this compound in normal and induced states of growth of considerable interest. Using the method of Grunert and Phillips (*Arch. Biochem.* 30:217, 1951), we have determined glutathione concentrations in liver, tibialis anticus muscle, and blood of rapidly growing immature rats (Group I), of hypophysectomized rats (Group II), and of hypophysectomized rats stimulated with growth hormone (Group III). Glutathione determinations were made in tissue and blood obtained from each animal and average group values calculated. Liver glutathione concentrations of 169,207, and 188 mg/100gm wet tissue were thus found for Groups I, II, and III respectively; while muscle glutathione gave average

\*From Edsel B. Ford Institute for Medical Research.

values of 15.4, 12.7, and 19.2 mg/100 gm wet tissue. Blood glutathione concentrations averaged 22.6, 18.7, and 22 mg% respectively for the 3 groups of rats. In another similar series of rats, N<sup>15</sup> labeled glycine was administered intraperitoneally and the uptake of N<sup>15</sup> label determined in the liver glutathione isolated as the copper mercaptide from the pooled livers of the animals in a group. Nitrogen from the liver glutathione of Groups II and III contained approximately 3 times as much excess N<sup>15</sup> as the nitrogen from the liver glutathione of Group I rats. The rate of incorporation of the N<sup>15</sup> label of glycine in glutathione thus appears to be higher in hypophysectomized than in rapidly growing immature rats and to be unaffected by growth hormone.

**\*ACTION OF DIHYDROCHOLESTEROL ON CHOLESTEROL TYPE FATTY LIVERS.** WILLIAM T. BEHER, WILLIAM L. ANTHONY, and O. H. GAEBLER. Fed. Proc. 13:180, 1954.

Several investigators have found that soy bean sterols and dihydrocholesterol (*I*) prevent hypercholesterolemia and deposition of cholesterol in arteries of rabbits and chicks fed high cholesterol diets. We have studied the effect of *I* on deposition and mobilization of liver cholesterol, and the possible mechanism of this action, in mice. In the first series of studies, 2 groups of mice were fed diets rich in cholesterol. One group also received a fixed amount of *I*. Each group was further separated into subgroups receiving varying amounts of cholic acid. Results showed that *I* was very effective in preventing cholesterol deposition in mouse liver. Furthermore, increasing dietary cholic acid increased the effectiveness of *I* in this respect, and optimal amounts kept liver cholesterol at the control level. Our second series of experiments was concerned with the mobilization of liver cholesterol. Several groups of mice were fed diets high in cholesterol until substantial amounts of liver cholesterol had been deposited. The animals were then separated into 2 groups, one of which received cholesterol-free diet, while the other group received the same diet with the addition of optimal amounts of cholic acid and *I*. The animals were sacrificed at intervals over a 6-wk. span. The results showed that liver cholesterol decreased at about the same rate in both groups of animals. Thus, *I* was effective in preventing cholesterol type fatty livers in mice, but was ineffective in hastening mobilization of deposited liver cholesterol.

**STUDIES ON CAPILLARY RESISTANCE AFTER INTRAVENOUS INFUSIONS.** V. G. BEHRMANN, and F. W. HARTMAN. Fed. Proc. 13:10, 1954.

In an evaluation of plasma expanders evidence of decreased capillary resistance was observed following a hemorrhage-replacement technic and a massive infusion in intact dogs with dextran, polyvinyl pyrrolidone and modified fluid gelatine. Oozing of wounds and autopsy findings of hemorrhagic areas in heart, duodenum, pancreas and kidney indicated increased capillary permeability. Current studies of variations in capillary resistance associated with the administration of intravenous solutions are extended to include other solutions, larger groups of animals and man, along with appropriate counter measures for combatting abnormal capillary permeability.

\*From Edsel B. Ford Institute for Medical Research.

CRYPTOCOCCOSIS (TORULOSIS) INVOLVING THE BRAIN, ADRENAL AND PROSTATE. HAROLD E. BOWMAN and JAMES O. RITCHEY. *J. Urol.* 71:373, 1954.

Cryptococcosis is a subacute or chronic infection and the lesion may occur in any part of the body. The fungus involves primarily deep-seated organs with a predilection for the brain. The casual agent is a *Cryptococcus* (frequently called *Torula histolytica*), a yeast-like fungus reported from many parts of the world. This is a hitherto unpublished case of meningo-encephalitis due to *Cryptococcus neoformans* with lesions in the left adrenal and prostate. This case is unusual in two aspects because of the lack of lung involvement and the presence of infection of the prostate. This is the third such case reported with prostatic involvement. The total number of cases of systemic torulosis now in the literature is well over the two-hundred mark. It is hoped that with the addition of new cases to the literature from many areas the clinician will become more aware of cryptococcus infections and increase the frequency of recognition of this entity.

USE OF CORTISONE IN THROMBOCYTOPENIC PURPURA; PREOPERATIVE AND POSTOPERATIVE MANAGEMENT OF PATIENTS. BROCK E. BRUSH, RAYMOND W. MONTGOMERY, JOSEPH ABRAHAM, E. J. GORDON and J. RALPH CALDER. *Arch. Surg.* 68:787, 1954.

Twenty-one patients with idiopathic thrombocytopenic purpura who had splenectomy without mortality are presented. Cortisone was of value in the management of those in the acute phases of the disease. While corticotropin and cortisone have been disappointing as a form of treatment for patients with idiopathic thrombocytopenic purpura, they are of value in the preparation of patients for splenectomy. No ill effects from this use of cortisone could be noted, and no postoperative complications occurred. The cortisone dosage used was 200 mg to 300 mg daily for 10 days preoperatively and 50 mg to 300 mg daily for 3 days postoperatively.

THE PULMONARY ASPECTS OF POLYARTERITIS (PERIARTERITIS) NODOSA. HOWARD P. DOUB, BEN E. GOODRICH and JAMES R. GISH. *Am. J. Roentgenol.* 71: 785, 1954.

The roentgen appearance of the lung in polyarteritis nodosa is of equivocal nature. Only a few accounts have appeared in the literature, consisting of reports of one or several cases with positive lung findings. Nineteen proved cases of polyarteritis nodosa are reported. Eight autopsied cases showed characteristic lesions in pulmonary or bronchial arteries or in both. Roentgenological pulmonary abnormalities were present in six cases. These findings are not specific but may be suggestive. Major pulmonary symptoms or parenchymal roentgenological abnormalities indicate a poor prognosis.

(The following summary is from a paper) THROMBOPHLEBITIS MIGRANS AND VISCERAL CARCINOMA PRESENTED BY DR. ROBERT H. DURHAM AT THE INTERNATIONAL CONGRESS ON THROMBOSIS AND EMBOLISM HELD IN BASLE, SWITZERLAND, JULY 20-24, 1954:

Thrombophlebitis migrans is frequently the initial manifestation of obscure

visceral carcinoma. Although the growth may originate in any organ, it is more often found in the body or tail of the pancreas. This unique relationship is unexplained. Local histological and bacterial factors are not consequential, etiologically. The usual measured factors in coagulation are unchanged. These recurrent and multiple thrombi almost invariably occur in the presence of a mucinous type of carcinoma. The same coagulative phenomenon is exhibited whether the carcinoma originates in the pancreas or is metastatic to that organ. The incidence of thrombophlebitis migrans increases as the gradient of malignancy is higher. Surgical removal of the original growth usually causes cessation of the thrombophlebitis. Resistance to usual doses of anticoagulant therapy is frequently observed. Etiological interest centers around a disturbance of proteolytic and mucolytic enzyme effects. These and other challenging tangibles offer newer investigative approaches in the study of this one facet of the problem of thrombogenesis.

A review of these basic facts warrants certain clinical assumptions:

The occurrence of typical thrombophlebitis migrans in a patient in the middle or latter decades warrants a presumptive diagnosis of visceral carcinoma, until disproved.

Prompt recognition of this type of thrombophlebitis may permit detection of carcinoma months earlier than it would otherwise be discovered.

Earlier diagnosis will afford more prompt use of protective anticoagulant therapy or earlier and more successful surgical procedures.

Unsuccessful control of thrombophlebitis migrans by ordinary doses of anticoagulants should make one suspicious of the presence of carcinoma.

A better understanding of the factors concerned in thrombophlebitis migrans should throw new light on the entire problem of thrombogenesis.

A more complete analysis of the biochemical changes involved in these associated conditions should also provide simultaneously a reliable test for the presence of carcinoma—a goal for which the medical world is waiting.

Interpreters simultaneously presented the paper and the ensuing discussion to the Congress in the other official languages, French and German.

#### **FRACTURE-DISLOCATION OF THE ANKLE WITH THE FIBULA FIXED BEHIND THE TIBIA. JOSEPH L. FLEMING and HAROLD O. SMITH. J. Bone & Joint Surg. 36A:556, 1954.**

In 1947, Bosworth reported five cases of fracture-dislocation of the ankle in which the proximal fragment of the fibula became caught behind the flaring distal posterolateral portion of the tibia. In the first case, a recent fracture, reduction by manipulation was impossible. At open reduction, the reason for this was found to be the posterior displacement of the fibular-shaft fragment, which was held tightly in place behind the posterolateral tibial ridge by the tense interosseous membrane. By prying the fibula away from the tibia, reduction of the dislocation was accomplished with a loud snap. In a second case, also a recent fracture, similar treatment was used. The authors were able to treat a similar displacement

by closed reduction. To their knowledge, it was the seventh case on record, and the first to be treated by closed reduction. Detailed description of the treatment with roentgenograms is included.

**EFFECTS OF ACTH ON STRENGTH OF INTESTINAL ANASTOMOSES IN DOGS.** THOMAS GEOGHEGAN and BROCK E. BRUSH. *Proc. Soc. Exper. Biol. & Med.* 86:235, 1954.

Since the original observations by Ragan concerning the retardation of wound healing in patients by ACTH, several studies have been done dealing with this phenomenon. The investigations of Ragan, Spain, and others in rabbits and mice indicate that ACTH retards the healing of wounds. Recent experiments on skin wounds in guinea pigs and rats, and on skin wounds and cardiovascular suture lines in dogs failed to demonstrate significant differences in the healing of wounds of control animals and those treated with ACTH or cortisone. The conflict in these experimental results may be attributable to differences in the species of experimental animal, the particular tissue studies, or to the dosage of the hormone used. Suture line leakage was not observed in a series of 10 dogs given large daily doses of ACTH following end to end anastomosis of the colon. The strength of the suture lines was not significantly altered by ACTH administration as compared with non-treated controls. No correlation was evident between the amount of ACTH given and the strength or gross appearance of the anastomoses.

**TUBE FEEDING IN ORAL SURGERY.** FRED A. HENNY and JAMES BARRON. *J. Oral Surg.* 12:238, 1954.

Substantially the same material appeared in the original article—Henry Ford Hosp. *M. Bull.* 2:13, June 1953.

**THE INCREASING IMPORTANCE OF LUNG CANCER AS RELATED TO METASTATIC BRAIN TUMORS.** EDWIN M. KNIGHTS. *J. Neurosurg.* 11:306, 1954.

Pulmonary carcinoma, which very definitely seems to be undergoing an absolute increase in frequency, accounted for almost one-fourth of the metastatic tumors of the brain in this series, and must be given very serious consideration in attempting to locate the primary site of a metastatic lesion. Carcinoma of the breast, however, is the most frequent primary site in females, and accounted for exactly half of the metastases in the females in this series. The necessity of careful study of the lungs in patients showing symptoms of cerebral tumors was further emphasized by the finding of either primary or secondary cancer in the lungs of 77 of the 102 patients. Approximately 6900 autopsies were reviewed in this study.

**THE SURGICAL TREATMENT OF CARDIOSPASM; PRELIMINARY REPORT.** CONRAD R. LAM. *Texas State J. Med.* 50:13, 1954.

The term "cardiospasm" has been used frequently to indicate a benign obstructive lesion at or near the junction of the esophagus with the stomach, usually associated with marked enlargement of the esophagus. Probably because the cause is obscure, there has been disagreement concerning the name which best

describes the condition. As early as 1913 the German surgeon Heller had described his operation of extramucosal cardioplasty. This was a Ramstedt procedure at the cardiac rather than the pyloric end of the stomach. Personal experience with 18 cases of cardiospasm (mega-esophagus, achalasia, esophageal dystonia) has been presented. Cardioplasties of the Wendel type were done in 9 cases with unsatisfactory end results because of the incidence of esophagitis and peptic ulceration. Extramucosal cardiomyotomy of the type proposed by Gottstein and first performed by Heller has been carried out in 9 cases with gratifying results.

**COMBINED PROCEDURES FOR VIRUS INACTIVATION IN BLOOD.**  
F. W. HARTMAN, GERALD LOGRIFFO and A. R. KELLY. Fed. Proc. 13:430, 1954.

The concentrations of virucidal chemical compounds which were found effective for the inactivation of test viruses in plasma were found inadequate for whole blood. Further, the larger concentrations of the chemical required for inactivation produced hemolysis. Multiple approaches to the problem have been studied: 1) chemical combinations below the hemolyzing level with nitrogen mustard, sulphur mustard, ethylene oxide, N-chloro-p-quinonimine, toluidine blue and ultraviolet. 2) Chemical neutralization of the virucidal agent used in large concentrations, after period of virus inactivation, on plasma and red cells. 3) Treatment of the red cells after concentration by removal of the interfering plasma followed by re-concentration of red cells and discard of sterilizing chemical solutions. 4) Treatment of large plasma volumes with diluted inactivating chemical in increased volumes and mixed continuously, with subsequent precipitation of the plasma proteins and fractionation.

**ANTIGENICITY OF BETA-PROPRIOLACTONE INACTIVATED VIRUS.**  
GERALD A. LOGRIFFO and FRANK W. HARTMAN. Fed. Proc. 13:503, 1954.

Beta-propiolactone (BPL) was reported by Hartman et al. to have in vitro virucidal properties in the presence of 90% plasma. In this study BPL inactivated MM-virus was tested for antigenicity. Aliquots from a 10% MM-virus suspension were used: a) in the untreated (active) state; b) treated with 0.2% BPL for 2 hr. at 37° C and c) treated with 0.3% formalin at 37° C for 48 hr. Five ml. of material from each group was injected intramuscularly into rabbits twice weekly for 4 wk. The rabbits were bled before and on the 10th, 20th and 30th days of immunization. The neutralization index for each group was as follows: a) untreated antigen— $5 \times 10^7$  on the 10th day; b) BPL inactivated antigen— $2.5 \times 10^6$  on the 10th day rising to  $5 \times 10^7$  on the 20th day and c) formalin inactivated antigen—no neutralization demonstrated under the same conditions. Complete virus inactivation can be obtained with BPL in 15 min. in 90% plasma at 37° C. In addition, the BPL treated material does not produce the protein denaturation and flocculation often found in formalin treated material. BPL inactivated viruses are fixed and not reversible upon storage, dilution or addition of reducing agents. The same degree of virus inactivation is obtained within the pH range of 5-9, permitting a choice of optimum pH. Although BPL hydrolyzes rapidly, the degradation products possess no virucidal activity. This study is being continued with other viruses.

ENDOCRINE ASPECTS OF INTERSEXUALITY. JEAN PAUL PRATT. *Am. J. Obst. & Gynec.* 68:341, 1954.

Intersexuality is a fascinating problem which has stimulated extensive medical writing. The definition of intersexuality should be simple, but indiscriminate use of the term and its synonyms has brought confusion. Since each human individual possesses male and female features in varying proportions, intersexuality is a normal condition and every human being is an intersex. In most instances it is not difficult to recognize the dominant male or female characteristics and without hesitation to classify each individual as male or female. It is possible, however, to find examples of all gradations of sex from a typical male to a typical female. The recent report of Moore and associates adds an interesting new approach. They found that the nature of the chromosomes in an individual may be detected by examining the epidermal nuclei in a small biopsy of skin. The sex chromosomes tend to remain compact while the autosomes are so diffuse that it is difficult to identify them individually. In 50 females the sex chromatin was identified in about two-thirds of the cells. It appeared as a plano-convex body lying against the nuclear membrane. In 50 male specimens they found an average of 5 per cent of the cells showing a small chromatin mass at the nuclear membrane. Exploration of the etiology of the intersexes has not yielded a value for the endocrines at all comparable with their use in treatment. The great variety of forms in which intersexuality may appear in man makes it impossible to give a definite scheme for rational therapy. It will be necessary to judge each case on its individual features. These unfortunate beings are sick people and they deserve sympathy and understanding. They are to be treated with all the resources of the art and science of medicine.

TOXICITY OF B-PROPIOLACTONE DEGRADATION PRODUCTS IN THE DOG AND MAN. A. R. KELLY, C. E. RUPE, JAMES J. TAZUMA and F. W. HARTMAN. *Fed. Proc.* 13:434, 1954.

The virucidal effectiveness and low toxicity of B-propiolactone (1) in plasma were reported previously (1951-53) by this laboratory. Because of possible potentialities as a sterilizing agent for plasma or biologicals, the toxicity evaluation of (1) and its degradation products has been extended to include 5 animal species. This report deals primarily with results obtained in dog and man. Dogs received 20 daily i.v. infusions of homologous plasma treated with 6 gm/l (2-3 x the effective virucidal concentration) of (1). Daily dosages were equivalent to 500 cc transfusions of plasma in man. EKG, hemogram, body-weight, liver and kidney function and tissue histology were not adversely affected. Three-month-old puppies received daily (for 3 months) the human equivalent of 250 cc of plasma treated with 3.5 gm/l of (1). No toxic effects were noted and growth curves remained unaffected, as compared with litter mate controls receiving untreated plasma. Plasma treated with (1) has been used clinically at Henry Ford Hospital for 2½ years; 82 patients received 185 transfusions of plasma treated at concentrations of 1-2 gm/l of (1), 12 patients received 27 transfusions at 2.5 gm/l, and 133 infusions treated at 3.5 gm/l were administered to 67 patients. Patient age ranged from 1 day-80 years. No clinical or laboratory evidence of toxicity was

observed, and the incidence of resulting hepatitis was zero. Comparative species toxicity of the purified degradation products of (1) in plasma will be discussed as well as EKG, hematopoietic and blood electrolyte effects, pathology produced, and excretion rate following massive dosages of these compounds in dogs.

**RECURRENCE OF MITRAL STENOSIS FOLLOWING COMMISSUROTOMY.** JOHN W. KEYES and CONRAD R. LAM. *J. A. M. A.* 155:247, 1954.

A patient with severe mitral stenosis received benefit from a commissurotomy that was maintained for a period of 18 months after which there was recurrence of all of the symptoms, indicating refusion of the valve leaflets. A gratifying result was obtained by repeating the operation on the mitral valve. Although recurrence of mitral stenosis after a technically adequate operation on the valve is extremely rare, when it does occur the possibilities of a second operation or even a third should not be overlooked. The successful principle in the surgical treatment of mitral stenosis has been proved to be that suggested by a London internist, Sir Lauder Brunton, in 1902. He thought the natural opening should be elongated. During the past four years, the practicability of accomplishing this by instrumental or digital commissurotomy has been well demonstrated. Naturally, there has been some speculation with regard to the possibility of healing of the divided commissures with consequent recurrence of the stenosis. Fortunately, although the number of mitral valve operations now numbers many thousands, true recurrence appears to be very rare. The unsatisfactory results that have followed in some instances have been due to other factors.

**FIBRINOLYSIS IN LABOR AND DELIVERY.** R. R. MARGULIS, J. H. LUZADRE and C. PAUL HODGKINSON. *Obst. & Gynec.* 3:487, 1954.

The purpose of this study was to evaluate the effects of labor and delivery on some of the various factors of the blood coagulation mechanism, including fibrinogen, fibrinolysin, prothrombin time, clotting time, and bleeding time. Blood of 20 uncomplicated obstetric patients was studied in serial fashion for fibrinogen, prothrombin times, clotting times and fibrinolysis as related to labor and delivery. Prepartum blood specimens were compared with specimens obtained at frequent intervals following delivery. Fibrinogen blood levels fell within the accepted normal range and were not significantly altered by delivery. Prothrombin times, bleeding times, and clotting time remained within normal limits. Of the 20 patients tested for fibrinolysis, 17 showed no lysis prepartum. Following delivery, lysis was present in the blood of 14 patients within 24 hours. By the fourth and fifth day postpartum, fibrinolysis was still present in 13 patients. Epinephrine, fear, muscular activity, preoperative medication, surgical stress, blood loss, and shock have been associated with increased fibrinolysis. In no instance was fibrinolysis sufficiently increased to interfere with blood coagulation or prothrombin activity.

**\*PREPARATION AND PROPERTIES OF HIGHLY PURIFIED ALKALINE PHOSPHATASE.** JAMES C. MATHIES *Fed. Proc.* 13:260, 1954.

Combination of previous purification steps (Abstracts 123rd Meeting Am. Chem. Soc. pp. 24c, 1953) with Sevag's procedure has led to enzyme preparations

\*From Edsel B. Ford Institute for Medical Research.

from swine kidneys with specific activities of 10,500 phosphatase units (mg phenol liberated from disodium phenyl phosphate in 15 min. at 25°) per mg of protein nitrogen (PU/mg PN). Material with a specific activity of 9,500 PU/mg PN was analyzed with the electrophoresis apparatus and the ultracentrifuge and appeared to be approximately 80-90% of one component. Qualitative spectroscopic analysis of this preparation demonstrated the presence of Zn, Mg, Cu and Fe (in approximate order of decreasing concentration) as major components. Minor amounts of Mn, Pb and P were also present. Of these elements, the Zn and Cu appear of primary interest. Copper has been found to be an efficient inhibitor of the spontaneous reactivation of alkaline phosphatase. Presumably it is present in this preparation as an inactive enzyme-copper complex. It is most likely that the copper is a contaminant which has accumulated during purification. The role of zinc, remains to be defined. Further study of the amino acid activation of alkaline phosphatase has shown that this property is not restricted to amino acids. Many compounds with the property of forming complexes with metal ions give the same effect as amino acids. It is probable that the principal effect of these agents is the reversal and/or prevention of trace metal inactivation.

**NASAL INSTILLATION AND INHALATION OF CRYSTALLINE VITAMIN B<sub>12</sub> IN PERNICIOUS ANEMIA.** RAYMOND W. MONTO and JOHN W. REBUCK. Arch. Int. Med. 93:219, 1954.

Inhalation and nasal instillation of crystalline vitamin B<sub>12</sub> in isotonic sodium chloride solution and lactose powder has resulted in adequate clinical and hematological response in 12 patients with pernicious anemia in relapse. The condition of 20 patients with pernicious anemia in remission has been maintained for periods up to 18 months. Detectable amounts of vitamin-B<sub>12</sub>-like growth substance in the urine were found after pulmonary administration and nasal instillation of this substance. This simple form of therapy is not only effective, but safe and economical.

**\*A NOTE ON A CHEMOGRAPHIC ARTIFACT IN AUTORADIOGRAPHY.** L. E. PREUSS and C. HARRISON. Science 120: 67, 1954.

Boyd and Board have defined the histochemograph as a gross image or gross image or grain grouping produced by chemical action when a specimen is in contact with the emulsion. Fitzgerald et al. apply the term *pseudophotographic* to agents, other than radiation, that will reduce the photographic emulsion. Such artifacts have been found superimposed upon autoradiographs of Cr<sup>51</sup> and Au<sup>198</sup> plaques. These chemographs corresponded to the debris dusted on the emulsion from a conventional lead pencil that was used to mark the emulsion near the autoradiograph. In view of these findings, markings of autoradiographs with pencil should be discouraged, particularly where the gross apposition technique is employed and especially where the specimen is likely to incorporate fine particulate radioactive material, autographs of which may be confused with the pencil chemo-graph.

\*From Edsel B. Ford Institute for Medical Research.

IMMUNOHEMATOLOGY WITH THE ELECTRON MICROSCOPE. JOHN W. REBUCK and ELTON E. HOFF. Fed. Proc. 13:442, 1954.

When control human erythrocytes, mixed with their own plasma, were studied with the electron microscope, desiccation resulting from electron bombardment produced shrinkage of erythrocytes from the plasma. In contrast, when human erythrocytes were mixed with plasma containing their specific antibodies or pan-agglutinins, shrinkage interference was brought about at variable areas on the surface ultrastructure by adherence to the antibody containing plasma (Anat. Rec. 115:591-614, 1953). The smallest unit of reactivity measured 30 $\mu$  in width. The size, height and frequency of such reactive sites varied with the antibody employed (Anti-A, Anti-Rh, panagglutinin). The reactive sites delineated by antibody adherence were plateau-like when viewed from the side, although umbilication or crater formation was at times apparent when concentrations of reactive units were separated by nonreactive sites. When human erythrocytes were studied after exposure to 1) high titered maternal antibodies which had proved to be lethal to the fetus, followed by exposure to 2) rabbit antihuman antibodies (positive Coombs test), reactive sites were similarly elicited although plasma adherence to the receptor areas was accentuated. Direct visualization of erythrocytes in erythroblastosis fetalis revealed structural changes similar to those produced experimentally *in vitro* by the addition of Anti-Rh grouping serum. Electron micrographs and tridimensional diagrams were presented depicting the structural changes described above.

TYPHUS FEVER (BRILL'S DISEASE) COMPLICATED BY DIABETES INSIPIDUS; Report of a Case. CLARENCE E. RUPE, HOWARD R. MARVEL, ROBERT J. RYAN and EDWARD L. QUINN. J. A. M. A. 155:433, 1954.

Typhus fever (Brill's disease) has been reported only sporadically from areas other than the costal region of the northeastern United States. As suggested by Brill and Zinsser and established by Murray, cases of recrudescing epidemic typhus would be expected to occur in all localities to which persons from foci in the Old World have migrated. To our knowledge, this is the first case of typhus fever reported from the Middle West despite the presence in this region of a large population of eastern European origin. This patient also showed unusual features including a transient diabetes insipidus. The temporary diabetes-insipidus-like picture in this patient and electroencephalographic abnormality suggests hypothalamic or posterior pituitary involvement perhaps due to petechial hemorrhages in this area. The diuresis (11,900cc. in 24 hours) was much greater than that seen after febrile diseases.

MODIFICATIONS OF THE REDDY PROCEDURE FOR 17-HYDROXY-CORTICOIDS IN URINE. R. W. SMITH, R. C. MELLINGER and A. A. PATTI. J. Clin. Endocrinol. & Metab. 14:336, 1954.

The original Reddy procedure for total butanol-soluble 17-hydroxycorticoids in urine was found often to yield zero values in specimens from clinically normal persons and, occasionally, from hypercortical patients. This was due to the non-specific chromogenic reactions of impure butanol with sulfuric acid, butanol with

phenylhydrazine-sulfuric acid reagent, and butanol extract of urine with sulfuric acid. These interfering colors were minimized by purifying reagent grade butanol with sodium bisulfite and re-distillation. The conditions of the Porter-Silber reaction were modified by lowering sulfuric acid strength and lengthening the incubation period. The addition of dried acid-activated kaolin to the urine prior to its extraction was found to remove urinary proteins which often produced emulsion during butanol extractions. Kaolin does not interfere with the recovery of the 17-hydroxycorticoids. When these changes are employed, generally higher values are found than by the original procedure. No inexplicable zero values have been encountered and correlations with various clinical conditions have been good.

**THE GENESIS AND IMPORTANCE OF THE ELECTROCARDIOGRAM IN COARCTATION OF THE AORTA.** ROBERT F. ZIEGLER. *Circulation* 9:371, 1954.

The electrocardiogram in uncomplicated coarctation of the aorta in infants reflects the pattern of the fetal circulation and serves as a useful prognostic guide. When the fetal ductus inserts proximally to the region of coarctation and closes at birth, right ventricular enlargement is present at birth but is retrogressive. Furthermore, in this situation collateral circulation has begun to develop before birth so that the left ventricle can compensate on assumption of the postnatal circulation, and the prognosis is good. When the insertion of the fetal ductus is distal to the coarctation, progressive, and frequently fatal, left ventricular enlargement and failure develop shortly after birth. Modifications of these electrocardiographic patterns in the production of right bundle branch block are also discussed and illustrated. Correlated data have been assembled in 57 patients with coarctation of the aorta, ranging in age from 10 days to 36 years. On the basis of this material the observations have been made.

**SOME ASPECTS OF ELECTROCARDIOGRAPHY IN INFANTS AND CHILDREN WITH CONGENITAL HEART DISEASE.** ROBERT F. ZIEGLER. *Dis. Chest* 25:490, 1954.

Some of the characteristic electrocardiographic patterns in normal infants and in infants and children with operable forms of congenital heart disease are briefly reviewed. One of the precordial lead patterns of right ventricular hypertrophy during early childhood is similar to that of normal infants during the first day of life. This is the pattern of upright T waves in leads from the right and flattened T waves in leads from the left side of the precordium. The prognostic significance of right ventricular hypertrophy in infants with uncomplicated coarctation of the aorta is reviewed. The diagnostic value of the electrocardiogram in patent ductus arteriosus is briefly summarized. A characteristic precordial lead pattern is described in typical cases of tricuspid atresia. This consists of broad P waves, short PR interval or segment, broad QRS, absence of Q waves and late activation in leads from the left side of the precordium.

