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READ BEFORE THE SCIENTIFIC SESSION

PRESIDENTIAL ADDRESS

By WILLIAM DOCK

During recent years this society has received some very pungent criticism from distinguished past presidents who felt we were not getting the best new members, and that our journal was accepting papers not up to the standards of former years. Our programs, arbitrarily selected by one man, remain subject to constant criticism from members active and emeritus. If we followed the spirit of the times, we would install a full-time salaried editor and secretary, such as now control many national, state, and special medical societies, and hope to benefit by the alleged efficiency of a dictatorship.

It would be well if every faculty member in our universities, every industrialist, and every physician would read, and each year reread, the address on "Academic Freedom in Germany" given by Helmholtz, who was distinguished alike as physician, physiologist, and physicist. It was written at the time when German universities were in their glory and attracted most of the physicians, physicists, and chemists who built up American science between 1870 and 1910. Helmholtz traced the greatness of Germany to the universities, whose students and faculty enjoyed greater freedom than has ever been granted in French, English, or American institutions. The full-time life-tenture dean and college president were not only unknown but were inconceivable to Virchow, Cohnheim, Emil Fischer, and Friedrich Mueller. Their deans, secretaries and other faculty officials were simply colleagues elected for terms of one to three years, a custom wisely followed by this society. This system survived fruitfully until it was abolished by the Nazis, and Helmholtz, who predicted how easily the German schools might be robbed of the freedom which was their proud heritage and chief asset, realized that, once lost, academic freedom probably could never be regained.

It is my hope that this society will not seek efficiency in a benevolent dictatorship, but that its members will manifest a livelier concern in its affairs, voicing criticism of its officers, and offering nominations in competition with those of the nominating committee. Our constitution calls for election of officers by secret ballot, and this certainly does not mean directing the secretary to cast the ballot for a straight ticket each year.

Two years ago your president pointed out the value of conflict in keeping societies alert and productive. We are now engaged in a great struggle which takes its character from the attempt of America and Western Europe to find security and avoid the normal competition and conflict of healthy peaceful civilization. Security, to the politician, meant a legally guaranteed status quo, an easy way of life. High tariffs, restricted immigration, farm subsidies, the forty-hour week, the peace pacts and treaties all were mere paper barriers against poorer and more energetic people. This game of make-believe led to slavery and chaos in most of Europe, and if we seek that sort of security we dare hope for no better fate.

In the academic world, the term security has long been potent, and, as in the political world, it means a guaranteed easy way of life. It has been held that a life-term appointment would attract to teaching those who so valued security that they would accept lower salaries than they could earn elsewhere. But even universities will not pay our salaries if we become physically disabled, and so long as a physician keeps his health, what security can the university offer him? If he has good judgment and training, is energetic, imaginative, and interested in his work, he will always find patients, institutions, and industrial concerns clamoring for him. Academic security in these days of changing values of money can scarcely attract such men, and it is difficult to see how the university gains by offering security to the mediocre or to those who have become historic monuments. While competent men will not become anatomists, bacteriologists, philosophers or professors of language without the promise of academic security, physicians, physicists, chemists, and engineers who are useful in the university can usually earn a much larger income in practice or in industry. At most, such men need only a sabbatical year for the transition to private life.

It has become quite clear that even in fields which change as slowly as the art of war, the highest effectiveness can be attained only if men reach responsible positions by the age of 35, and full command before 50. Most officers must be retired between the ages of 35 and 55 in order to effect this gravitation of responsibility into the most capable hands. The art of medicine is changing much more rapidly, as is obvious if one compares the medical and military discoveries since 1918. In order to effect the most productive utilization of the facilities given us by society for studying disease and training physicians, we must do everything possible to bring out the best efforts of every member of a medical faculty and profit by the most fertile and productive years of good physicians, regardless of their age. Obviously there must be ample opportunity for young men to bring up families while devoting most of their time to teaching and research, but I have seen no evidence that full-time schools were attracting any better or more productive

men than the part-time medical schools with proper salary levels for the younger staff members.

Stagnation is a very serious problem in many medical schools. It can be avoided if all salaried staff members, all heads of special clinics are appointed for terms of not more than five years. Reappointment should not be automatic, but should mean that no more capable person can be found after thorough search. We should encourage or insist on sabbatical or exchange years in other clinics and facilitate the movement of teachers, and especially of departmental executives, from school to school, or from one department to another. It should be neither unusual nor disgraceful for us to rejoin our colleagues in practice after some years or decades in the academic vale. None of us should hesitate to accept responsibility, nor avoid reentering practice when younger men, as capable as ourselves, are available and can bring new energy and a fresh point of view to the staff. Life might not be so snug for us under such a system, but it would be more stimulating and we would aid greatly in keeping medicine preeminent in a sound social system.

The bureaucracy which is a manifestation of the security complex must be combated in our societies and schools, and in government. Why should one face the arduous life in mine or factory if one can be a salaried labor official? Why should one risk the hazards of industry or finance when from a snug office in Washington one might control industry and finance, avoiding blame or loss if things go badly? Why practice or teach medicine if from a full-time position as secretary of a society, administrator of a school or foundation, one can wield great influence? The men who have accepted such positions are charming and capable people, and are anxious to relieve us of the necessity for managing our own affairs. Few of them believe in rotation in office; like labor leaders and the New Deal, they favor long tenure and do not share the poet's fear that "one good custom (or official) should corrupt the world."

By seeking the type of academic freedom Helmholtz praised, by resisting bureaucracy in our societies, cities and nation, by setting a personal example of willingness to accept short-term appointments, we can contribute, as good physicians, to prolonging the useful life of this civilization. We should see that our practice and curricula are abreast of the best facilities made available by science and society. There is no excuse for commanders who do not understand, insist on having, and fully utilize the modern equipment for security, victory, and providing defense with minimal loss of life; nor for leaders of medicine who do not understand and fully exploit all the chemical and physical discoveries, the techniques, therapeutic methods and devices, no matter how complex or novel, which contribute to safety, accuracy, and speed of diagnosis and treatment. The failure of our generation to make the X-ray a familiar and routine instrument for physical diagnosis is the outstanding evidence that medicine, like some military establishments, may for years misunderstand and undervalue instruments of extraordinary merit, and thus physicians come to use the gifts of science "too little and too late." We must all be on guard against stagnation in our departments and against falling into rigid patterns of thought.

Three years ago your president offered as the solution of our problems picking executives and teaching personnel of great talent and "contagious fire." But even this is not enough. There are men, like Cushing, Rosenau, and Hektoen, who are ready to accept and eagerly sought for new positions when they reach the legal retirement age. They are rejuvenated by their new tasks. There are men of extraordinary ability who go into the mental menopause prematurely, in some instances rapidly losing a forced and hectic fire when they achieve the academic goal which they had set for themselves. Never forget that Vesalius, at the age of 30, one year after his revolutionary *de Fabrica* came from the press, became a court physician and never contributed anything thereafter. Many similar, if less dreadful, examples are seen about us today, and we must not only select good men but retire those who are not maintaining the "contagious fires" at a healthy glow. None of us are secure if our profession declines, all must give much and risk much to achieve any worthy goal. Today, as in Milton's stormy lifetime, "the immortal garland is to be run for, not without dust and heat.'" May we neither "slink out of the race" nor seek to bury ourselves in a "fugitive and cloistered" security.

A Study of Calcium Metabolism in Nephrosis. By WILLIAM W. BECKMAN and KENDALL EMERSON, JR. (introduced by Dr. Homer F. Swift), New York, N. Y.

Children with nephrosis characteristically exhibit osteoporosis, hypocalcinuria, and hypocalcemia. A detailed study of calcium metabolism in these patients has shown that there is an excessive loss both of this element and of phosphorus from the gastro-intestinal tract, which leads to insufficient retention for the ordinary calcium requirements of growing children. The mere addition of calcium to the diet served only to increase the fecal excretion without improvement in the balance. Large doses of vitamin D failed to influence absorption from the intestines, in spite of which fact there is no evidence of rickets. Likewise the administration of citrate-sodium citrate mixtures had no effect. On the other hand, when lactose was fed, absorption was considerably enhanced, not only of calcium but also of phosphorus, nitrogen, and potassium. Similar results were obtained with dihydrotachysterol (A. T. 10).

The serum calcium concentration was raised to nearly normal by A. T. 10. In spite of this, no increase in urinary calcium was observed. The elevation of the serum calcium to toxic levels by intravenous administration of the ion, caused only a very slight rise in renal excretion. Acidosis increased the loss of calcium in the feces, but had no effect on the urine.

A patient, who was studied during a spontaneous remission when these abnormalities largely disappeared, will be described.

Studies on the Relation of Fat Metabolism to Nutrition of the Skin. By ARILD E. HANSEN, Minneapolis, Minn.

In a study of 119 children and adults with intractable eczema, it has been found that the majority have an abnormally low degree of unsaturation of the serum lipids. This decrease in the iodine numbers of the serum fatty acids is of the same magnitude as found previously in the rats suffering from the fat-deficiency syndrome described by Burr and Burr. In a more intensive investigation of the factors concerned with the nutrition of the skin, puppies reared on a diet practically devoid of fat developed marked flaky desquamation and dryness of the skin and hair. Litter-mate control puppies given the same diet except for the isocaloric substitution of lard for sucrose had skins of normal appearance. In addition, 71 human subjects suffering from chronic eczema were given dietary supplements of unsaturated fatty acids in the form of lard, raw linseed oil, and corn oil. Clinical improvement was noted in over half of these and in some the skin cleared entirely. The fatty acid distribution in the various fractions of the serum lipids is being determined at various intervals in both the experimental animals and human subjects, and in the puppies, histologic study and chemical analysis of the lipid components of the skin are being made.

A Study of Experimental Hypothalamic Obesity in the Rat. By JAY TEPPERMAN (by invitation), JOHN R. BROBECK (by invitation), and C. N. H. LONG, New Haven, Conn.

Bilateral, symmetrical, electrolytic lesions were placed in the hypothalami of rats by means of the Horsley-Clarke stereotaxic instrument. Almost immediately after operation the operated rats began to eat voraciously, often consuming 2 to 3 times the amount of food eaten by their littermates, and they soon became very obese. Ten operated rats pair-fed with their controls frequently ate their day's ration in less than 2 hours, but only 1 outgained its control. The development of the obesity is apparently a consequence of increased appetite, and is not associated with any fundamental disturbance in metabolism.

The basal oxygen consumption of pair-fed operated rats was normal. The absolute oxygen consumption of fat rats, however, was sometimes as much as twice that of their controls.

The fasting R.Q.'s of both fat and pair-fed operated animals were similar to those of normal rats, but the R.Q.'s, after glucose, of all operated rats were abnormally high.

Albumin and casts were observed in the urine of 13 out of 15 operated rats from 6 to 12 weeks after they became obese, and 4 of these subsequently showed striking histological changes in both tubules and glomeruli. Littermate controls and pair-fed operated rats showed no evidence of renal damage.

Effect of Continuous Intravenous Infusion of Glucose in Normal Dogs. By E. B. ASTWOOD, J. M. FLYNN, and O. KRAYER (introduced by W. P. Murphy), Boston, Mass.

By means of a simple automatic apparatus, 10 to 70 per cent glucose solutions in water or salt solutions were injected intravenously into unrestrained, unanesthetized dogs. Rates of infusion of less than 12 grams per sq. m. per hr. were tolerated indefinitely, while rates exceeding 40 grams per sq. m. per hr. caused glycosuria, dehydration fever, and death within a few hours. Intermediate amounts were tolerated with minimal or no glycosuria, but death invariably occurred in 3 to 25 days, the length of life being inversely proportional to the rate of glucose administration. Death was preceded by signs of marked hepatic insufficiency, *i.e.*, bilirubinemia, bilirubinuria, retention of bromsulphalein, lowered serum albumin, bleeding tendency, failure of blood clotting, and a terminal hyperglycemia. Post mortem examination revealed wide-spread intra-abdominal hemorrhages, and great enlargement of the liver from glycogen deposition. This course of events was not modified by supplying extra sodium, potassium, chloride, bicarbonate, or phosphate, nor by insulin, vitamins, or liver extract. It is estimated that about 12 grams of glucose per sq. m. per hr. can be used by oxidation and conversion to fat. Larger amounts exceed the maximal rate of fat formation and thus must accumulate as glycogen, which, when stored to excess, fatally impairs the function of the liver.

Studies on the Absorption Defect in Sprue. By FRANZ J. INGELFINGER and ROBERT E. MOSS (introduced by Harold Jeghers), Boston, Mass.

In 4 patients with sprue, vitamin A absorption tests showed that fasting plasma vitamin A levels were low, and that oral administration of a vitamin A concentrate produced little or no rise in plasma levels.

In 2 of the patients whose pancreatic lipase secretion was shown to be normal, repeated tests were done. One or more tests indicated that the flat vitamin A absorption curve was not improved by intra-duodenal injection of the concentrate, by maintaining a high vitamin A concentration in the intestine for over 6 hours, by injections of mecholyl and prostigmine, by injections of adrenal cortical extract or of desoxycorticosterone acetate. Nor was the absorption curve elevated after one month of oral yeast therapy, or of massive parenteral B-complex therapy, or of parenteral vitamin A injections.

The intra-duodenal administration of a vitamin A concentrate which had been thoroughly mixed with normal human succus entericus was the only procedure which consistently elevated the absorption curve. This improvement in the absorption curve may occur because normal human intestinal juice supplies an unknown factor, or because the intra-duodenal administration of the test dose mixed with succus entericus provides for a more adequate dispersion and emulsification of the test substance in the gut, and thus partially corrects the intestinal motor

abnormalities of sprue. At present, our experiments suggest that the latter possibility is the more likely one.

Studies on the Synthesis of Total Coenzyme from the Oral and Parenteral Administration of Nicotinic Acid and Nicotinamide. By CHARLES L. HOAGLAND and ROBERT E. SHANK (introduced by Thomas M. Rivers), New York, N. Y.

The requirement of the influenza bacillus for coenzyme, the physiologically active form of nicotinic acid, was reported by Lwoff and Lwoff in 1936. Since that time a number of attempts have been made to use this organism in the quantitative determination of coenzyme. These techniques have been limited in that turbidity of test material has contributed large errors to the turbidimetric determination. On the other hand, extraction of coenzyme is tedious, often incomplete, and may result in partial destruction of this labile compound.

We have found that the production of nitrite from nitrate by the influenza bacillus parallels closely its metabolic activity, and, in turn, can be related quantitatively to the coenzyme which the medium contains. The method is simple, reproducible, requiring no preliminary extraction of coenzyme, and can be done on less than 1 cc. of blood. By means of the nitrate reduction technique, it has been possible to study quantitatively the synthesis of coenzyme in the blood of animals and human beings, following the ingestion of nicotinic acid and nicotinamide. A definite and reproducible increase in total coenzyme has been observed in the blood when these coenzyme precursors are given orally. Studies will be presented which link the extent of this increase to the stores of coenzyme in tissues and organ depots.

Vitamin B Complex Studies in Dogs. By PAUL J. FOUTS, Indianapolis, Ind.

Dogs fed a high (41 per cent) casein diet supplemented with thiamine hydrochloride, nicotinic acid, riboflavin, pyridoxine hydrochloride, and either pantothenic acid, or a purified liver extract containing "Filtrate Factor," showed suboptimal growth but appeared normal over long periods of time.

When casein in the diet was reduced to 15 per cent, a deficiency developed, consisting of loss of appetite, loss of weight, moderate to severe anemia, and high incidence of skin ulcers.

Of those examined after death, all showed fatty cirrhotic livers, and many showed peptic ulcers.

Para-aminobenzoic acid, inositol, an eluate of a clay absorption of liver extract, and small amounts of choline did not prevent or cure the deficiency. Large amounts of choline produced temporary improvement in some animals. Powdered liver extract was followed by disappearance of all symptoms and satisfactory gain in weight but more rapid gain in weight was noted in dogs receiving the large amounts of choline in addition to the liver extract.

Insulin Resistance. By JACOB LERMAN, Boston, Mass.

Many diabetic patients receiving insulin for the first time develop local reactions. Such reactions usually disappear after a few injections. The serum from several such patients was found not to have any circulating antibodies to insulin. They did show a small titer of antibodies to bovine and pig serum. The serum of two patients with persistent local reactions to insulin also failed to show antibodies to insulin. They responded to insulin in the usual fashion.

This inability of insulin to produce antibodies was verified in numerous animal experiments. Rabbits and guinea pigs receiving insulin subcutaneously or intraperitoneally failed to develop antibodies, nor did their serum protect a normal animal against a minimal lethal dose of insulin.

Occasionally, a patient receiving insulin becomes resistant to its effects and requires tremendous doses to control the diabetes. One such patient required 500 to 700 units daily. This resistant state was verified by the fact that 10 units of insulin intravenously failed to produce the expected drop in blood sugar. The serum of this patient contained circulating antibodies to insulin to a dilution of 1:200,000 and also gave a positive Prausnitz-Kustner test. Later, when the requirement for insulin dropped to 100 units daily, the titer of antibodies in the serum dropped to 1:800. Two other patients who had required 2,000 to 2,200 units of insulin daily at the peak of their resistance, gradually lost resistance over a 1 to 2 year period. When their requirement returned to the normal level (40 to 50 units daily), no circulating antibodies to insulin were detected.

Consequently it may be concluded that (*1*) antibodies to insulin are antihormonic, (*2*) insulin resistance is dependent upon the appearance and concentration in the blood of antibodies to insulin, and (*3*) the return of normal insulin sensitivity is dependent upon the disappearance of circulating antibodies. Similar fluctuations in antibodies have been observed in humans, such as the appearance of antibodies to cow's milk protein, egg white, and other proteins when infants are first exposed to these foods and the subsequent disappearance of the antibodies, in spite of continued ingestion of such foods.* Likewise, I have observed the disappearance of antibodies to thyroglobulin in rabbits repeatedly injected with thyroglobulin.

The Male Climacteric: Its Physiology, Symptomatology, Diagnosis and Treatment. By CARL G. HELLER and GORDON B. MYERS (introduced by Elmer L. Sevringhaus), Detroit, Mich.

Urine gonadotropic titers of three orchidectomized males and five eunuchoids proved to be as high as that found in oophorectomized and menopausal women. Since this loss of gonadal function in the human male was

* Anderson, A. F., Schloss, O. M., and Myers, C. The intestinal absorption of antigenic protein, Proc. Soc. Exper. Biol. and Med., 1925, 23, 180.

shown to be accompanied by a rise in urine gonadotropic hormone, such assays were used as a diagnostic measure to determine testicular function in a selected group of male patients. Eleven of these, ranging in age from 36 to 65 years, exhibited gonadotropic titers considerably above normal. Some of the titers were as high as those found in castrated males and females.

The symptoms of these eleven patients fell into three general groups: (*1*) Diminution to absence of libido and sexual potency, which was present in all; (*2*) vasomotor symptoms present in ten; (*3*) psychoneurotic symptoms present in all.

Gonadotropic titers and symptomatology were closely followed through a four to five week period of intensive testosterone propionate treatment. Similar observations were made after therapy ceased.

It is concluded that gonadotropic assays can serve as an aid in establishing the diagnosis of the male climacteric, and have been helpful in delineating it as a clinical entity. The male climacteric is an aberrant and pathological accompaniment, whereas the female climacteric is an invariable and physiological accompaniment, of the aging process.

Stimulation of Growth in Pituitary Dwarfs with Chorionic Gonadotropin and Sex Hormones. By WILLARD O. THOMPSON and (by invitation) NORRIS J. HECKEL and RICHARD P. MORRIS, Chicago, Ill.

We have previously demonstrated that chorionic gonadotropin and male sex hormone are the most potent stimulators of growth available at the present time, with the exception of the thyroid hormone in patients with cretinism. The effect of chorionic gonadotropin is the result of stimulation of production of male sex hormone by the interstitial cells of the testis. It therefore produces the same effect on the skeleton as male sex hormone. Because of lack of effective preparations of pituitary growth factor it seemed desirable to observe the influence of these materials on the growth of the skeleton in pituitary dwarfism. When either substance is administered to boys with pituitary dwarfism, the following effects on the skeleton are noted:

Rapid increase in length of the skeleton.
Rapid aging of bone, as determined by the roentgen ray, to such extent that the bone age tends to approach the chronologic age.
Development of the musculature and lengthening of the trunk.
Rapid aging of the facial expression.

These changes are associated with growth of the genitalia and development of other secondary sex characteristics. The influence of male sex hormone is not limited to the skeleton but it appears to be a general growth stimulant. Our observations have been correlated with studies in growth by Burgess, Wetzel, Todd, Hodges, Camp and Ciley, and others.

Alterations in Biological Oxidations in Thyrotoxicosis. By ROBERT H. WILLIAMS, ENRIQUE EGANA, PAUL ROBINSON, SAMUEL P. ASPER, JR. and CHARLES H. DUTOIT (introduced by Henry Jackson, Jr.), Boston, Mass.

A number of observations in the past indicate certain interrelationships between the brain, pituitary thyroid, and body cell. For example, removal of the thyroid leads to increased pituitary activity; removal of the pituitary is followed by atrophy of the thyroid; vitamin B deficiency has been observed to cause changes in the metabolic rate and in the histology of the thyroid gland. The question of whether disturbances in the metabolism of the body cell may lead to the development of thyrotoxicosis warrants investigation.

We have been studying various segments of the system of biological oxidations in hyperthyroidism, but this report is concerned chiefly with pyruvic acid metabolism.

In a group of 40 unselected thyrotoxic patients from 7 different hospitals in Boston, the blood pyruvic acid, obtained from the patients in a resting and fasting state, was definitely elevated in the majority of instances. Diphosphothiamine, in combination with magnesium and carboxylase, is necessary for the decarboxylation of pyruvic acid. However, in almost all the 40 patients studied, the blood diphosphothiamine and free thiamine were low. It is also of interest that the protein-bound magnesium of the serum is increased in nearly all thyrotoxic patients.

Thiamine balance studies indicate that in some patients it is difficult to get the blood diphosphothiamine to return to normal. Some of the factors which account for this are (*1*) increased rate of oxidation; (*2*) relatively high carbohydrate diet; and (*3*) polyuria, which is common in thyrotoxic patients. These patients excrete more thiamine in the urine than do other vitamin B deficient patients with the same low thiamine blood level and the same diet. Tests on 2 thyrotoxic patients showed that they could phosphorylate thiamine readily.

To study further the changes in carbohydrate metabolism, a series of tests was performed on a group of 6 thyrotoxic and 6 normal subjects. Fifty grams of glucose were given intravenously and 8 specimens of blood were taken during the succeeding 4 hours. The concomitant changes in the glucose, pyruvate, lactate, thiamine, and diphosphothiamine were noted.

In thyrotoxic subjects, the fasting glucose, pyruvate, and lactate were higher than normal and rose to higher levels following the administration of glucose. After the injection of 5 grams of sodium pyruvate, intravenously, the pyruvate and lactate also rose to much higher levels than in normals and they remained high. Marked variations occurred in the response of thiamine and diphosphothiamine; however, in the thyrotoxic patients these substances remained at a lower level throughout the experiment.

In some cases, intramuscular injections of magnesium tended to suppress the rise in the pyruvate and lactate. Administration of diphosphothiamine, intravenously, also had this effect in some instances.

The cause of the development of these alterations in

the biological oxidations and their relationship to the thyrotoxicosis need further study.

Cyanate Goiter in Man. Report of a Case with Histological and Metabolic Studies. By RULON W. RAWSON (by invitation), SAUL HERTZ, and JAMES H. MEANS, Boston, Mass.

Chesney, Clawson and Webster, and Marine, Spence and Rosen, and others, have observed marked hyperplasia in the thyroids of rabbits fed a cabbage diet. Suk has reported large nodular goiters occurring endemically in a community where cabbage is a principal dietary item. The goitrogenic factor in cabbage has been reported to be certain cyanide compounds found in cabbage and other members of cruciferae family. Subsequently goiters have been produced in experimental animals treated with sodium cyanide, potassium cyanide and methyl cyanide. Robinson and O'Hare, and Barker have reported the development of goiters in hypertensive patients being treated with sodium or potassium thiocyanate.

We are reporting certain metabolic studies and the thyroid histology of one patient who developed a goiter after one year's treatment with potassium thiocyanate administered in treatment of hypertension. The blood cyanate during the period of treatment varied between 3.8 mgm. per cent and 8.9 mgm. per cent. While following the prescribed regimen, the patient improved symptomatically and the blood pressure fell from 220/130 to 140/100 mm. Hg. However, after taking the thiocyanate for one year, the patient complained of swelling in the neck. The swelling was found to be a large goiter over which a loud bruit could be heard. The gland was estimated to weigh about 180 grams. A definite bilateral lid lag and exophthalmos were present. The basal metabolic rate was minus 17. Blood plasma iodine was at the level of myxedema. A biopsy taken from the gland, which at operation was very vascular, disclosed extreme hyperplasia with architecture resembling papillary cystadenoma. The cyanate therapy was stopped, and one month later the thyroid was of normal size and the basal metabolic rate and blood plasma iodine had returned to normal levels.

We feel that the paradoxical findings in this case, *i.e.*, the extreme hyperplasia in the gland, but laboratory signs of hypothyroidism, are of interest and may be of fundamental importance in interpreting thyroid physiology.

Recent Clinical Developments in the Therapeutic Application of Radio-Phosphorus and Radio-Iodine. By JOSEPH G. HAMILTON (by invitation) and JOHN H. LAWRENCE, Berkeley, Calif.

Radio-phosphorus has been employed for the treatment of a group of patients with polycythemia vera during the past two and a half years. A marked remission of the clinical and hematological signs of this disease has been observed in the majority of the patients following the administration of radio-phosphorus. No evidence of either leukopenia or anemia has been observed in any of the patients and none developed any symptoms of radiation sickness.

A series of experiments with radio-iodine have been undertaken with the collaboration of Drs. Mayo H. Soley and Karl Eichorn. In these studies, a series of rabbits and two dogs were given large doses of radio-iodine (I^{131} half-life 8 days) and it was noted that almost complete destruction of the thyroid took place in all of the animals without evidence of damage to the other tissues of the body. Later, much smaller doses of radio-iodine were administered orally to three patients with hyperthyroidism. Four to six weeks later a marked clinical improvement was noted in each of the patients, with a parallel approach of the basal metabolic rate to normal levels. No adverse effects from the radio-iodine were noted either during or after the administration of this substance. Four and a half months later two of the patients were in a state of complete clinical remission and the third required another small dose of radio-iodine.

Application of Radioactive Iodine in Therapy of Graves' Disease. By SAUL HERTZ and (by invitation) A. ROBERTS, Boston, Mass.

Previous publications of this series have dealt with tracer studies in animals and man. Our present report is a preliminary one which gives an account of our early experiences, both failures and successes, in an attempt to evaluate the possibility of using radioactive iodine in a practical clinical manner in the treatment of patients with Graves' disease. It is in the nature of a progress report on this work up to date.

The general plan of the treatment is described and an analysis of the 10 (or more) cases in which it has been tried is given.

Information which we have obtained by careful study of the radioactive iodine uptake by the goiters and the urinary excretion studies is presented and discussed in relation to the problem of finding the best means for the administration of this new therapeutic agent.

A Chemical Test for the Differentiation of Adrenocortical Tumor from Hyperplasia in Markedly Masculinized Women. By HARRY B. FRIEDGOOD (introduced by Samuel A. Levine), Boston, Mass.

Previously reported observations from this laboratory are in general accord with those recorded by others in that the total 24-hour urinary 17-ketosteroid (17–KS) excretion is above 45 mgm. equivalents of crystalline androsterone in cases of virilizing adrenocortical tumor, and from 15 to 35 mgm. in instances of adrenogenital syndrome due to adrenocortical hyperplasia. Two cases of hyperplasia have been encountered, however, in which the 17–KS excretion equaled that found in tumor cases; and in one of these, which was a striking example of pseudohermaphroditism, the 24-hour 17–KS excretion was more than 80 mgm. Thus it is not the total 24-hour 17–KS excretion which is of significance in differential diagnosis. A differential point may have been found,

however, in the percentage composition of the 17–KS excretion. Determination of the α and β-steroids disclosed that the latter constituted less than 15 per cent of the total 17–KS excreted by the patients with adrenocortical hyperplasia, whereas in the virilizing adrenocortical tumors the β-steroid fraction accounted for more than half of the total 17–KS excreted.

A. A Method of Determining the Digestive Activity in any Portion of the Human Gastro-Intestinal Tract. B. Some Measurements of Protein Digestion in the Stomach and Small Intestine. By KENDALL A. ELSOM and (by invitation) FRANCIS W. CHORNOCK and FRANCIS G. DICKEY, Philadelphia, Pa.

A method has been devised for measuring the digestion of suitable solid food substances anywhere in the human gastro-intestinal tract. The substance to be tested is placed in a fenestrated metal cylinder that is housed in an outer cylinder which protects the contained material from the digestive juices. The apparatus is introduced to any desired portion of the gastro-intestinal tract by intubation. At the desired moment, the fenestrated cylinder is partially ejected from its housing by air pressure, thus exposing the test substance to the intestinal juice. The amount of material lost by digestion in a measured period of time is determined chemically.

Data are presented on the digestion of pork heart muscle in 10 normal and 10 achlorhydric stomachs and at varied levels of the small bowel of 2 normal subjects. The relationship between the time of exposure and digestion of the test material was determined in the normal duodenum. Even though all digestive juice is withdrawn from the duodenum by suction before it reaches the apparatus in the jejunum, the amount of digestion of pork heart muscle in 3 hours is not reduced.

Tests have been made in certain diseases such as regional enteritis, ulcerative colitis, etc., to determine whether abnormalities in protein digestion can be detected.

Studies on a Man with a Large Permanent Gastric Fistula: Correlation of Acid Production, Motility and Blood Flow in the Stomach. By STEWART WOLF (by invitation) and HAROLD G. WOLFF, New York, N. Y.

Through a gastric fistula 4 cm. in diameter, larger than Alexis St. Martin's, the stomach mucosa was readily examined for long periods with the subject at rest. A wide range of color changes was observed in the mucous membrane from moderate pallor to intense blushing. These color changes were shown to reflect changes in blood flow by radiometric measurements and by a modification of the stromuhr technic. Acid production and motility were correlated with vascular changes in the stomach. The following relationships obtained: 1. Increased acid secretion, however induced, was invariably accompanied by increased vascularity. 2. At such times there might or might not be increased motility, but increased motility never occurred when the mucosa was pale and the acid output low. 3. The amount of motility determined the extent of emptying. No emptying occurred in the absence of stomach contractions. 4. The hydrogen ion concentration of the stomach content did not directly influence emptying time.

Gastric Secretion: Absorption of Radioactive Sodium and Heavy Water from Pouches of the Body and Antrum of the Stomach of the Dog. By OLIVER COPE and (by invitation) WALDO COHN and A. G. BRENIZER, JR., Boston, Mass.

Three dogs with pouches of the body of the stomach, the acid secreting area (Cope, Oliver, Charles E. MacMahon, Anders Hagstromer and Richard H. Thompson, Gastric Secretion. I. A new gastric pouch with a non-leaking stoma and an intact nerve supply; description of a two stage technic used on the dog. Arch. Surg., 1940, **40**, 717), and two with pouches of the antrum were used. Radioactive sodium, as the chloride in hypo-, iso- or hypertonic solution, was placed in the pouch and the absorption measured by the concentration of radioactivity in the blood. Small but reproducible amounts of sodium were absorbed from the acid secreting area; twice as much was absorbed when the animal was fasting and the pouch was secreting a neutral mucoid secretion as when the pouch was producing acid. The tonicity of the solution made no difference. In the dogs with antral pouches, approximately 100 times as much sodium was absorbed per unit of surface area of mucosa. There was slightly greater absorption from the hypertonic solution but it made no difference whether the animal was fasting or digesting.

The absorption of heavy water was measured by its disappearance from the pouch. It was made isotonic by using sodium chloride, and phenol red was added before introducing it into the pouch. Half of the heavy water had been absorbed from the acid secreting pouch in 15 minutes and from the antral pouch in 20 minutes. It made no difference whether the animal was fasting or digesting.

It is concluded that the juice collected from a pouch of the stomach is contents, not secretion. In any study of gastric secretion, concomitant reabsorption of the sodium ion and water must be considered.

The Effects of Sudden Changes in Peripheral Circulation Upon Cardiac Output. By ROBERT W. WILKINS and (by invitation) JOHN S. HUNT, and CARL K. FRIEDLAND, Boston, Mass.

Cardiac output was measured ballistocardiographically in supine, normal subjects before, during, and after procedures designed to alter the peripheral circulation. In some experiments, simultaneous records of arterial and venous pressure were obtained with Hamilton manometers.

Decreasing the effective circulating blood volume by congesting 2 or more limbs with blood pressure cuffs at 70 mm. Hg had only a slight effect upon cardiac output, while increasing the circulating blood volume by releasing the cuffs likewise had a small effect. Decreasing peripheral blood flow by completely occluding the circulation in the limbs caused only a small change in cardiac

output, as did peripheral vasodilatation or vasoconstriction produced by warming or cooling the body. Greatly increasing peripheral blood flow in the limbs by releasing an arterial occlusion of some duration (reactive hyperemia) caused a considerable increase in cardiac output but of shorter duration and of lesser magnitude than the estimated increase in blood flow in the limbs. The relatively small changes in cardiac output produced by the above procedures were attributed to the buffering effects of the vasomotor system. For example, the presence of a compensatory vasoconstriction elsewhere during reactive hyperemia in the limbs could be demonstrated if the circulation in these limbs were suddenly reoccluded a few seconds after being released. There was then temporarily a rise in arterial pressure, and a reduction in cardiac output, often beyond the levels which had existed prior to the release.

The Relation of Postural Hemodilution to Paroxysmal Dyspnea. By GEORGE A. PERERA and ROBERT W. BERLINER (introduced by Robert F. Loeb), New York, N. Y.

The present study was undertaken to see whether the well-established shifts of body fluid to the blood stream following rest in the horizontal position might be a factor in inducing left-sided heart failure as manifested by paroxysmal dyspnea.

In order to study the degree of hemodilution which may take place in the horizontal position and to correlate these changes with the time of appearance of attacks of paroxysmal dyspnea, observations were made on the serum protein concentration at 2-hourly intervals during the course of 24 hours in 30 normal, ambulatory cardiac, and bed patients. Confirmed by exercise and tilt-table experiments, the results indicated that recumbent rest was associated with a 10 to 15 per cent drop in serum proteins, presumably due to an increase in plasma volume. Supportive evidence of hemodilution was obtained from hematocrit and red blood cell count determinations. Hemodilution was associated with a tendency toward an increasing venous pressure and a reduced vital capacity. No change was noted in the ratio of albumin and globulin.

Diurnal studies of 8 patients with paroxysmal dyspnea showed that the attacks took place at a time when maximal hemodilution was present, *i.e.*, during the early morning hours when the episodes are classically most apt to occur. The attacks were terminated by assuming the erect position and moving about, activities which were associated with a rapid rise in serum protein concentration.

The effect of assuming the horizontal position with its attendant hemodilution is the equivalent of giving a slow but sustained infusion. In support of this are the observations of Caughey and others that infusions in patients with a diminished cardiac reserve may precipitate pulmonary edema. Furthermore, Swank, Porter, and Yoemans have recently shown that increases in blood volume of 50 per cent or more can induce manifestations of left-sided failure in normal dogs.

It is concluded that the increase in plasma volume induced by horizontal bed rest is a possible factor in the production of paroxysmal dyspnea.

Relationship Between Edema and Rate of Peripheral Blood Flow. By DAVID I. ABRAMSON and SIDNEY M. FIERST (introduced by Louis J. Soffer), Cincinnati, Ohio.

The rate of peripheral blood flow was investigated in a series of patients with edematous extremities, using the venous occlusion plethysmographic method. The results varied, depending upon the etiological factors producing the condition.

In three patients, unilateral edema was present as a result of metastasis to regional lymph glands. In two of these, the upper extremity was involved, and in both instances the blood flow to the hand was practically twice as great as that to the normal extremity. In the remaining case, the edema was present in one lower limb, and the involved leg demonstrated a rate of blood flow which also was almost double that in the other.

In two patients, edema of the affected upper extremity was present during the acute stage of hemiplegia. In the one in whom the condition was more marked, the blood flow in the involved hand was almost three times that in the normal one. In the other, no difference in the flow was noted between the two hands.

In four patients, bilateral edema, unassociated with heart failure, was present in the lower extremities; the circulation time in each case being within normal limits. The blood flow in the leg in every instance was significantly increased as compared with the average flow in the control group.

In five patients, bilateral edema of the lower extremities was present as a result of cardiac decompensation. The rate of blood flow in the leg in this group fell within the range of the figures obtained for the control series.

The possible mechanisms responsible for the changes in blood flow in edema are considered.

Renal and Total Circulation in Two Cases of Constrictive Pericarditis. By MILTON LANDOWNE (by invitation), ALF S. ALVING and (by invitation) WRIGHT ADAMS, Chicago, Ill.

The criteria for renal ischemia with "increased efferent arteriolar constriction" were satisfied for each of two patients with proven chronic constrictive pericarditis. The deviation from normal was more marked than that encountered in arterial hypertension although the blood pressures were 134/98 and 84/70. The "effective renal blood flow" (C_D/hematocrit = 752 and 528 cc. per minute per 1.73 m.^{2}) was reduced proportionately more than the cardiac output (C. I. = 1.84 and 1.58), the renal fraction being 83 per cent and 65 per cent of its expected value. Glomerular filtration was slightly reduced (C_I = 120 and 90 cc. plasma per minute per 1.73 m.^{2}). The plasma "filtration fraction" was, therefore, extremely high (31.7 per cent and 31.9 per cent, increases of six times the

standard deviation (σ) of the mean normal values). Maximal tubular excretion of diodrast was normal ($Tm_D = 46.0$ and 50.5 mgm. I_2 per minute per 1.73 m.^{2}), and consequently, the "plasma flow per unit of functioning tubular mass" was very low ($C_D/Tm_D = 8.27$ and 5.55 cc. per mgm. I_2, reductions of 3.6 and 5.5 σ). Plasma from each of these patients, when tested by Dr. I. H. Page upon the denervated rabbit ear, was markedly constricting.

Elevated systemic venous pressure, by increasing resistance to post-glomerular perfusion, may mimic "increased efferent arteriolar resistance." These observations are also compatible with the hypothesis that the kidney participates in a vascular regulation, where, in the presence of a reduced cardiac output, renal efferent arteriolar constriction and a generalized peripheral vasoconstriction are produced to maintain normal blood pressure.

*Search for Renin and Determination of Hypertensin Precursor in Plasma of Normal and Hypertensive Patients.** By LEWIS DEXTER and FLORENCE W. HAYNES (introduced by E. S. Emery, Jr.), Boston, Mass.

The relationship of experimental to human hypertension is of exceeding importance and is as yet unclarified. A search for the presence of renin in the blood of hypertensive patients has therefore been made, together with estimations of hypertensin precursor in normal and hypertensive patients.

Modifications of the direct renin method and of the precursor method of Leloir and his associates were used. Human renin was prepared as described by Braun-Menendez and his associates and their assay method was employed in cats which are 10 to 20 times more sensitive than dogs.

The concentration of hypertensin precursor in human plasma in 11 hypertensive and 8 normal patients was found to be the same, averaging 2.67 and 2.45 cat units per cc. of plasma respectively. This is approximately the same concentration present in dog and beef plasma.

In our hands, the direct renin method is capable of detecting 0.005 cc. (0.4 cat unit) of a solution of human renin added to human plasma. This method eliminates non-specific substances and has the same order of sensitivity as the perfusion methods of isolated organs as described by other workers. No renin was demonstrable by this method in 10 cc. of plasma of 7 patients with severe chronic hypertensive disease, one of whom had malignant hypertension.

On the Pressor Activity of Extracts of Hypertensive Blood. By HENRY A. SCHROEDER and C. CHESTER STOCK (introduced by C. P. Rhoads), New York, N. Y.

An attempt has been made to find whether the blood of patients exhibiting arterial hypertension contains pressor or other abnormal substances not present in normal individuals.

Concentrates were made from the acidified alcoholic filtrates of 50 large samples (120 to 400 cc.) of arterial blood so that 1 cc. equalled 20 cc. of original blood. They were taken from 38 patients of whom 24 had hypertension and 14 did not. Certain differences were found in the extracts taken from the two groups.

A. Picrates of these extracts were formed and the intensity of color was measured according to Richter's method. A color scale was used of concentrations of iso-amyl amine picrate. In 32 samples of hypertensive blood, the range ran from 1 to more than 10 γ per cc. of original blood, the average being 5.6 γ. In half, it was more than 4. In 14 samples of normal blood, it varied from 6.7 to 0 γ per cc. (average 2.2), in only 3 being more than 4. Extracts of plasma gave more color than did those of cells.

B. The extracts from 18 of 20 hypertensive patients caused pressor responses in rats on intravenous injection, lasting 15 to 30 minutes; and in only 2 of 14 normal subjects. That portion of the extracts occasioning pressor effects was insoluble in petroleum ether and when alkaline was soluble in toluene. It was partially purified by chromatographic adsorption, and disappeared after treatment with amine oxidase. Toluene extracts containing picrates made from 12 samples of hypertensive blood were likewise pressor; those made from 5 samples of normal blood were not.

In 15 hypertensive patients, the extracts contained the pressor material and the picrates together; in normal patients, both were present in only 2 cases. These observations indicate that there are differences between the bloods of hypertensive and of non-hypertensive patients.

Further Studies of the Mechanism of Nephrotoxic Nephritis in Rabbits. By CALVIN F. KAY (introduced by O. H. Perry Pepper), Philadelphia, Pa.

Nephrotoxic nephritis, produced by the injection of anti-renal sera, has been studied extensively because of its remarkable clinical and pathologic similarity to human glomerulonephritis. The virtue of the disease as an experimental medium has, however, been dulled by the lack of analogy between the supposed mechanism of the disease—an attack by injected antibodies directly upon the antigen inherent in the kidneys of the recipient—and any conceivable mechanism in human nephritis.

Two years ago it was suggested (Kay) that immunologic affinity binds nephrotoxic duck protein to the kidneys of the injected rabbit, but that nephritis ensues *only* when the nephrotoxin-kidney combination is attacked by anti-duck protein antibodies formed by the rabbit. The latent period between injection and the onset of the nephritis was found to be related to the rate of formation of anti-duck antibodies by the rabbit. Inhibition of antibody formation by the use of x-ray prevented the development of the nephritis.

The validity of this concept appears to be proven by the demonstration in the present experiments, fully con-

* The expense of this investigation was defrayed in part by grants from the Armour Laboratories and from the Markle Foundation.

trolled, that nephritis is readily induced in rabbits exposed to x-ray and injected with nephrotoxic serum by the passive transfer of antibodies to duck serum. The concept is interestingly analogous to the hypothesis that human glomerulonephritis develops as the result of the interaction of antibodies with an antigen formed as the result of the action of some product of the streptococcus upon the kidney.

The Relation of the Serum Antistreptolysin Titer to the Exacerbation in Chronic Glomerulonephritis. By DAVID P. EARLE, JR. (by invitation), DAVID SEEGAL, and (by invitation) JOHN D. LYTTLE, EMILY N. LOEB, and ELIZABETH L. JOST, New York, N. Y.

Thirty-three exacerbations in chronic glomerulonephritis were observed in 15 of 81 nephritic patients, studied for from 4 months to 8 years. Each exacerbation was preceded by an infection. An examination of the antistreptolysin titer response to these infections followed by exacerbation in chronic glomerulonephritis revealed the following:

1. Twenty-four of the 33 exacerbations were associated with rises in serum antistreptolysin titer. In 6, there were no rises and in 3, the data were insufficient to determine whether a rise in titer had occurred.
2. When it occurred, the greater the magnitude of the rise in antistreptolysin titer, the greater was the incidence of associated exacerbation in chronic glomerulonephritis.
3. The exacerbation preceded the onset of the rise in serum antistreptolysin titer in 7 of the 8 instances in which determinations were performed at intervals that permitted conclusions on this point.
4. There was a high incidence of transient impairment of renal function in exacerbations associated with and also without rises in serum antistreptolysin titer.

A Quantitative Analysis of Sulfonamide Bacteriostasis. By HARRY M. ROSE and CHARLES L. FOX, JR. (introduced by A. R. Dochez), New York, N. Y.

The bacteriostatic effects of sulfanilamide, sulfaguanidine, sulfapyridine, sulfathiazole, and sulfadiazine were studied in relation to (*1*) the minimal effective concentration (MEC) of the drugs, (*2*) the amount of para aminobenzoic acid required to prevent bacteriostasis, (*3*) the size of inocula, and (*4*) the type of media employed.

With *E. Coli* as the test organism in two different synthetic inhibitor-free media, the lowest molar concentration of each drug required to prevent visible growth with inocula of 25 to 25,000 cells per cc. was determined. The following values in millimoles per cc. were obtained: sulfathiazole and sulfadiazine 4, sulfapyridine 20, sulfaguanidine 500, and sulfanilamide 2500. The minimal amount of PAB required to abolish bacteriostasis with the MEC of each drug was found to be constant (0.5 mM. per cc.), giving PAB/drug ratios: sulfathiazole and sulfadiazine $\frac{1}{8}$, sulfapyridine $\frac{1}{40}$, sulfaguanidine $\frac{1}{1000}$, and sulfanilamide $\frac{1}{6000}$. The ratios were shown to be the same with drug concentrations above the MEC.

Cultures inoculated with less than 50,000 cells per cc. consistently showed no visible growth with the MEC of the drugs. However, large inocula invariably produced visible turbidity, even when much greater amounts of the drugs were used. Serial counts on growing cultures revealed that the number of cell divisions that occurred before bacteriostasis was approximately the same (6.5), regardless of the size of the inoculum up to 12,000,000 per cc. The larger inocula, therefore, produced visible turbidity although the bacteriostatic effect of the drugs, as judged by the limitation of cell division, was as great as with the smaller inocula. Similar effects were noted with hemolytic streptococci, although the number of cell divisions was less than with *E. Coli.*

The following conclusions seem warranted:

(*1*) The bacteriostatic potency of the sulfonamides is directly related to the amounts of PAB required to abolish their action.

(*2*) Bacteriostasis is dependent upon critical concentrations of the sulfonamides and sulfonamide inhibitor, and is unrelated to the number of bacteria.

Enzymatic Identification of p-Aminobenzoic Acid (PAB) in Cultures of Pneumococcus and Its Relation to Sulfonamide-Fastness. By G. S. MIRICK (introduced by O. T. Avery), New York, N. Y.

It has been previously reported that varying amounts of substances which are inhibitory to the bacteriostatic action of the sulfonamides are formed when pneumococci are grown in an inhibitor-free medium, prepared from fresh liver. The chemical nature of the sulfonamide inhibitor produced by bacteria has not been reported, nor has PAB been shown to occur in nature except in yeast. The amount of sulfonamide inhibitor produced by a sulfonamide fast strain of pneumococcus Type I is ten times greater than that produced by the parent strain. In each case, this inhibitor has certain of the chemical characteristics of PAB, being extractable in acid ether and giving the diazo reaction.

There is strong evidence that this substance is actually PAB since it is rapidly destroyed by a suspension of soil bacilli which have been specifically adapted to oxidize PAB, and is not attacked by the basal inactivated cells of this bacillus. Furthermore, the inhibitor produced by the pneumococci specifically activates the PAB oxidizing enzymes of the soil bacilli grown in its presence.

The pneumococcal cells themselves contain none of this substance. The PAB must be either synthesized by the pneumococci or enzymatically released from a precursor in the liver medium.

Do Sulfonamide-Resistant Pneumococci Develop During Treatment of Human Infections? By MORTON HAMBURGER, JR., L. H. SCHMIDT, and J. M. RUEGSEGGER (introduced by M. A. Blankenhorn), Cincinnati, Ohio.

To determine whether sulfonamide-resistant pneumococci develop during treatment of human infections, a study was made of the *in vitro* sensitivity of microorgan-

isms isolated from patients before and at various times during and after treatment.

In 62 cases of pneumonia, treated with 15 to 50 grams of a sulfonamide drug, the sulfonamide sensitivity of pneumococci isolated during and after treatment was essentially identical with that of organisms obtained prior to therapy. In three cases, a moderate increase in resistance was detected.

Three cases were studied in which the total sulfonamide dose exceeded 240 grams. In all three, the organisms recovered after treatment showed a striking increase in their resistance to sulfonamides. In a case of unresolved pneumonia, the type II pneumococci obtained prior to treatment were unable to grow in media containing 0.6 mgm. per cent sulfathiazole, whereas organisms isolated after five weeks of treatment multiplied in 20 mgm. per cent of this drug. In another case, that of a patient with subacute endocarditis due to pneumococcus type VII, organisms isolated prior to therapy failed to grow in media containing more than 2.5 mgm. per cent sulfapyrazine, but organisms isolated after four months of treatment grew in media containing 80 mgm. per cent of this sulfonamide.

These findings indicate that there is little hazard of producing sulfonamide-resistant organisms during the short intensive treatment required for pneumococcal pneumonia. However, where prolonged treatment is necessary, this hazard is considerable.

Effect of Food and Alkali on the Absorption of Sulfonamide Drugs After Oral and Duodenal Administration. By OSLER L. PETERSON (introduced by Laurence B. Ellis) and MAXWELL FINLAND, Boston, Mass.

A standard 5-gram dose of the various sulfonamide drugs was used and absorption was studied by following the concentrations of drug in the blood and the amount excreted in the urine. The drugs were administered alone, with sodium bicarbonate, and as the sodium salt. They were given orally and directly into the duodenum, in the fasting state and after an ordinary meal (breakfast).

Sulfapyridine, sulfathiazole, and sulfadiazine behaved similarly in comparative studies. When these drugs were administered directly into the duodenum, they appeared quickly in the blood, but the total amount absorbed was small, as indicated by the low maximum levels attained and the small percentage of the administered drug that could be recovered in the urine. When the drug was given orally in the fasting subject, absorption was slightly delayed, but the amount recovered was greater. The administration of sodium bicarbonate in equal amounts usually resulted in earlier attainment of the maximum level, but the total amount absorbed was not increased. When given orally after a meal, the maximum blood concentration of the drugs was higher and the total amount recovered in the urine was greater. When given as the sodium salts orally before a meal, the levels of drug attained and the total amount recovered in the urine were almost similar to those obtained from intravenous injection. After a meal, absorption was reduced and retarded. When put into the duodenum, the sodium salts were absorbed rapidly and completely. Sulfanilamide was absorbed more rapidly and more completely than the other three drugs, when given by mouth or into the duodenum. Absorption of this drug also was retarded when it was given after a meal.

The Effects of Thymectomy upon Neuromuscular Function in Myasthenia Gravis. By A. M. HARVEY and (by invitation) J. L. LILIENTHAL, JR., and S. A. TALBOT, Nashville, Tenn.

Five months after extirpation of the thymus by Dr. Alfred Blalock, three patients with severe myasthenia gravis have shown striking clinical improvement and the following alterations in the electromyogram, and in the reactions to prostigmine and acetylcholine injected into the brachial artery. (*1*) A maximal nerve stimulus excites 70 to 100 per cent more muscle fibers. (*2*) The characteristic partial block in neuromuscular transmission has disappeared or has been diminished significantly. (*3*) Prostigmine injected into the brachial artery produces fasciculations in the injected area in contrast to their absence before operation. (*4*) Intra-arterial prostigmine produces normal local motor weakness and a normal depression of neuromuscular transmission in two patients; the third shows greatly increased prostigmine response. (*5*) Prostigmine induces repetitive responses to single stimuli, as in normal subjects. (*6*) In one subject, the myasthenic sensitivity to acetylcholine has diminished. These changes represent a return of neuromuscular function to or toward a normal state.

The occurrence of thymus hyperplasia in myasthenia, and the repair of the neuromuscular defect after thymectomy, indicate a pathogenetic relationship between the thymus and myasthenia. It suggests, further, that the thymus plays a role in the control of neuromuscular function.

Sporadic Meningoencephalitis of Undetermined Etiology. By ALISON H. PRICE (introduced by Hobart A. Reimann), Philadelphia, Pa.

One may gain the impression from recently published tables of classification (Toomey, J. A. M. A., 1940, **115**, 1985; Webster, J. A. M. A., 1941, **116**, 2840) that most of the cases of nonbacterial encephalitis or meningoencephalitis encountered can be grouped as known entities. This is apparently not the case, since the majority of cases (probably 80 per cent) cannot as yet be diagnosed etiologically by immunologic tests now in use or by animal inoculation. Only recently three more entities have been discovered to be added to the list, namely the Russian tick-borne spring encephalitis, West Nile fever, and African Bwamba fever; and evidence that other specific encephalitides occur is suggested by our recent experience in Philadelphia.

In a few weeks of June, 1941, 4 cases of non-fatal meningoencephalitis occurred. They were undistinguished clinically by any but the usual symptoms or signs of the syndrome, with a gradual onset usually preceded

by a mild respiratory tract infection, nuchal rigidity, photophobia, mental confusion or somnolence, lasting from 3 to 9 days. Laboratory data were at variance with the usual neurotropic virus diseases in that polymorphonuclear leukocytosis was uniformly present in the blood and spinal fluid. Furthermore, immunologic tests and animal inoculation with spinal fluid and blood serum, performed by Doctors Joseph Smadel and Charles Armstrong, gave entirely negative results, which rules out lymphocytic choriomeningitis, equine encephalitis, St. Louis encephalitis, Japanese B. encephalitis and louping ill. Viennese (von Economo) encephalitis and atypical poliomyelitis were also considered in clinical differentiation but could not be tested for, for the want of helpful tests. The 4 cases we dealt with therefore appear to be ones of a still unclassified form of so-called aseptic meningitis or meningoencephalitis.

German Measles as an Incitant of Rheumatic Fever. By MARK P. SCHULTZ, Washington, D. C.

Reports in the British military medical literature recently have expressed concern over the possible association of carditis with German measles. In the study of a recent epidemic, we have found that although arthritis is frequently associated with such infection, carditis appears to be a manifestation of rheumatic fever activity, apparently provoked by the measles infection. This study comprised the use of throat cultures and antistreptolysin titrations of serum to evaluate the possibility of hemolytic streptococcus infection being responsible.

*Studies of Biotin Metabolism in Man.** By THEODORE W. OPPEL (introduced by David P. Barr), New York, N. Y.

Biotin, the most recently purified member of the vitamin B complex, is used by many microorganisms and at least several species of animals. Chicks become deficient if they receive less than 7 to 10 gamma of biotin per 100 grams of ration, but rats cannot be made deficient by a low biotin diet. They must be fed large quantities of egg white. This contains a material called avidin which prevents the absorption of the vitamin.

The metabolism of biotin in human subjects has been studied. Ordinary diets contain from 30 to 65 gamma, and alterations in the amount of biotin in the food were accompanied by corresponding alterations in the urine. The amount in the urine, however, often exceeded the amount in the diet, and even when no food was consumed the urine continued to contain quantities of biotin that were relatively normal. This urinary biotin was provided by synthesis of the vitamin by the bacteria in the intestinal tract, for the stools invariably were found to contain more biotin than the diet. From 3 to 6 times as much biotin was eliminated in the urine and stools as the diet contained.

Apparently in man there is a relatively constant level of biotin excretion in the urine, based on biotin synthesis by intestinal bacteria and, superimposed on this, sudden variations occur due to changes in the biotin content of the diet. The quantity of biotin provided by bacterial synthesis seems to be adequate for the needs of man, and human subjects probably do not require any biotin in their food.

* This investigation has been aided by a grant from the Josiah Macy, Jr. Foundation.

Studies with Radioactive Di-Azo Dyes. By FRANCIS D. MOORE * and LESTER H. TOBIN (introduced by Joseph C. Aub), Boston, Mass.

Radioactive analogues of two colloidal dyes (trypan blue and Evans blue or T–1824) have been synthesized. The synthesis is not time-consuming and produces a dibrom radioactive dye of known chemical structure and adequate radioactivity for studies in the intact animal or excised tissue. Chemical and biological properties of the radioactive dyes are those of their non-radioactive counterparts, and include accumulation in areas of increased capillary permeability, such as abscesses and tumors.

Potential use as a means of localizing abscesses has been studied in rabbits. Peripheral abscesses were detectable in all instances, the dye being given intravenously and the animal "scanned" with an externally-placed Geiger counter. Abscesses on the abdomen were less reliably diagnosed, 77 per cent giving positive results.

Possible usefulness as a means of internally radiating tumors has been investigated in mice. Ten per cent of the tumors accumulated the dye in concentrations equal to or greater than the kidneys and spleen. Only a very small group accumulated the dye in concentrations greater than the liver. Such radioactive colloids might be useful as internal radiation therapy if the tumor were widespread and of high sensitivity. Tumors undergoing haemorrhagic necrosis accumulate significant radioactivity in the haemorrhagic fluid, suggesting the usefulness of coincident therapy with agents increasing the permeability of capillaries within the tumor.

The Prevention of Electrocardiographic Evidences of Myocardial Anoxemia by Chemical Means. By SAMUEL PROGER and (by invitation) MARK AISNER, and RAYMOND B. SQUIRES, Boston, Mass.

Certain chemical substances of the C_4 dicarboxylic acid group have been shown to promote tissue oxidation catalytically.

Under conditions of decreased oxygen tension, the catalytic effects *in vitro* of succinic, fumaric, malic, and oxaloacetic acids are even greater than under conditions of normal or high oxygen tensions; in some cases, in a 10 per cent oxygen environment, the oxygen uptake of minced heart muscle of a dog is increased by more than 100 per cent by these substances.

In intact anesthetized dogs, and under the conditions of our experiments, certain electrocardiographic changes which occur in the presence of 10 per cent anoxemia are sometimes apparently prevented by the previous intravenous administration of sodium succinate.

* Fellow in Medicine, National Research Council.

The Effect of Varying Blood Sugar Levels on the Electroencephalogram in the Normal Adult During Normal Breathing and Hyperventilation. By JACOB E. FINESINGER and (by invitation) M. A. B. BRAZIER and ROBERT S. SCHWAB, Boston, Mass.

The results of previous workers with very small numbers of subjects have shown that there is a great individual variation in the electroencephalographic pattern. The present study deals with quantitative changes in blood sugar level, respiratory volume, electroencephalographic rhythm, and their intercorrelations in a series of 45 normal subjects. Repeated electroencephalographic tracings were obtained on each subject during a 3-minute period of normal breathing, followed by a 3-minute period of controlled and measured hyperventilation. Blood sugar determinations were made after each test.

The following results were obtained:

1. *Normal ventilation.*

(*a*) No delta activity was observed during normal breathing at any blood sugar level.

2. *Hyperventilation.*

(*a*) In 22 per cent of the subjects, no delta wave activity at fasting blood sugar levels was observed. Delta wave activity could be elicited after the administration of insulin.

(*b*) Fifty-three per cent of the subjects showed delta waves at fasting blood sugar levels, but not after the ingestion of glucose.

(*c*) The remaining 25 per cent showed the presence of delta activity at all blood sugar levels, even after the ingestion of glucose.

3. In some subjects, low blood sugar levels produce a slowing of the alpha rhythm during normal breathing.

4. In subjects in whom the ingestion of glucose inhibits the production of delta activity on hyperventilation for 3 minutes, the critical blood sugar level is approximately 130 mgm. per 100 cc.

5. In tests in which the blood sugar level was the same, the depth of respiration was the deciding factor in determining the amount of delta activity present.

6. Since the frequency of alpha rhythm and the presence of delta waves are now used in assessing normal electroencephalographic records, it is essential that all tests be carried out at non-fasting blood sugar levels.

Central Sympathetic Paralysis. By EUGENE A. STEAD, JR. and (by invitation) JOHN ROMANO and RICHARD V. EBERT, Boston, Mass.

The disturbances in function of the sympathetic nervous system, resulting from lesions in the medulla produced by thrombosis of the posterior inferior cerebellar artery, have been studied in 6 patients. This central sympathetic paralysis differs strikingly from that produced by pre- or post-ganglionic sympathectomy. Instead of the complete loss of sympathetic function which peripheral sympathectomy produces, these patients showed selective impairment. Sweating and vasoconstriction in response to cooling the body were markedly impaired. Other functions, such as vasodilation from heating the body and vasoconstriction in response to sensory stimuli or a deep inspiration, were not affected.

The mechanism which inhibits vasoconstriction when the body is cooled, without interfering with vasodilation when the body is heated, is of both theoretical and practical importance. The patient with Raynaud's disease tends to improve after either pre- or post-ganglionic sympathectomy, because cooling the body no longer reduces the blood flow to the extremities. In a cool room, however, he has the severe disadvantage that heating the body by wearing warm clothes no longer increases the blood flow to the extremities. In the sympathetic paralysis produced by lesions in the lateral medullary area, this disadvantage does not exist.

Experiments were performed which showed that vasoconstriction is an active process, while vasodilation is a passive one caused by inhibition of vasoconstriction. This fact explains why, in this type of central sympathetic paralysis, vasoconstriction on cooling the body is incomplete, whereas vasodilation is unaffected. The lesion in the medulla destroys the main uncrossed vasoconstrictor tract, but partial vasoconstriction still occurs either because the lesion in the medulla does not destroy all the uncrossed descending sympathetic fibers or because there are some fibers from the opposite side which cross below the lesion. Inhibition of vasoconstriction, however, results in normal vasodilation, because while there is not enough sympathetic activity to produce full vasoconstriction, there is enough sympathetic function to prevent the marked increase in tone of the blood vessels which occurs after pre- or post-ganglionic sympathectomy.

Cutaneous and Visceral Pain Sensitivity in Normal Subjects. By WILLIAM P. CHAPMAN (by invitation) and CHESTER M. JONES, Boston, Mass.

One hundred and eighty normal subjects of various ages, races, occupations, and emotional types have been studied for their perception and reaction to cutaneous pain, by a modification of the heat-radiation apparatus of Wolff, Hardy, and Goodell. Thirty of these individuals were tested for visceral pain sensitivity by distending the lower end of the esophagus with a balloon. The perception of the pain threshold for cutaneous pain has been taken as a beginning, sharp jab sensation, and the "reaction" to pain as the first motor response to the pain stimulus. The only reliable end-point for visceral sensitivity appeared to be the lowest stimulus which produced a substernal sensation of beginning fullness. A correlation of this visceral sensory threshold was made with the cutaneous pain threshold in those subjects tested by both procedures.

The results of the cutaneous pain tests indicate a wide range of sensitivity as regards variation in pain threshold and reaction to pain. Pain sensitivity appeared to decrease with age and to vary with race. A group of individuals of Nordic stock were less sensitive than similar groups of Negroes, Italians, and Russian Jews. There

was a significant correlation between the cutaneous pain and visceral sensory thresholds.

The Effect of Cigarette Smoking on the Peripheral Blood Flow. By WILLIS F. EVANS (by invitation) and HAROLD J. STEWART, New York, N. Y.

In recent years, there has been added interest in the effects of smoking tobacco on the human organisms. This has to some extent paralleled the increase in interest in the peripheral circulation. There are in the literature data relating to the effect of smoking cigarettes on the peripheral blood flow, blood pressure, and heart rate. The inferences about peripheral blood flow have been made from volume changes in a digit or extremity by modified plethysmographs or from local change in temperature. We have now measured the average peripheral blood flow for the whole body surface in cc. per M^2 per minute, by a modification of the method of Hardy and Soderstrom, in the course of which we secured not only temperatures of various areas of the body but also the average surface temperature; in addition, we have recorded blood pressure, pulse rate, and basal metabolic rate for correlation with the changes in peripheral blood flow.

Observations were made of 10 normal male subjects. All observations were made in the morning while the subjects were in a basal metabolic state, data being recorded before, during, and after smoking. Each subject smoked on successive days regular or standard cigarettes, so-called commercial "denicotinized" cigarettes, and cigarettes made of cornsilk. In addition, 4 observations were made of 3 subjects to secure data about "fully denicotinized" cigarettes. The following effects were observed: regardless of the type of cigarette smoked, whether "regular," "denicotinized," "fully denicotinized," or cornsilk, there occurred, in all except 4 instances, a moderate fall in peripheral blood flow, that is to say, the average amount of blood allotted to the periphery was decreased. There occurred rise in blood pressure and in pulse rate, fall in temperature of the extremities and in the average surface temperature, and increase in rectal temperature of essentially the same magnitude and duration regardless of the type of cigarette which was smoked. Nicotine has been credited in the previous studies with inducing these effects. Since changes of the same magnitude occurred from the smoking of commercial denicotinized cigarettes, from those fully denicotinized, and from those made of cornsilk, it appears that it is not nicotine but some other unknown substance which is responsible.

The Relationship of the Coagulation Defect in Hemophilia to a Plasma Proteolytic Enzyme. By HENRY J. TAGNON, CHARLES S. DAVIDSON, and F. H. L. TAYLOR (introduced by George R. Minot), Boston, Mass.

By shaking oxalated or citrated platelet free human plasma with chloroform, a clot is produced which redissolves entirely in the subsequent 5 to 10 days; when dissolution is complete, the preparation, called chloroform plasma, contains an active proteolytic enzyme, responsible for the dissolution of the clot, and for the proteolytic behavior of subsequent preparations. This enzyme is associated with the globulin fraction of the chloroform plasma from which it can be separated by precipitation at pH 6 or by dialysis against water. The proteolytic activity of this preparation is evidenced by its digestive action on gelatin and casein as well as on fibrinogen and fibrin, in the absence of bacterial contamination.

Previous investigations have shown that the coagulation defect in hemophilia is due to the deficiency of a cell free plasma factor associated with the globulin fraction obtained by precipitation of blood plasma at pH 6 or by dialysis. When hemophilic plasma is shaken with chloroform, the clot formed redissolves in a longer time than that of normal plasma. Also, when the dissolution is complete, the enzymic activity of preparations from hemophilic plasma when tested on fibrinogen and fibrin and compared to preparations from normal plasma is markedly lower.

These results indicate that, in hemophilia, the deficiency of a factor associated with the globulin fraction of the plasma ("globulin substance") is paralleled by a deficiency in proteolytic activity associated with the globulin fraction of chloroform plasma.

Observations on the Effect of Promin on the Blood of Tuberculous Patients. B. E. HALL, H. C. HINSHAW, and KARL PFUETZE (introduced by H. Z. Giffin), Rochester, Minn.

In tuberculosis, treatment with sodium p,p'-diaminodiphenylsulfone-N,N'-didextrose sulfonate ("promin") necessitates administration of the drug over long periods and affords the opportunity of studying the delayed as well as the immediate effects of this substance. This is in contrast to most diseases in which chemotherapeutic agents of sulfonamide type are administered for only short periods. Eighty-one cases are included in this study. Of these, seventy-six were cases of pulmonary tuberculosis, three were of renal tuberculosis, one was of tuberculosis of bone, and one was of tuberculous meningitis. Of the cases of pulmonary tuberculosis, hematologic studies extended over a period of from four to nine months in sixty-seven cases and from three to three and a half months in five cases.

The principal effect of promin on the blood was the development of anemia as a result of excessive destruction of blood. It occurred in all cases and was used as one of the criteria for gauging doses. Moderately severe acute anemia was observed during the administration of comparatively large doses of the drug; on smaller doses, chronic anemia was noted. In one case, extremely acute hemolytic anemia developed with alarming rapidity during the administration of small doses of promin over a period of three days.

Leukopenia with neutropenia of moderate degree was observed in four cases and agranulocytosis associated with ulcerative lesions in the throat occurred in one case.

A Report of Clinical Studies with the Synthetic Dicoumarin 3,3'-Methylenebis (4-hydroxycoumarin). By OVID O. MEYER and (by invitation) JAMES B. BINGHAM, Madison, Wis.

Dr. Karl Paul Link and his associates of the Wisconsin Agricultural Experiment Station have reported the isolation of the agent in spoiled sweet clover responsible for the hemorrhagic disease of cattle, and the subsequent successful synthesis of a dicoumarin which is biologically identical.

During the past 18 months, this synthesized substance, 3,3'-methylenebis (4-hydroxycoumarin) has been employed in animal experiments and clinical studies. Published reports have described the experiences in dogs, the significant pathologic changes, which included dilatation of smaller vessels, the lack of toxicity attendant upon its use in reasonable dosage and the efficacy in prolonging the prothrombin time and coagulation time when administered orally, or intravenously in the form of the disodium salt.

The present report deals with additional clinical experiences in cases with thromboses, peripheral vascular disease, subacute bacterial endocarditis, and other conditions. A total of 98 cases have been treated. The present dosage, the indications and contraindications, the advantages over heparin, and the hazards associated with the use of this dicoumarin will be discussed. Briefly it may be stated that a satisfactory oral dose for most patients (there is considerable individual variation in response) is 5 mgm. per kgm., followed by daily doses of 1.5 mgm. per kgm. To date, it has not been demonstrated that any clinical condition contraindicates the use of the drug if local bleeding, hemorrhagic states, and probably advanced hepatic disease be excluded. The advantages of the material over heparin include the ready availability and low cost, the two successful routes of administration, and the sustained effect. The chief disadvantage observed to date is the protracted effect after the drug is stopped. The coagulation time can be reduced temporarily with fresh blood transfusions, but not with vitamin K administration.

The Dicoumarin-3,3' Methylenebis 4 Hydroxycoumarin. Its Pharmacological and Therapeutic Action in Man. By IRVING S. WRIGHT and (by invitation) ANDREW PRANDONI, New York, N. Y.

This paper presents data obtained from the study of thirty patients who have received this substance under well controlled conditions. Data on bleeding and coagulation times, prothrombin studies, clot retraction, liver and kidney function tests, gastric analysis, and other laboratory and clinical observations will be presented.

This dicoumarin produces prolongation of the clotting and prothrombin times. The mechanism of action and the clinical effects and complications will be discussed. Therapeutic indications will be evaluated. Recommended dosage, methods of administration and of producing cessation of action when desired will be outlined.

Report of Experimental and Clinical Studies with Dicoumarin. By E. V. ALLEN and (by invitation) J. L. BOLLMAN and N. W. BARKER, Rochester, Minn.

Experimental and clinical studies indicate that dicoumarin administered orally increases greatly the prothrombin time of the blood and increases less markedly the extravascular coagulation time of the blood. Clinical and experimental studies indicate that when the dosage of the drug is carefully regulated, no harm results, as no morphologic or physiologic effects upon the blood, liver, kidneys, and other vital structures have been noted, with the exception of the effect on prothrombin and coagulation time. Two hundred milligrams given on two or three successive days usually prolongs the prothrombin time greatly for from seven to ten days, after a latent period of twenty-four to thirty-six hours after the original dose. When large amounts of the drug are given to animals, fatal hemorrhage may occur. The drug has been administered to approximately seventy-five patients without harmful effects, except for controllable hemorrhage from operative wounds in six instances. The prothrombin time and coagulation time of the blood of both animals and human subjects can be temporarily restored to normal by the transfusion of fresh blood. Vitamin K is almost entirely ineffective in reducing the prothrombin time when it has been increased by administration of dicoumarin. The preparation has been found to be very useful in experimental studies where it is desired to avoid the intravascular coagulation of the blood. Intravascular thrombosis, such as that which occurs in thrombophlebitis, has not affected any of the treated patients after treatment was begun and pulmonary embolism has been entirely lacking, although many of the cases were those in which the dangers of venous thrombosis and pulmonary embolism were great. The series is, of course, too small to allow a statement relative to the use of this drug for prophylaxis against intravascular thrombosis. It appears that the use of dicoumarin may replace the use of heparin. Obvious advantages are effectiveness by oral administration, and cheapness. Since dicoumarin has been used clinically, the authors have almost entirely ceased the use of heparin.

READ BY TITLE

Studies on the Administration of Normal Human Plasma Preserved in the Liquid State. By L. R. NEWHOUSER, D. B. KENDRICK, and EUGENE L. LOZNER (introduced by Clark W. Heath, Boston), Washington, D. C.

The results of over 600 administrations of normal human plasma, preserved in the liquid state, to over 300 patients have been analyzed. This plasma was prepared by a closed system without any filtration. A glass cloth or steel mesh filter was used during the administration. The elapsed time between drawing the donors' blood and administering the plasma varied from 2 weeks to 12 months. The average time was 2½ months. The temperature at which the plasma was preserved varied from 4° to 25° C. The amount administered to any one patient varied from 30 ml. in an infant to 2500 ml. in a

patient with severe peripheral circulatory failure. The average amount administered was 500 ml. The most frequent indications for which plasma was administered were the treatment and prevention of secondary shock and the treatment of hypoproteinemia. In 86 per cent of the administrations, the therapeutic result was beneficial, and in 14 per cent, it was equivocal. In 1 per cent of the administrations, untoward reactions attributable to the plasma occurred. The most frequent of these was urticaria. It may be concluded that normal human plasma may be preserved in the liquid state for periods up to at least 12 months and be administered to patients with safety and benefit.

An Experimental Evaluation of the Intensive Drip and Other Intensive Methods for the Treatment of Syphilis. By HARRY EAGLE and (by invitation) RALPH B. HOGAN, Baltimore, Md.

The total curative dose of mapharsen in syphilitic rabbits was only slightly affected by wide variations in the frequency of injection, and in the total duration of treatment. On any method of treatment, whether intravenous drip, or intravenous injections repeated several times daily, daily, three times weekly, or weekly, the total amount of arsenical tolerated did, however, increase directly with the duration of treatment. It follows that the margin of safety (chemotherapeutic index) on any treatment schedule may be increased many-fold by suitable prolongation of the treatment period.

In the experimental animal, an intravenous drip over a four day period provided a margin of safety between the effective and toxic levels only one-third to one-fourth that afforded by standard clinic practice of weekly injections over a period of many months. The animal studies did, however, suggest that it may be possible to concentrate treatment safely along more conservative lines, and to administer effective amounts of arsenical within a period of four to ten weeks, with a margin of safety comparable to that afforded by current procedures. Clinical studies in this direction are now in progress.

Familial Mediterranean (Target-Oval Cell) and Familial African (Target-Sickle Cell) Anemias. By WILLIAM DAMESHEK,* Boston, Mass.

Studies of Italian families have revealed several syndromes ranging in severity from Cooley's erythroblastic anemia and the previously described "Target Cell" Anemia to cases with mild hypochromic anemia. Severe cases show splenomegaly and jaundice, milder ones either "hypochromic polycythemia" or mild hypochromia, target and oval erythrocytes, increased hypotonic resistance, basophilic stippling, and refractoriness to iron therapy.

These syndromes, inherited as a Mendelian dominant, present a high incidence of transmission in the offspring. Milder syndromes are inherited from one parent, but the severe Cooley's anemia apparently requires transmission from two mildly affected parents. Mediterraneans with splenomegaly, a cardiac systolic murmur, diminished hemoglobin, erythrocytosis, refractory hypochromic anemia, hemolytic jaundice, or basophilic stippling should be suspected of a target-cell syndrome. The fundamental inherited abnormality is probably a disturbed hemoglobin metabolism with the resultant production of abnormally thin erythrocytes.

Numerous clinical and hematological resemblances between the essentially Mediterranean target-oval cell syndromes and the essentially African target-sickle cell syndromes suggest a fundamental relationship between them. This is confirmed by transition forms between the two diseases. A large reservoir of flat red cells ("leptocytosis") exists in both racial groups, appearing frequently as either target-oval or target-sickle-cell syndromes.

A New Conception of the Cause of Patency of the Ductus Arteriosus Based upon Experiments on Its Physiology. By J. ALLEN KENNEDY (introduced by C. Sidney Burwell, Boston), Nashville, Tenn.

There have been many theories of the mechanism of closure of the ductus arteriosus at birth, none of them backed by experimental evidence. Our studies on the physiology of the ductus arteriosus in guinea pigs have resulted in the following:

(*1*) The mechanism of closure of the ductus arteriosus at birth has two phases:

(*a*) An immediate one much like the contraction of a muscular sphincter which functionally closes its lumen, and

(*b*) A slower histological change during which the ductus is transformed from a muscular tube to the fibrous connective tissue ligamentum arteriosum.

(*2*) The ductus arteriosus will close in response to the following:

(*a*) Normal breathing.

(*b*) Mechanical or electrical stimulation to the ductus.

(*c*) Artificial inflation of the lungs through a tracheal cannula with either air or oxygen.

(*d*) Injection of adrenalin.

(*e*) Massage of the carotid sinus.

Closure of the ductus is not a neurological mechanism. Under the proper condition the ductus may be closed and opened many times.

Based on these experiments we have arrived at a new conception of the cause of patency of the ductus arteriosus. Instead of being a developmental anomaly or abnormality, it may be due to failure of the normal physiological process of closure.

The Quantitative Response of the Smallest Blood Vessels of the Human Skin to Graded Mechanical Stimulation and to Local Ischemia in Arterial Hypertension, Arteriosclerosis and Certain Allied Disorders. By JOSEPH R. DIPALMA and FRANCES I. FOSTER (introduced by J. Hamilton Crawford), Brooklyn, N. Y.

It has been repeatedly confirmed that the smallest blood vessels (precapillary arterioles, capillaries, and venules)

* From the J. H. Pratt Diagnostic Hospital and the Blood Clinic, Boston Dispensary.

take little or no part in the peripheral resistance of the hypertensive states. This, however, does not constitute absolute proof that such small vessels may not be involved in generalized vascular disease in ways other than can be demonstrated by the mere mensuration of arteriolar and capillary pressures. In this investigation, an attempt was made to elucidate this problem by other means.

The functional responses of the smallest vessels of the human skin were quantitated in suitable groups of hypertensive and arteriosclerotic patients, utilizing two methods recently devised and for which physiological, individual, seasonal, segmental, and aging characteristics have been described. One method measured the constricting responses of the small dermal vessels to graded mechanical stimulation; the other measured their ability to respond by reactive hyperemia to a standardized period of local ischemia. Comparison was made with normal data simultaneously obtained.

It was found that neither the patients with arterial hypertension nor those with arteriosclerosis had small dermal vessel responses in any way significantly different from the expected normal. There was no correlation between the severity or duration of the lesions and the quantitated responses. However, patients with the malignant syndrome of hypertension had responses which indicated small cutaneous vessels far less sensitive than normal. On the other hand, a number of hypertensive patients with various associated diseases, especially central nerve lesions, had small dermal vessels much more sensitive than the normal.

Avoidance of the Vasoconstrictor Action of Shed Blood in Perfusion of the Rabbit's Ear. By J. L. GUERRANT (by invitation), J. E. WOOD, JR. and E. M. LANDIS, Charlottesville, Va.

Attempts to perfuse the rabbit's ear with defibrinated blood from rabbits or dogs, normal or nephrectomized by the method of Page (J. Exper. Med., 1940, 72, 301) proved difficult in our hands because of immediate, or steadily increasing, intense vasoconstriction, beginning as soon as the diluted defibrinated blood entered the ear. In control observations, to maintain slow flow of defibrinated blood it was necessary to raise the perfusing pressure progressively. Assays of the pressor activity of heparinized plasma from hypertensive rabbits, dogs, and man were not convincing, partly because the tone of the auricular vessels increased unevenly in response to the perfusing fluid itself.

The intense constrictor action of heparinized whole blood and defibrinated blood on surviving blood vessels has been known for a long time and has been ascribed to powerful vasoconstrictor substances released by disintegrating platelets in latent or obvious clotting (Bayliss and Ogden, J. Physiol., 1933, 77, 34P, Janeway *et al.*, Arch. Int. Med., 1918, 21, 566). In agreement with these observations it was found that blood drawn from the heart of a normal rabbit into a syringe containing heparin and then perfused through the ear also produced progressive constriction, though at a much slower rate than defibrinated blood.

It was observed, however, that the vessels of the rabbit's ear could be kept from constricting and could be perfused for two hours or longer, at a constant rate at a low and constant perfusion pressure, without edema, only if greatest pains were taken to avoid even slight latent coagulation. It was necessary to (*a*) heparinize the donor rabbit fully, (*b*) remove the blood into a syringe containing heparin, (*c*) dilute with heparinized Ringer Locke solution, and (*d*) bubble oxygen and CO_2 through the blood constantly. Cleaning all glassware of traces of constrictor material by preliminary soaking in alcohol or by boiling in sodium bicarbonate solution is also advisable. Under these conditions, the vascular tone remains low and variations in tone over a two hour period are small. The effect of vasoconstrictor substances can be demonstrated more clearly because these precautions eliminate the more vigorous constrictor action of substances associated with clotting.

In such preparations, it was found (*a*) that 0.2 cc. of defibrinated rabbit's blood always produces complete and persisting constriction, (*b*) that rabbit or human serum is only slightly less constrictor, (*c*) that heparinized plasma of normal rabbit or man is usually inactive or very slightly constrictor, and (*d*) that pressor substances of renal origin are far weaker than the vasoconstrictor substance of partially heparinized blood, serum, or defibrinated blood. It appears that assay of renin or allied substances in the blood of hypertensive animals or patients must be carried out with utmost care to avoid artifacts due to liberation of powerful constrictor substances in the course of latent or obvious coagulation, *in vitro* or even *in vivo*.

Analysis of Breathing Pattern. By JOHN L. CAUGHEY, JR., New York, N. Y.

Little clinical use is made of the thousands of spirographic tracings which accumulate in metabolism laboratories which employ the closed-circuit method for measuring oxygen consumption. To determine whether information of value could be derived from study of these spirograms, a method was devised for carrying out detailed analysis of breathing pattern.

Breathing characteristics which could be studied on the usual type of tracing, and which represented basic components of breathing were selected. These were rate, variation in rate, depth, variation in depth, volume of ventilation, expiratory pause, expiratory mid-position, sighs, swallows, contours of single breaths, and general regularity of the whole pattern.

Careful appraisal of these characteristics was made for a series of routine metabolism spirograms obtained from 500 female and 200 male patients who had a total of 984 tests.

On the basis of this material, a range of average breathing behavior under the conditions of the test could be defined. The results obtained suggest that: (*1*) breathing behavior may indicate poor attainment of "basal

conditions" during the test, (*2*) some types of breathing pattern are not compatible with accurate measurement of oxygen consumption, and (*3*) analysis of spirograms may give significant information about the physiological characteristics of the individual patient.

A Simple Method for the Laboratory Diagnosis of Subclinical Deficiencies of Thiamin, Riboflavin and Nicotinic Acid. By VICTOR A. NAJJAR (introduced by L. Emmett Holt, Jr.), Baltimore, Md.

The problem of assaying early deficiencies of these B factors has been approached by studying the urinary excretion of thiamin, of riboflavin, and of the fluorescent substance F_2, the excretion of which has been shown * to depend upon available nicotinic acid. In previous work, by ourselves and others, several procedures have been employed:

(*1*) The 24-hour urinary excretion,
(*2*) Oral load tests,
(*3*) Parenteral load tests, in which an arbitrary dose of vitamins is given subcutaneously, intramuscularly, or intravenously, and the urinary excretion is followed during the succeeding 3 or 4 hours.

Each of these procedures has been found to have serious objections. The 24-hour excretion tends to be low or absent in vitamin deficiency, but it is unfortunately influenced by the immediate vitamin intake; even markedly deficient individuals will excrete considerable amounts after ingesting a single vitamin-rich meal. When subjected to load tests, deficient individuals tend to retain the administered vitamin and non-deficient ones to excrete it. Oral load tests are, however, subject to errors caused by differences in rate of absorption, particularly in gastrointestinal disorders. The parenteral load tests avoid this particular difficulty but are open to two other objections: (*a*) The quantity of vitamin presented for renal excretion is so great that it may exceed the renal threshold, particularly if there is renal impairment, and the tests are therefore of limited value in subjects with renal disease. (*b*) We have found that the administration of one vitamin may influence the excretion of other B factors, and conversely, a deficiency of one B factor may influence the excretion of another B factor. Such vitamin interrelationships, which complicate the interpretation of excretion tests, are more conspicuous under "load" conditions.

In order to avoid the difficulties mentioned, we have employed a new procedure, designated as the *fasting "hour excretion" test.* We have found that the effects of ingested vitamin on vitamin excretion are transitory, being limited to the first few hours. Within 12 hours after a vitamin rich meal, the resulting surplus vitamin excretion has ceased and the excretion assumes a constant level which is dependent upon the body reserve of that particular vitamin.

* Najjar, V. A., Stein, H. J., Holt, L. E., Jr., and Kabler, C. V.: J. Clin. Invest., 1942, 21, 263.

The *fasting "hour excretion" test* is conveniently performed as follows. The subject is allowed to eat his ordinary evening meal. The following morning, 12 hours later, he voids on rising and discards the voiding. One hour after this he voids the specimen used for analysis, after which he is allowed to eat his breakfast. The specimen is analyzed for thiamin, riboflavin, and F_2, the levels of these factors indicating the body stores of thiamin, riboflavin and nicotinic acid, respectively.

When the *fasting "hour excretion"* of any of these factors falls to zero it may be presumed that, for some brief period at least, there is a potential vitamin deficit, whereas a positive urinary excretion at this most critical period of the day (*e.g.* the longest period between meals) indicates that a surplus is available for urinary excretion and that the development of deficiency is not to be feared.

The *fasting "hour excretion" test* promises to give a more reliable answer than has hitherto been obtainable to the question of who needs vitamin supplements and who does not. We have studied it only in relation to the three vitamins mentioned, but it is possible that it may be applicable to other water soluble factors as well.

Sternal Marrow in Aplastic Anemia. By L. H. BEIZER (by invitation) and C. H. WATKINS, Rochester, Minn.

Sternal aspirations were carried out, and the bone marrow was examined, in 12 cases of refractory anemia in which the clinical picture was typical of aplastic anemia. Those cases presenting evidence of depression of the activity of the bone marrow, and having a relative lymphocytosis, followed the usual clinical course and death occurred within a short period of time. Those cases in which there was evidence of hyperplasia of the bone marrow, and in which a lymphocytosis was not observed, did not terminate fatally.

The Relation of Blood Pressure to Alpha Waves in the Tips of the Fingers Recorded Simultaneously with a Hamilton Manometer and a Plethysmographic Method. By CHARLES NEUMANN (by invitation) and ALFRED E. COHN, New York, N. Y.

This report deals with exploring whether alpha waves, as detected in finger tips, depend upon fluctuations in blood pressure. Simultaneous alpha waves and ipsolateral intra-radial blood pressures were recorded in ten adults, using a plethysmograph and a Hamilton manometer.

There were apparent a number of well recognized waves. All subjects exhibited slight inspiratory lowering of blood pressure which was concomitant with a small decrease in the volume of the finger tip (respiratory waves). Four subjects exhibited spontaneous fluctuations (10 mm. Hg) in blood pressure, occurring five times a minute (? Traube-Hering waves). These were accompanied by small (5 c. mm.) concordant fluctuations in volume of the finger tip.

But in addition there were many large (10 to 50 c. mm.) fluctuations (alpha waves) unrelated in time or direction to variations in blood pressure. From these data and from previous observations that the alpha waves

of adjacent fingers can vary independently, it is concluded (1) that the major rhythmic fluctuations in the volume of a finger tip have their origin elsewhere than in systemic blood pressure changes, probably in variations in local vasomotor tone, and (2) that rhythmic fluctuations in systemic blood pressure are accompanied by small concordant changes in the volume of the finger tips; that is to say, there are waves both dependent and independent of intra-arterial pressure.

During the past year and a half, it has been shown in this laboratory that the blood vessels of fingers, toes, and ears continuously undergo fluctuations in volume. As recorded by a sensitive pneumoplethysmograph these can be divided into five types of waves. Two are dependent upon the cardiac pulse and respiration. The other three are slower, larger and more irregular. Because they have not been shown to be related to other bodily functions, they have been named alpha, beta, and gamma. The alpha waves occur on an average of eight times a minute, with an average volume of 15 c. mm. (in a finger tip of 5000 c. mm.). Their rhythm is totally irregular, even for any one individual. The beta and gamma waves represent slower and larger variations in volume. There is evidence to show that in excitable individuals alpha waves tend to be large and variable in size, while in more placid individuals they are all small. Subjects have been classified into psychological types on the basis of their alpha waves.

*Neutralizing Antibodies to the Lansing Strain During the Acute and Convalescent Stages of Poliomyelitis.** By THOMAS B. TURNER and (by invitation) LAWRENCE E. YOUNG, Baltimore, Md.

Numerous reports in recent years have indicated that a majority of normal adults have in their blood serum neutralizing antibodies against various strains of poliomyelitis virus, including the Lansing strain which has been adapted to mice. However, the relationship of the presence of these antibodies to onset or recovery in clinical poliomyelitis has not been clearly defined.

During the summer and early fall of 1941, blood specimens were obtained on 64 poliomyelitis patients in Baltimore at the time of admission to the hospital, and convalescent specimens at intervals up to 6 months. Acute and convalescent sera were tested simultaneously against the Lansing strain of virus, using 12 mice for each serum. Seventeen or approximately 27 per cent of the admission specimens completely protected the test groups of mice, 11 or 17 per cent showed partial protection, and 36 or 56 per cent showed little or no protection. In all but 10 of the 64 patients, the series of convalescent sera showed exactly the same degree of protection as the admission sera, and extensive titrations failed to reveal even slight differences. The changes observed in the sera of 9 patients were slight and occurred in both directions. The admission and one-month specimens from one patient failed to neutralize the virus, but a sample taken 4 months after the onset of the disease showed definite neutralization.

It is clear that no relationship was demonstrated between the presence or absence of neutralizing antibodies to the Lansing strain and the onset of clinical poliomyelitis, in the outbreak studied. Moreover, recovery from acute poliomyelitis was not accompanied by a rise in the titre of these neutralizing antibodies. The significance of these findings were briefly discussed.

* Aided by a grant from The National Foundation for Infantile Paralysis, Inc.

Effect of Addition of Dextrose Without Extra Insulin to Usual Regimen in Diabetics and Normals Upon Oxidation of Dextrose, Protein and Fat During Different Periods of Day. By JAMES A. GREENE and (by invitation) ANN DAVID, Iowa City, Ia.

Previous data indicated that a diabetic stored most of the dextrose which was added to the usual regimen without extra insulin, but clinical observations do not substantiate it. The dextrose, protein, and fat oxidized and caloric output have been ascertained, therefore, in diabetics and normals with usual diabetic regimen and with added dextrose without extra insulin, for 24 hours which has been divided into morning, afternoon, evening, and night periods. Normals oxidized over 90 per cent of added dextrose, whereas, diabetics oxidized only 50 to 60 per cent. Proportionately more was stored by diabetics, but urine excretion increased appreciably in 2 instances. Data for morning confirm previous observations indicating storage of most of the added dextrose, and as a rule less of it was oxidized during this period than during afternoon and evening. The oxidation per hour, however, does not show any consistent difference for the 3 periods. That for the night was consistently lower. The grams oxidized per hour were not related to height of blood sugar levels. Caloric output and oxidation of protein were not materially altered, but fat oxidation varied inversely to that of dextrose.

"Body Water" in Pneumonia. By DAVID D. RUTSTEIN, K. JEFFERSON THOMSON, DANIEL M. TOLMACH, ROBERT J. FLOODY, and WILLIAM H. WALKER (introduced by Walter S. McClellan), Albany, N. Y.

As a part of a study on the circulation of patients with typed pneumococcus pneumonia, the relationships of those simultaneous observations, indicated below, concerning "body water" were studied, and the results obtained during and after recovery from pneumonia were compared.

The following results were obtained: The plasma volume, total blood volume, and extracellular fluid volume were increased during pneumonia and returned to "normal" following recovery; the hemoglobin, red blood count, and hematocrit (mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration) were unchanged; and the plasma specific gravity and total blood chlorides were decreased during pneumonia and returned to "normal" following recovery.

The results of each of the above determinations were analyzed from the point of view of age, sex, pneumo-

coccus type, bacteremia, duration of disease, and extent of lung involvement. That analysis indicated that age is a significant factor in that young individuals tend to show these changes to a more marked degree than do older individuals.

The Relationship of Vitamin A to Infection in the Chick Embryo. By W. D. HAZELHURST, W. O. JOHNSTON, and E. W. PATTON (introduced by John B. Youmans), Nashville, Tenn.

The relation of vitamin A to infection has been studied, using the chick embryo as the test animal.

The diet of the pullets was controlled with respect to vitamin A as well as other foods. Eggs from the control and deficient group were incubated, and at the 13th to 16th day the embryos were inoculated with various strains of staphylococci.

Alterations in the vitamin A intake of the pullets resulted in parallel alterations in the vitamin A content of their eggs, and in the vitamin A content of the embryos developing from these eggs. The number of embryos surviving to the date of inoculation was significantly greater in the deficient group than in the control group.

A deficient supply of vitamin A did not influence significantly the course of infection in the developing embryo as judged by survival rates and blood cultures.

Infection of a chick embryo definitely reduced the vitamin A content of the liver and of the total embryo.

Separation of the Renal Anti-Pressor Substance from Certain Non-Specific Depressor Substances Present in Renal Extract. By T. R. HARRISON, J. R. WILLIAMS, JR., and (by invitation) ARTHUR GROLLMAN, Winston-Salem, N. C.

Since our report before this Society three years ago, describing the renal anti-pressor substance, efforts have been made to purify this compound. A number of different fractions which may lower the blood pressure of rats have been obtained:

(*1*) Histamine and similar toxic substances which are not precipitated by ammonium sulphate and are inactive orally.

(*2*) Non-dialyzable substances which are ineffective orally but may lower pressure when injected.

(*3*) Ammonium sulphate: This salt (which is used to precipitate the active principle) may, when fed in sufficient quantity, lower the blood pressure. It may be removed by extraction with aqueous picric acid.

(*4*) Certain as yet unidentified substances, possibly of phenolic nature.

(*5*) The renal anti-pressor substance which is present in the original ammonium sulphate precipitate and which passes through a dialyzing membrane may be precipitated from the dialysate by saturated aqueous picric acid. This is active orally and has little or no toxic effect. The amounts of this fraction needed in order to induce a striking decline in blood pressure correspond to large amounts of kidney.

The Effect of Changes in Body Temperature on Peripheral Circulatory Failure in the Mouse. By JOHN R. WILLIAMS, JR., Winston-Salem, N. C.

Peripheral circulatory failure, as seen in the terminal stages of infectious diseases, seems to differ from that seen in hemorrhage and trauma, the most outstanding variation being the presence of fever in the former. The effect of raising and lowering body temperature, and noting its effect on peripheral circulatory failure, has been studied in an attempt to further elucidate this phenomenon.

Peripheral circulatory failure was produced by the intraperitoneal injection of 50 per cent succrose in mice, a technique which is easily standardized.

Results indicate that mice kept at a body temperature of 39 to 40° C. appear more active and in better condition, but they die in a very short time. Mice kept at normal body temperature do not appear as well clinically but survive a considerably longer time. When the body temperature is lowered to 28 to 32° C., the mice become comatose and cyanotic and appear very ill. However, these mice survive longer and a higher percentage ultimately survive than in the other groups. The amount of fluid that exudes into the peritoneum in all three groups is approximately the same and is apparently not influenced by their body temperature.

*Observations on the Rate of Water Loss from the Skin of Humans in a Subtropical Climate.** By G. E. BURCH and W. A. SODEMAN, New Orleans, La.

The rate of water loss from localized surfaces of the body, including areas of high and low rates of clinical sweating, was studied quantitatively in a subtropical climate, in normal and diseased subjects. These areas included representative segments of the head, trunk, and upper and lower extremities. Observations were made under controlled atmospheric conditions which were varied from comfortable to hot environments, 75° F. and 50 per cent relative humidity and 95° F. and 75 per cent relative humidity respectively. They were taken in the winter and spring.

One hundred and ten observations were carried out on 31 subjects. In the normal subjects, a relative typical consistent pattern was found. The rate of water loss per unit time per unit area was greater in the finger tips and palm of the hands, toe tips and sole of the feet, and head, in that order, was lowest in the trunk, leg, thigh, and forearm, and intermediate in the axillae. A more or less uniform increase of water loss occurred in all areas following a change of the atmosphere of the room from a comfortable one to a hot one. Strikingly different findings were obtained in the diseased individuals. In scleroderma for example, impairment of water loss in the areas of high sweating resulted in a compensatory increase in areas normally low. A patient who experienced marked discomfort in a hot atmosphere failed to respond normally to increased environmental temperature. Similar observations of equal interest were found on other abnormal subjects.

* Financed by the Rockefeller Foundation, New York.

Quantitative Studies of the Effect of Concentrated Solutions of Human and Bovine Serum Albumin on Blood Volume after Acute Blood Loss in Man. By JAMES T. HEYL (by invitation), JOHN G. GIBSON, 2ND, ANNE SHWACHMAN (by invitation), LADISLAS WOJCIK (by invitation), and CHARLES A. JANEWAY, Boston, Mass.

The preparation of highly purified albumin from human plasma by Edwin J. Cohn, Lawrence E. Strong, John L. Oncley, and S. Howard Armstrong, Jr., and the recent crystallization of bovine serum albumin by Edwin J. Cohn and Walter L. Hughes, Jr., has made available concentrated and stable solutions of these proteins as substitutes for plasma. It was felt important to investigate their action under carefully controlled conditions.

From 10 to 12 per cent of the circulating blood volume was rapidly removed from normal human subjects by venesection, and a 25 per cent solution of human or crystalline bovine albumin immediately given by vein. Changes in the blood volume were carefully followed over a three-day period, as measured by the values for hemoglobin, hematocrit, total protein, and plasma volume determined by the Evans blue dye technique. It was found that regardless of whether the subject was dehydrated or not, concentrated albumin solutions rapidly augmented the plasma volume. One hour after injection, the amount of fluid added to the circulation by each gram of albumin averaged approximately 17 cc. This is very close to the amount expected from calculations based on the related studies of the osmotic pressure of these albumin solutions by George Scatchard, Alan C. Batchelder, and Alexander Brown.

The physiologic response was identical with both types of albumin. If the preliminary period of dehydration was prolonged after the injection of albumin, a slight decrease in plasma volume occurred, which was not observed in subjects given salt and water by mouth. Serum and urine potassium did not increase following the administration of these hypertonic protein solutions.

Normal human serum albumin has been proven an osmotically powerful blood constituent, whose use in concentrated hypertonic solution has not been followed by untoward reactions. Although there have been no harmful effects from the injections after several months, further studies of sensitivity to crystallized bovine albumin must be made before its general use will be recommended.

A "Vitally" Stainable Structure in Young Erythrocytes. Its Relation to the Howell-Jolly Bodies or "Nuclear Rests." By SAVAS NITTIS (introduced by Raphael Isaacs, Chicago), New York, N. Y.

When normal erythrocytes in early stages of development, from avian or mammalian embryos, or new born animals, or from bone marrow of adults, are placed in weak solutions of a "vital" dye, large, azure colored "droplets" develop slowly, long after the "reticulum" is formed. They vary in size, being single or multiple, and they are apparently not formed at the expense of the reticulum forming substance. When counterstained with the Wright stain they resemble the nuclear chromatin in color, and are entirely indistinguishable from the so-called Howell-Jolly bodies, or "nuclear rests," observed especially in pathologic conditions.

When red blood cells from patients suffering from certain anemias, such as hemolytic icterus, erythroblastic anemia, sickle-cell anemia, hemolytic reactions caused by chemotherapeutic agents, etc., are placed for a few minutes in a weak solution of a "vital" dye, then filmed and counterstained, the percentage of cells showing "nuclear rests" is many times greater than that found on films prepared and stained in the usual manner.

It is presumed that the substance responsible for these formations is not of chromosomic or nuclear origin, but rather a lipoid, which fills the cell during its embryonic stage, and which enters into the formation of, or is replaced by, the hemoglobin, as the cell matures. It may be precipitated *in vivo* by a toxic agent, thus becoming readily stainable with the Wright, or similar stains, forming the so-called "nuclear rests." The nuclear rests stand in the same relation to the formations here described as "stippling" does to "reticulum," the former being precipitated *in vivo* by a toxic agent, the latter *in vitro* by a "vital" dye.

The Cause of Low Synovial Fluid Glucose Concentrations in Joint Disease. By MARIAN W. ROPES, ERIC G. L. BYWATERS (by invitation) and WALTER BAUER, Boston, Mass.

The present studies were undertaken to determine the cause of the low synovial fluid glucose concentrations that occur in some cases of joint disease. Significantly low concentrations are inadequate for the nutrition of articular cartilage, an avascular tissue that is nourished by synovial fluid. The normal fluid glucose level depends on the difference between the rates of entrance and utilization. In the past, such low concentrations have always been ascribed to increased utilization.

In order to test this assumption, we have studied the entrance of utilizable (glucose) and non-utilizable (thiocyanate) substances into joints with normal fasting synovial fluid glucose levels (traumatic type of joint disease) and joints with low fasting levels (rheumatoid and infectious arthritis).

In the former type, the appearance time of glucose was normal (20 minutes) and equilibrium was attained rapidly. Thiocyanate entrance was also normal. In the joints with low fasting fluid glucose levels, the appearance time of glucose was much slower (40 minutes) and the concentration rose only slightly in 2 hours. In such cases, thiocyanate entrance was slightly decreased.

To determine whether these findings were due to increased utilization or decreased entrance, similar studies were made with a non-utilizable sugar, galactose. Results very similar to those of the glucose experiments were obtained. The possibility of any utilization of galactose was excluded by intra-articular injection of galactose and demonstration of an essentially constant fluid level for 2 hours.

The results indicate that the rate of entrance of glucose plays a greater rôle than utilization in determining the fluid level. Normally glucose enters more slowly than thiocyanate. The rate of entrance is decreased in severe cases of rheumatoid and infectious arthritis even when thiocyanate enters fairly rapidly. Further evidence that the delayed entrance is not due to a decreased "permeability" is the fact that the entrance of proteins into the same joints is increased. The mechanism whereby the entrance of glucose is retarded is unknown. It seems probable that it is due to an intermediary chemical reaction which occurs fairly rapidly in normal synovial tissues but more slowly in certain types of joint disease. Elucidation of the mechanism will presumably indicate the mode of transfer of glucose to tissue fluid in all parts of the body, a process which even normally causes some delay in the entrance of glucose, as is most apparent in the case of spinal fluid.

Capillary Permeability as Determined by the Protein Content of Edema Fluid. Studies in Normal Subjects with Venous Congestion and in Patients with Acute Nephritis. By JAMES V. WARREN (introduced by Marshall N. Fulton), Boston, Mass.

Knowledge of the protein content of the capillary filtrate in a given portion of the body and of the extent to which physiologic or disease processes alter this fluid by changes in the capillary permeability is of both theoretical and practical importance. The purpose of this investigation was to determine the degree of capillary permeability during low-grade venous congestion and in acute nephritis.

Minimal pitting edema was produced in 8 normal subjects by obstructing the venous return from the leg for a 12-hour period. Thirty mm. Hg was chosen as the congesting pressure because this degree of venous obstruction produced little decrease in the resting blood flow of the part. From 1.5 to 25 mgm. of edema fluid were obtained by inserting several small needles into the subcutaneous tissue. The fluid was collected in capillary tubes of known weight and its nitrogen content was determined by the method of Kjeldahl. The average protein concentration of the edema fluid was 0.9 gram per cent. As the protein concentration of normal capillary filtrate is not known, it is impossible to say to what degree the increased venous pressure changed the capillary permeability. In view of these experiments, it is unlikely that the normal capillary filtrate in the leg exceeds 0.9 gram per cent protein; it is probably considerably lower.

The protein content of the edema fluid in 5 cases of acute nephritis ranged from 0.2 to 1.0 gram per cent, with an average of 0.5 gram per cent. The protein concentration was not significantly greater than that in cardiac edema. These data indicate that the edema of acute nephritis does not result from a generalized increase in capillary permeability, but from retention of salt and water because of renal disease.

The Comparative Effectiveness of Arsenical Compounds and Sulfonamide Drugs Against Bacterial Infections. By EDWIN E. OSGOOD, with the technical assistance of Inez E. Brownlee, Jane M. Armentrout, and Julia Joski, Portland, Ore.

The comparative effectiveness of neoarsphenamine, and many other trivalent and pentavalent arsenical compounds, and the sulfonamides, against many different bacteria was tested, using the technic of human marrow culture which permits controlled quantitative studies of the relative toxicity and effectiveness of drugs in an environment similar to that in the human body.

Arsenic trioxide and the six pentavalent arsenicals tested were relatively ineffective against all the organisms investigated. The ten trivalent organic arsenicals tested were more effective than any of the ten sulfonamides against all strains of staphylococci and most strains of Streptococcus hemolyticus and Streptococcus viridans. They were highly effective against diphtheria bacilli, gonococci, and H. influenzae, but were not as effective against these organisms as the most effective sulfonamides. The trivalent organic arsenicals were ineffective against pneumococci and of relatively little value against typhoid and colon bacilli.

In the concentrations safely attainable clinically, the order of decreasing effectiveness was neoarsphenamine, arsphenamine, sulfarsphenamine, trisodarsen, clorarsen, and mapharsen; for the sulfonamides, it was sulfathiazole, sulfadiazine, sulfapyridine, and sulfanilamide.

Neoarsphenamine, therefore, should be the drug of choice in many serious bacterial infections, and, of the sulfonamides, sulfathiazole and sulfadiazine should displace sulfanilamide as the drugs of choice in most bacterial infections.

The Absence of Erythrocyte Reserves in Human Subjects as Indicated with Radioactive Tagged Cells. By JOSEPH F. ROSS and MILAN A. CHAPIN (introduced by James M. Faulkner), Boston, Mass.

It is generally believed that the spleen is an important reservoir for erythrocytes, and that in times of stress (*e.g.* after hemorrhage or during shock) it contracts and liberates 20 to 30 per cent of the total erythrocyte volume into the vascular system.

Erythrocytes containing radioactive iron in their constituent hemoglobin are "labelled" during their lifetime, and can be detected quantitatively after injection into compatible human subjects. The total volume of cells in such subjects can be determined by applying the formula:

$$\text{Total volume of cells} = \frac{\text{Total radioactivity of injected cells}}{\text{Radioactivity per ml. of recipient's cells after mixing.}}$$

Volumes determined by this technique 10 minutes after injection of the tagged cells were similar to those observed 24 hours after injection. It is believed that 10 minutes is too short a period of time to allow mixing of the tagged cells with any considerable volume of im-

mobilized cells, although complete mixing would have occurred after 24 hours. The volume of cells in active circulation thus appears to be the same as the total volume of cells in the vascular system (including the splenic sinusoids) and no significant reserves of erythrocytes could be demonstrated.

The total volume of erythrocytes was not increased by administering adrenalin, although the venous hematocrit and plasma protein concentration increased 4 to 6 per cent. The increase in hematocrit was therefore assumed to be due to hemoconcentration or to redistribution of circulating cells and plasma in the vascular system rather than to the addition of more cells from the spleen or other hypothesized reservoirs.

Evidence for an Immune Mechanism as a Cause of Resistance to Insulin. By FRANCIS C. LOWELL (introduced by Chester S. Keefer), Boston, Mass.

Insulin tolerance tests with commercial crystalline insulin made from beef and pork pancreas and a preparation of human insulin were done in a diabetic patient exhibiting marked sensitivity and resistance to crystalline insulin.

Commercial crystalline insulin failed to produce a fall in the blood sugar, whereas human insulin caused a marked drop. Both types of insulin were capable of causing generalized urticaria. Passive transfer skin-sensitizing antibodies for both crystalline and human insulin were present in the patient's serum. The patient's serum was capable of protecting mice from convulsive doses of crystalline insulin but failed to protect mice against similar doses of human insulin. When the allergic antibody was destroyed by heating to 57° C., the insulin-neutralizing effect of the patient's serum in mice was still demonstrable.

These studies suggest that this patient had two immunological mechanisms involving insulin, one accounting for the allergic reactions, the other accounting for the resistance. Furthermore, evidence is presented that a patient resistant to insulin derived from beef and pork pancreas is not necessarily resistant to all insulins.

The Production of Microspherocytosis of Red Cells and Hemolytic Anemia by the Injection of Rattlesnake (Crotalus Atrox) Venom. By FRANK H. BETHELL and (by invitation) KARL BLEYL, Ann Arbor, Mich.

The venom of crotalus atrox (Texas diamond back rattlesnake) was administered in sublethal and lethal doses to 12 dogs by either intravenous or subcutaneous injection. Within 30 minutes, a fall in blood pressure occurred associated with an increase in the cell plasma volume ratio and the concentration of plasma proteins. Subsequently, the plasma proteins fell, usually to a value below the pre-administration level. The cell plasma volume ratio continued to increase and the hematocrit value attained a level up to 50 per cent higher than the reading before administration of venom. Although the animals presented the picture of surgical shock, the rise in the hematocrit level could not be explained entirely by loss of fluid from the vascular system, since it was not paralleled by increases in the erythrocyte count and hemoglobin value. Within a few minutes after the intravenous injection of either large or relatively small amounts of venom, the erythrocytes showed evidence of swelling and change from biconcave to more nearly spherical shape. A decrease in the mean cell diameter and an increase in the mean thickness were observed. Greatly decreased resistance to hypotonic salt solution occurred. By repeated administration of doses of venom too small to produce evidence of vascular damage it has been possible to induce hemolytic anemia, accompanied by hyperbilirubinemia and reticulocytosis, without apparent intravascular destruction of the red cells. This experimental anemia is analogous to familial hemolytic icterus with respect to changes observed in the circulating red cells. These studies support the view that the spherical and "fragile" erythrocytes characteristic of the latter condition do not represent an inborn error in formation of erythrocytes but rather an alteration in shape and resistance which occurs after their release into the circulation.

Kidney Extracts: Chemical Properties and Therapeutic Effects in Hypertension. By OTTO SCHALES and JAMES V. WARREN (introduced by James P. O'Hare), Boston, Mass.

Kidney extracts similar to those of Page and his coworkers have been prepared and administered to hypertensive patients. The concentration of the final product was such that 1 ml. represented 75 to 100 grams of fresh hog kidney. The extracts contained 2.5 to 4.3 grams of nitrogen in 100 ml., 23 to 28 per cent of which were present in the form of pseudoglobulins, while the rest existed in the form of proteoses, soluble in trichloracetic acid, but precipitated by ammonium sulfate and by picric acid. Ammonium sulfate and other dialyzable material was absent due to prolonged dialysis at 0° C. The renin content was about 180 to 250 rabbit units (method of Schales and Haynes) in 1 ml. The extracts showed diastatic activity, 100 ml. producing 0.5 to 1.1 grams of reducing sugar from an excess of starch in 30 minutes at 37° C. All extracts were rich in hypertensinase. In 2 hours, 1 ml. inactivated *in vitro* all the angiotonin that is formed by incubating 1 to 3 liters of beef plasma with renin under optimal conditions.

Seven patients with malignant and essential hypertension have been given daily intramuscular injections of 10 ml. of this renal extract. In 2 patients no decrease in arterial pressure occurred. In 5 patients the pressure decreased after 5 to 10 days of treatment. Local reactions, often accompanied by fever, were observed. Inactivation of hypertensinase by incubating, for 9 hours at 37° C., extracts brought to pH 3.70 did not change the depressor effect of the material.

The data suggest that the depressor effect is probably better correlated with the occurrence of non-specific reactions than with a specific depressor agent.

Quinidine Hydrochloride with Urea Intramuscularly in the Treatment of Acute Cardiac Arrhythmias. By JOSEPH E. F. RISEMAN, and (by invitation) ELLIOT L. SAGALL, MELVIN I. STURNICK, and CHARLES HORN, Boston, Mass.

The sudden onset of paroxysms of rapid heart action, either spontaneous or complicating other conditions such as acute myocardial infarction, may require emergency treatment. Such episodes may be accompanied by vomiting, shock, or other conditions, making oral therapy inadvisable. No practical injectable preparations of quinidine have been available, however.

The addition of antipyrine and urea to quinidine hydrochloride results in a clear, colorless solution. This is sufficiently soluble so that a 2 cc. ampule containing 0.3 grams of quinidine hydrochloride can be prepared. This solution has been found suitable for intramuscular injection and has been stable for 9 months up to the time of writing. The present communication deals with measurements of the speed and duration of action of this preparation and the results obtained with its use in the treatment of cardiac arrhythmias in man.

The duration of action of cinchona derivatives on the human heart was estimated by repeated measurements of the Q–T interval of the electrocardiogram after oral and intramuscular administration of quinidine and quinine. These studies showed that all cinchona preparations in therapeutic dosages exert their maximum effect 1½ to 3 hours after administration. Intramuscular injection produced earlier and more decided effects than oral administration of an equivalent dose. As a result of these studies, it was evident that if conversion of an abnormal rhythm did not occur within 2 hours after the administration of a dose of quinidine, additional medication would be required.

Twenty-three instances of arrhythmias in 19 patients were treated by intramuscular injection of quinidine hydrochloride with urea. The optimum initial dose was 0.6 grams. This was repeated or increased after 2 hours, depending on the response. This method of treatment was successful in all patients except 3 with sinus tachycardia. No untoward systemic or local effects were observed.

Studies on the Persistence of Pneumococci in Patients with Pneumonia Treated with Sulfonamide Drugs. By ROBERT A. GOODWIN (by invitation) and MAXWELL FINLAND, Boston, Mass.

Serial studies of sputum were made in patients with pneumococcus pneumonia, during treatment with sulfathiazole or sulfadiazine. The approximate numbers of the original and other types of pneumococci were estimated and the presence of other organisms noted. In about one-half of the cases, pneumococci disappeared from the sputum or throat cultures within 48 hours after drug therapy was started, and in another 30 per cent they could not be found after 3 to 10 days. In the remaining cases, those who were followed for more than 10 days were shown to have chronic or persistent basilar infection of the lungs. In occasional cases, new types appeared during the course of treatment and after the original type could no longer be found. Antibodies developed in these cases at the usual time. Morphological changes, similar to those previously described by Frisch, were observed in the pneumococci during the course of sulfonamide therapy.

The Treatment of Bronchiectasis by Means of Continuous Postural Drainage (A Preliminary Report). By CLAUDE E. FORKNER and (by invitation) ALPHONSE E. TIMPANELLI, New York, N. Y.

An ideal to be accomplished in the medical treatment of bronchiectasis would be (*a*) to drain the bronchiectatic cavities by some method to keep them clean and dry; (*b*) to prevent resoiling of lungs with infected material from the upper respiratory tract.

These objectives can be accomplished by constant drainage with elevation of the middle of the bed on a suitable rack. Six patients have been so treated with encouraging results—decrease in quantity of sputum, improvement in the character of the sputum, decrease in cough, cessation of hemoptysis, gain in body weight, lessening of physical signs of the disease, and betterment of the general health of the patients.

In conjunction with this study, a preliminary series of observations showed that, in thirty-five unselected cases of bronchiectasis, 86 per cent had an absent (twenty-one cases) or markedly reduced (nine cases) pharyngeal reflex. A control series of normal adults exhibited this phenomenon in only 15 per cent of cases. No definite conclusion has been drawn from this observation, but it may have an important bearing as a causative factor in bronchiectasis.

Heat Production in Muscular Disease. By A. T. MILHORAT and (by invitation) J. D. HARDY and A. FAIR, New York, N. Y.

The heat production of 150 subjects, including 50 normals and 100 patients with muscular disease, was determined. The muscular syndromes included dystrophy, wasting subsequent to disease of the nervous system, and various disturbances of muscular function. Investigations of the metabolism of creatinine and creatine furnished data for computing the total functioning muscular mass of the body and for estimating the reduction in muscular mass due to wasting. Several of the patients were studied in the calorimeter of the Russell Sage Institute of Pathology, which permitted observations on direct and indirect calorimetry and respiratory quotient. In patients who had not yet reached puberty, muscular wasting was without significant effect on heat production, even when the excretion of creatinine and other observations suggested a reduction of as much as 60 per cent of the total muscular mass. In the adult patients, muscular wasting often was associated with decrease in total heat production, but this change was only slight or moderate in comparison with the reduction in muscular mass and in excretion of creatinine. These observations were

practically uniform in all the various muscular disorders that were investigated, with the notable exception of myotonia atrophica in which the decrease in heat production sometimes was greater than were the changes in muscular mass and function. The findings in this condition are postulated as being related to changes in organs other than the muscles.

The Influence of Secondary Factors on Induced Leukemia. By FRANKLIN R. MILLER, Philadelphia, Pa.

Cellular proliferations which resemble human leukemia may be induced in the organs of guinea pigs by the injection of extracts of urine from patients with the disease.

It seems possible that various factors such as infection, injections of proteins, anaphylactic shock, and exposure to benzol may have an influence on the induced disease.

Small doses of avirulent cultures of staphylococcus albus caused the death in twenty-four hours of animals previously prepared by injections with the urinary extract.

These animals had myeloblastic bone marrows and two had reductions of white blood cell counts to 600 prior to death. Normal animals given ten times the dose of the same culture of staphylococcus albus showed no ill effects.

Horse serum when given simultaneously with the injection of urinary extract increased the cellular proliferations in the organs of guinea pigs. With this combination the lymphoid disease also has been induced in rabbits. Treated animals which were sensitized to protein have shown few signs of anaphylaxis when tested for this phenomenon.

The injection of benzol prior to and simultaneous with the injection of urinary extract has not increased the disease, but in some instances seems to have retarded the process.

The lack of resistance to infection and the lack of anaphylaxis may indicate lowered immunity in these animals. A sparing action of one substance for the other may be elicited when benzol and urinary extracts are used together.

The Effect of Paravertebral Sympathectomy on Circulatory Functions in Essential Hypertension. By WRIGHT ADAMS and IRENE SANDIFORD (introduced by C. Phillip Miller), Chicago, Ill.

Seven patients with essential hypertension have been studied before and at intervals after removal of the paravertebral sympathetic chains from the stellate ganglion to the eleventh dorsal level or below. The data are not sufficient to justify conclusions regarding the value of this procedure in the treatment of hypertension, but its effect on some physiologic functions is uniform and in certain respects unexpected.

The pulse rate and oxygen consumption were progressively diminished during the first six months after operation, with little tendency to change during the second six months. The arteriovenous oxygen difference increased during the first six months and decreased during the second six months in most cases. The cardiac output per minute was usually progressively reduced for the first six months. None of these changes was regularly related to blood pressure changes. Marked postural reduction of blood pressure occurred after operation, with little or no tendency to recovery during the first year. Measured exercise caused a further fall of blood pressure with comparatively little acceleration of the pulse.

The progressive nature of some of these changes is contrary to the usual concept that interruption of nervous pathways causes abrupt changes in function with a tendency to recovery. None of these patients showed clinical evidence of reduction of cardiac reserve.

Prenatal Electrocardiography. By ARTHUR J. GEIGER and (by invitation) ALLAN V. N. GOODYER and WILLYS M. MONROE, New Haven, Conn.

A clinically practicable technique for recording the electrocardiogram of the human fetus *in utero* has been developed by using a single stage resistance-coupled amplifier of simple construction in conjunction with a conventional portable electrocardiograph. The amplified fetal heart potentials were successfully picked up by disc electrodes on the pregnant subject's abdomen as early as the fourth month of pregnancy. Positive results have been found in 80 per cent of the tracings obtained during the last six lunar months of pregnancy, and with more recent refinements in technique the results have been practically 100 per cent positive in the last three lunar months.

The technique permits the prompt differential diagnosis of pregnancy from other abdominal tumors, it is free from false positive results, and it is less time-consuming than biological tests for pregnancy. A positive result is certain proof of life of the fetus.

The clinical value of the procedure is illustrated by twelve instances in which the question of dead fetus was answered correctly in all but one. Twin pregnancy has been recorded electrocardiographically in each of three available instances, and a case of triplets has been recorded.

Observations on the Vascular Volume and Blood Pressure in Minute Vessels of Patients with Hypertension and Certain Other Conditions. By J. C. HORTENSTINE (introduced by E. M. Landis), Charlottesville, Va.

By means of the pressure plethysmograph (Landis and Gibbon, J. Clin. Invest., 1933, 12, 105), graded external pressures ranging from 5 to 140 mm. Hg were applied to the forearm. At each pressure "dynamic vascular volume" was measured (*a*) by decrease in the volume of the forearm when circulation was stopped by inflating to 300 mm. Hg a narrow cuff at the axilla, and (*b*) by increase in the volume of the forearm when circulation was resumed after 2 minutes' complete occlusion.

In normal subjects, characteristic pressure-volume curves were observed in which the greatest "dynamic vascular volumes" appeared at external pressures between 20 and 35 mm. Hg. The maximal "dynamic vas-

cular volumes" averaged 1.3 cc. per 100 cc. of forearm for (*a*) and 1.8 cc. per 100 cc. of forearm for (*b*). These values were the same in subjects during fasting and after meals. Known grades of venous congestion reduced the "dynamic vascular volume" and moved the left limb of the pressure-volume curve toward higher pressures, without affecting the right limb. Simple dehydration lowered "dynamic vascular volume" without changing pressure relationships. Anemia had no effect on either volume or pressure. Free aortic regurgitation tended to move the pressure-volume curve toward lower pressures. Vasoconstriction and decreased circulating blood volume produced by venous congestion of 3 extremities reduced "dynamic vascular volume," and moved the summit of the curve to slightly higher pressures.

In hypertension, vascular volume remained approximately normal, but the summit of the pressure-volume curve was extremely flat and extended to pressures over twice the normal magnitude. The observations indicate that in hypertension the "dynamic vascular volume" is still approximately normal, suggesting, as have studies by others on blood flow, that the vasoconstriction of hypertension differs from vasoconstriction of neurogenic origin.

An Evalution of the Use of Dicoumarin (3,3'-Methylenebis-4-Hydroxycoumarin) as an Anticoagulant, and Its Effect on Certain Plasma Constituents. By CHARLES S. DAVIDSON and HARRIET MACDONALD (introduced by Maurice B. Strauss), Boston, Mass.

The use of dicoumarin as an anticoagulant which may replace heparin in clinical medicine has been advocated by several investigators.[1, 2]

The chemical nature of the substance differs widely from that of heparin, as does its physiological action. These physiological differences of action of the two substances are presented.

As compared to heparin, dicoumarin develops its anticoagulant effect slowly, and the recovery of the patient from the effects of the drug is much slower than from heparin, the effect of which is usually transitory.

Transfusion of whole blood in at least one case was inadequate for the control of the prolonged coagulation time produced by dicoumarin.

The coagulation time of venous blood measured by glass tubes does not give an index of the early changes in the coagulability of the circulating blood. The present observations suggest that the employment of lusteroid[3] tubes shows marked changes in the coagulability of the circulating blood.

Dicoumarin causes changes in the plasma that are at the moment not fully understood. There is no doubt that dicoumarin increases the coagulation time of the circulating blood and lowers the prothrombin concentration. There are certain characteristics of dicoumarin, such as difficulty of control, and its chemical nature, which suggest that caution should be used in the acceptance of the material as a general anticoagulant.

[1] Butt, H. R., Allen, E. V., and Bollman, J. L., Proc. Staff Meet., Mayo Clin., 1941, **16**, 388.

[2] Bingham, J. B., Meyer, O. O., and Pohle, F. J., Am. J. M. Sc., 1941, **202**, 563.

[3] Obtainable in the form of centrifuge tubes from the International Equipment Company, Boston, Mass.

The Effect of Separate Inoculation of Vaccine Virus and Immune Serum on the Protection Test. By ROBERT F. PARKER, Cleveland, Ohio, and (by invitation) ROBERT H. GREEN, New York, N. Y.

Protection against infection with vaccine virus has been shown to result when immune serum is inserted intradermally in rabbits, with the virus inoculated later. This passive immunity gradually disappears. The present experiments were designed to measure the rate at which the protection is lost by inoculating graded amounts of virus at various intervals after the administration of serum. It was found that with the serum used, the amount of protection which was afforded declined regularly with time, but some was still demonstrable 96 hours after administering serum. Other experiments were done with the administration of serum by intradermal infiltration at different times after graded amounts of virus had been inserted. Although it has been stated that protection can be secured by this method only if the serum is inserted almost at once, the results of these more exact measurements show that good protection is afforded with a serum-virus interval of 6 hours. Slight, although probably significant, protection was obtained when serum was administered as late as 48 hours after virus inoculation. This is well within the incubation period for a lesion which might result from the small inoculum of virus.

A Statistical Study of Certain Etiologic Factors in Rheumatoid Arthritis. By CHARLES L. SHORT, WALTER BAUER and (by invitation) NATHAN R. ABRAMS and PHILIP E. SARTWELL, Boston, Mass.

Results are presented from a statistical study of 293 unselected patients with rheumatoid arthritis and a similar number of controls of corresponding age and sex. Our object was not only to confirm or refute some prevailing conceptions of the natural history of the disease, but also to uncover etiologic implications, especially by comparison with other diseases of less obscure origin.

Of the patients studied, 64 per cent were females, but this ratio was reversed in the 39 cases with spinal involvement. Special localizations of other diseases show a similar change in sex ratio. Our findings for the age of onset were compared with census figures for the age distribution of the population at risk and the chi-square test applied. No significant departure was found in males, but in females a marked increase was discovered in the age group 50 to 54. This finding suggests the influence of the menopause but our studies show no close relationship between the cessation of menstruation and the onset of the disease.

A significantly increased familial incidence of both rheumatoid arthritis and rheumatic fever was found in

patients as compared with controls, but the evidence is not sufficient to establish an hereditary factor. No relationship could be shown between rheumatoid arthritis and diseases of known allergic origin on the basis of familial or personal incidence of allergic manifestations. The validity of fatigue and anorexia as prodromal symptoms was established by means of questioning both patients and controls. Our data suggest that these and other constitutional symptoms may mark the real onset and that so-called precipitating factors, including acute infections and strain, merely determine a more easily recognizable phase with articular localization of the morbid process.

Changes in Blood Histamine Following Burns, Surgical Operations and Hemorrhage. By PAUL G. WEIL (by invitation) and J. S. L. BROWNE, Montreal, Canada.

Previous studies by Rose and Browne showed that the changes in blood histamine after severe burns could be divided into three phases: (*1*) an immediate, inconstantly occurring rise, (*2*) a fall below the normal level, and (*3*) a subsequent rise to or above normal. The second phase was the most constant and was associated with the period of edema and hemoconcentration. Further studies in twelve cases of burns confirm these findings for severe burns. In the case of mild burns showing slight or no hemoconcentration, the fall of blood histamine was slight or not present at all. The early rise occurred inconstantly as before.

Rose and Browne also reported lowered blood histamine levels after surgical operations. In cases developing shock, the blood histamine fell to low levels; in those not developing shock, it fell slightly. Twelve further cases have been studied before, immediately after, and at daily intervals, for one week after surgical operations. The previous findings are confirmed.

In order to estimate the role of hemorrhage in these changes, a study on blood donors was made. After loss of 500 cc. of blood in ten healthy male donors there was a fall to an average level 40 per cent below the initial level at the end of the bleeding which occupied about fifteen minutes. At this time, an average fall of 7 per cent in hemoglobin had already occurred.

In order to determine whether the decrease in blood histamine represented destruction or transfer to extravascular spaces, the cerebrospinal fluid histamine content was determined in four cases undergoing brain operations. There was no shock in these cases. The blood histamine fell moderately and simultaneously histamine which was absent before operation appeared in the cerebrospinal fluid, rose to a maximum at a time when the blood histamine was at its lowest level and disappeared again as the blood histamine rose. In general, the results suggest that a fall of blood histamine occurs in conditions in which a transfer of fluids to extravascular spaces is occurring and a subsequent rise in blood histamine takes place when fluid is being transferred in the opposite direction. The possible significance of these findings is discussed.

Gold Metabolism Following the Administration of Calcium Aurothiomalate and Aurothioglucose in Oil to Patients with Rheumatoid Arthritis. By R. H. FREYBERG and (by invitation) W. D. BLOCK and G. S. WELLS, Ann Arbor, Mich.

Patients with active rheumatoid arthritis were injected intramuscularly with different amounts of calcium aurothiomalate (a relatively insoluble salt suspended in oil); other patients were treated similarly with aurothioglucose (a readily soluble salt prepared in an oily suspension). The gold content of plasma, synovial fluid, and saliva, was determined frequently, and the daily excretion of gold in urine and feces was measured for many weeks during and after treatment. The plasma gold concentrations and twenty-four-hourly urinary excretion of gold of many other patients were determined at intervals during and after treatment with these same salts.

The gold content of plasma of patients injected with calcium aurothiomalate was always distinctly and often markedly less than previously observed after the administration of water soluble salts of gold (gold sodium thiomalate and gold sodium thiosulfate), containing equivalent amounts of gold. Similarly the excretion of gold was considerably less than occurred following injections of soluble gold salts. Rapid increases in plasma concentration and urinary excretion of gold never occurred following injections of the calcium salt, a result sharply in contrast to results after injection of soluble gold salts.

The plasma concentration and excretion of gold following administration of an oily suspension of aurothioglucose was usually about 70 per cent as large as obtained after the injection of comparable amounts of gold contained in aqueous solutions of other gold salts. Greater variations occurred when the oily suspensions were employed.

The significance and implications of the results will be discussed in regard to possible therapeutic and toxic effects.

Effects of Cozymase Upon the Growth of Staphylococci and Antistaphylococcal Action of the Sulfonamide Compounds. By WESLEY W. SPINK and (by invitation) JEAN JERMSTA VIVINO and OLAF MICKELSEN, Minneapolis, Minn.

West and Coburn have stated that cozymase (coenzyme I) inhibited the bacteriostatic action of sulfapyridine for the staphylococcus, whereas nicotinic acid and thiamin chloride did not. Strauss, Dingle and Finland were unable to confirm this finding. They pointed out, that although nicotinic acid and thiamin chloride are essential growth factors for the staphylococcus, cozymase would act as a growth stimulus in place of both nicotinic acid and thiamin chloride. We are reporting the results of our observations concerning the inhibitory effect of cozymase upon the bacteriostatic action of the sulfonamides, and also offering an explanation for the confirmed observation that cozymase will stimulate growth of the

staphylococcus equally as well in the presumed absence of both nicotinic acid and thiamin chloride.

Utilizing two preparations of cozymase, it was found that the material contained small but adequate enough quantities of thiamin chloride to support growth of the staphylococcus in a synthetic medium. It is reasonably assumed that the organisms, in the presence of nicotinic acid and thiamin chloride, utilize the former compound as cozymase for cellular reproduction. When certain experimental conditions were fulfilled, cozymase, but not thiamin chloride and nicotinic acid, inhibited the bacteriostatic action of sulfanilamide and sulfapyridine against staphylococci.

Experience with the Heller and Heller Test for Follicle-Stimulating-Hormone in the Urine in Endocrinological Diagnosis. By HARRY F. KLINEFELTER, JR., and GRACE GRISWOLD (by invitation), and FULLER ALBRIGHT, Boston, Mass.

With impaired gonadal function in either sex, one finds an excess of follicle-stimulating-hormone (FSH) in the urine if the trouble lies primarily within the gonads themselves. Hence, tests for excess of FSH have been very useful in endocrine diagnosis. Furthermore, the assumption has been made that, if an individual had obvious gonadal insufficiency and did not have an excess of FSH in the urine, the cause of the gonadal insufficiency was in all likelihood a decrease in FSH production. The present studies were planned to throw further light on this assumption.

In order to test the urine for a subnormal amount of FSH, it was first necessary to separate the toxic products from the hormone. This has been accomplished by the use of the Heller and Heller procedure which dialyses off the toxic products. The authors have used this method with minor modifications.

The present studies include observations on normal individuals to show how many mouse units of FSH can be expected in the urine of a normal individual per 24 hours. The remainder of the data concern quantitations of FSH in the urine of patients in whom there was reason to believe that the FSH was decreased or absent.

Antithromboplastin in Hemophilia. Effect of Intravenous Injection of the Hemophiliac's own "Thromboplastinized" Plasma. By LEANDRO M. TOCANTINS, Philadelphia, Pa.

Incubation of normal or hemophilic plasma, *collected with especial precautions,* with dilute aqueous extracts of brain tissue reduces the thromboplastic activity of these extracts. The antithromboplastic potency of hemophilic plasma is greater than that of normal plasma. This excess constitutes perhaps the primary defect responsible for the slow coagulation of hemophilic blood and the low thromboplastin content of citrated hemophilic plasma.

Antithromboplastin may be neutralized *in vitro* by incubating citrated plasma, for a given time interval, with sterile aqueous extracts of brain tissue. A transitory diminution in the venous blood coagulation time of hemophiliacs follows the slow intravenous injection of their own thromboplastinized plasma. There were no unusual symptoms, or any changes in the blood prothrombin and fibrinogen, following injections of the plasma.

Aseptic Meningitis of Known and Unknown Etiology. By JOS. E. SMADEL, New York, N. Y.

Materials from 165 individuals with aseptic meningitis have been studied in an attempt to establish the etiology of each patient's disease. Twenty-five of the group had choriomeningitis; this was proved by isolating the virus or by demonstrating complement-fixing or neutralizing antibodies in their convalescent bloods. Sera collected 2 to 5 weeks after onset contained the former antibody in 17 of 19 instances but the latter in only 3 of the 19. Subsequently, all 25 patients developed neutralizing substances and 23 had complement-fixing antibodies. Four years' experience with the complement-fixation technique has proved its value in the early diagnosis of choriomeningitis.

Five of 50 patients with aseptic meningitis not caused by the virus of lymphocytic choriomeningitis had in their early and late sera significant amounts of complement-fixing antibodies for psittacosis. The interpretation of these findings must rest on additional observations; however, the neurotropic tendencies of viruses of the psittacosis group in experimental animals are established and their capacity to produce aseptic meningitis should be considered, even though the present observations do not conclusively prove that this group of agents was active in these cases.

Six patients developed aseptic meningitis during or following mumps and were thought to have mumps meningitis. No etiology could be assigned for the disease of 129 of the 165 patients. Aseptic meningitis apparently is a clinical syndrome, caused by a number of infectious agents. The responsible agent should be identified, if possible, in each case.

The Fate of Colchicine in the Body. By AUSTIN M. BRUES, Boston, Mass.

The distribution and excretion of colchicine, following intravenous administration to rats, has been studied by means of a new colorimetric method, and the findings checked by bioassay using mice (for toxicity) and tissue cultures (for cytological action). Following injection, the blood concentration falls rapidly and reaches an almost constant level after a few minutes. This blood level is slightly higher than that in most tissues. Colchicine is excreted in bile, and also directly into the intestine, so that for several hours after administration between 10 and 25 per cent of the administered dose is found in the small intestine and its contents. This high intestinal concentration would appear to be responsible for certain toxic manifestations of the drug. There is no evidence for its specific accumulation in other tissues or in tumors. Urinary excretion occurs rapidly only during the brief period when the blood concentration is high. About 50 per cent of the injected dose has been recovered from whole mice

16 hours after injection. There is no evidence to support the belief that the delayed action of colchicine is due to its conversion to a more toxic compound; its cumulative action is probably dependent upon its prolonged retention in the body.

The Relation of a Somatic Factor to Virulence of Pneumococci. By COLIN MACLEOD and (by invitation) MACLYN MCCARTY, New York, N. Y.

The property of virulence of pneumococci has been generally assumed to depend almost solely upon the integrity of the capsule. That a somatic factor may also exert a pronounced effect on virulence is suggested by the occurrence of strains of encapsulated pneumococci which are entirely avirulent although culturally and immunologically identical with virulent strains of the same type.

In order to demonstrate more conclusively the relation of a somatic factor to virulence, the technique of type transformation has been used, whereby pneumococci of one type may be converted to another specific type by way of the rough intermediate.

Two strains of pneumococcus Type III, one virulent for the rabbit, the other avirulent, were transformed to pneumococcus Type II. The virulence of the newly-derived strains of Type II corresponded to that of the original Type III strains, indicating that the differences in virulence are related to a somatic factor and not dependent upon the capsule.

In other instances, the somatic factor may be present and yet masked because of the nature of the capsule. When a rough variant derived from a virulent strain of Type II pneumococcus was transformed into Types I, III, and XIV, the Types I and III were fully virulent and the Type XIV strain was avirulent.

The Effect of Sulfonamides on Virulence of Pneumococci. By FRANK L. HORSFALL, JR., New York, N. Y.

A quantitative study was made of the survival, growth, and virulence of pneumococci in solid media containing sodium sulfathiazole. The number of pneumococci and the concentration of sulfathiazole per unit volume of medium were varied independently. Only a very small but constant proportion of the total number of pneumococci were capable of growing in the presence of sulfathiazole and this proportion was inversely related to the concentration of drug. Secondary cultures derived from individual colonies grown once in sulfathiazole contained much higher proportions of cells capable of growing in the presence of the drug and these proportions were directly related to the concentrations in which the first growths had occurred. This increased capacity remained constant through numerous subcultures in drug free media.

The virulence of the organisms thus derived was decreased, often very markedly, although in all instances the pneumomocci remained fully encapsulated and type specific. The degree of reduction in virulence was not definitely correlated with the concentration of sulfathiazole in which growth occurred. The reduced virulence did not change through numerous subcultures in the absence of the drug.

These results suggest that there are marked differences in the metabolic potentialities of individual cells of pneumococci. They indicate also that the cellular factor associated with the property of virulence, in contrast to the capsular factor, is susceptible of striking alteration as a result of a single exposure to the action of sulfathiazole.

The Relaticve Antimalarial Effects of Atabrine, Certain Acridine and Quinoline Derivatives, Quinine and Sulfonamides on Experimental Infections with P-Lophurae-Ducks. By O. W. BARLOW (introduced by Theodore G. Klumpp), with the technical assistance of E. Homburger, Rensselaer, N. Y.

Following the intravenous inoculation of young Peking ducks with infected blood (*P. Lophurae* Strain 12A), groups of birds were medicated with one of a series of preparations by incorporation of the medicament in the dry poultry mash (Bieter, *et al.*, 1939). Studies of the effects of various drug percentages in the diets permitted the quantitative evaluation of acridine, quinoline and sulfonamide derivatives with standard controls, *i.e.*, atabrine, plasmochin, or sulfanilamide and quinine.

The comparative order of efficiency of the various compounds tested from high to low is as follows: plasmochin > atabrine > P.2 > P.3 > quinine > acranil > neoacranil. Certain of these compounds on the basis of their margins of safety and therapeutic effects appear promising and merit further careful study.

Sulfamethylthiazole, sulfathiazole, or sulfadiazine are therapeutically active under the conditions of test. Their value appears to be in the order named, although inferior to the poorest of the above acridine derivatives. Therapeutic effects of combinations of these compounds with atabrine were not significantly superior to atabrine alone. No clear-cut therapeutic effects were demonstrable with sulfapyridine, sulfanilamide, sulfaphenylthiazole, or other derivatives.

Variations in Citric Acid Excretion During the Menstrual Cycle. By EPHRAIM SHORR and (by invitation) ALICE R. BERNHEIM and H. TAUSSKY, New York, N. Y.

Citric acid has long been recognized as a normal metabolic intermediary, but its significance remains obscure. From work on minced tissue, Krebs has assigned it an important rôle in the oxidative metabolism of carbohydrates. Small amounts are present in blood (2 to 3 mgm. per 100 cc.) and 400 to 1200 mgm. are excreted daily in urine. Alkalies increase its urinary excretion; but, except for trivial amounts, ingested citric acid is oxidized.

The present studies have brought out a relation between urinary citric acid excretion and the menstrual cycle in women. Vaginal smear studies were correlated with the chemical observations. Urinary citric acid is lowest during menstruation, increases significantly throughout the intermenstrual phase, and again falls to

menstrual levels usually just before the onset of bleeding. In some cycles, a sharp transitory midmenstrual fall in excretion has been observed at about the twelfth day. Citric acid excretion is also significantly increased in amenorrheic girls by administration of estrogenic hormone. Apparently estrogenic hormone is at least one factor related to increased citric acid excretion of the intermenstrual period. The mechanism underlying the cyclic variation in citric acid excretion during the menstrual cycle is now under investigation.

The Subcutaneous Administration of Sulfathiazole Sodium in Various Clinical Conditions. By J. J. A. LYONS, D. R. CLIMENKO (by invitation) and L. W. GORHAM, Albany, N. Y.

The clinical efficacy of sulfathiazole in the treatment of certain infectious diseases is well established. One of the principal difficulties in the clinical use of drugs of this type is the necessity of maintaining therapeutically effective concentrations in the body over relatively long time intervals. Occasions arise when the oral administration of the drug constitutes a serious practical difficulty in the management of the patient, or becomes an actual impossibility. Under such circumstances, the usual practice is to administer the drug in the form of its sodium salt by intravenous injection. A practical difficulty is associated with the intravenous administration of the drug: under these circumstances, a peak concentration is reached in the blood, soon after administration is completed, which rapidly falls off as the drug is excreted. Excessive concentrations are rapidly followed by therapeutically ineffective concentrations. Therapeutic effectiveness attainable under this form of administration is far from optimal. This method of administration is admirable for rapidly attaining a distribution of the drug in the body, but it cannot be depended upon as a sole route of administration in the treatment of an acute infection.

Finland and his coworkers using the water-soluble glucoside of sulfapyridine, showed that this addition compound might be administered intravenously or subcutaneously. Unfortunately, they also pointed out that the glucose derivative was relatively inert from a therapeutic standpoint. Flippin advocated the intramuscular administration of concentrated (33 per cent) solutions of sodium sulfapyridine.

It has been repeatedly pointed out (Powell and Chen, and Marshall) that the alkaline solutions of the sodium salts of drugs like sulfapyridine are extremely irritant and that the subcutaneous administration of such solutions could cause severe local reactions with tissue destruction. We have found this to be true when concentrations of the order of 10 per cent or higher are administered subcutaneously or intracutaneously to experimental animals. We have also found that such experimental animals tolerate the subcutaneous administration of 1 per cent aqueous solutions of the anhydrous sodium salt of sulfathiazole without showing any sign of tissue reaction, and that only a transient hyperemia results from the subcutaneous administration of 2 per cent solutions.

Our clinical evidence, which agrees with the observation of Taplin and his coworkers, bears out these experimental findings. Up to the present time more than 300 cases on the Medical, Gynecological, and Surgical Services of the Albany Hospital have received up to 2000 cc. of an 0.5 per cent aqueous solution of sodium sulfathiazole per day, administered subcutaneously by hypodermoclysis, without showing any untoward local reactions. This group was made up of a large variety of clinical cases which should have received sulfathiazole therapy, but in whom oral administration was contraindicated. It included such cases as abdominal and pelvic peritonitis, severe traumatic infections, late stages of lobar pneumonia, postoperative infections after section of the alimentary canal, acute infectious diseases in infants, etc. Both sexes and all age groups from infants through to advanced senility were represented in the series.

Blood concentrations of the drug during this type of medication were somewhat lower than would be expected if the same quantity of the drug had been administered orally. This is probably due to the fact that large quantities of fluid are administered and the resultant diuresis tends to speed up the passage of the drug through the body. This observation is substantiated by the small proportion of acetylated drug which is present in the tissues under these circumstances. Following oral administration, from 10 to 20 per cent of the drug in the body is conjugated, while less than 5 per cent of the total amount is conjugated after subcutaneous administration.

The Interrelation of the Venous Pressure, Tissue Pressure, and Blood Flow Through the Veins. By HENRY W. RYDER, WILLIAM E. MOLLE (by invitation), and EUGENE B. FERRIS, JR., Cincinnati, O.

Factors which influence venous pressure have been studied in intact and isolated veins and in models. When the vein under study is collapsed either by elevating it with respect to the heart level or by increasing the tissue pressure about it, the pressure in it is independent of the central venous pressure (pressure at any point nearer the heart) and exactly reflects the tissue pressure. When the vein is in such a collapsed state, the tissue pressure about it also becomes a function of the volume flow of blood through the vein. It is shown that the essential factor which causes this interrelation of venous pressure, tissue pressure, and blood flow in collapsed veins is the property of the vein of freely transmitting pressure across its wall over a wide range of volume change.

These studies demonstrate that when the tissue pressure is high enough to collapse the vein at any point between the heart and the point of measurement, the peripheral venous pressure becomes a function of this tissue pressure and is independent of right auricular pressure. Contrariwise, when the vein is distended throughout its course, the peripheral venous pressure is then a function of right auricular pressure and is independent of the tissue pressure. Thus, the collapse factor in veins is of great sig-

nificance in the interpretation of peripheral venous pressure.

Circulatory Changes Resulting from Trauma After Sympathectomy and After Spinal Cord Transection. NORMAN E. FREEMAN and (by invitation) M. L. CULLEN and A. E. SCHECTER, Philadelphia, Pa.

Trauma to the limbs of dogs anesthetized with ether resulted in a reduction of blood volume greater than could be accounted for by the measured local fluid loss. Reduced circulation was consistently observed and preceded the development of shock. After total sympathectomy, even though the circulation was well sustained, a comparable reduction in blood volume occurred. In dogs, after recovery from spinal cord transection, trauma produced a loss of blood volume, although the circulation was well maintained as indicated by an adequate peripheral circulation, cardiac output, and normal oxygen saturation of venous blood obtained from the right heart.

It is concluded that reduced circulation after trauma is of diagnostic and prognostic significance but that the process of shock, as indicated by a loss of blood volume, may be initiated in spite of a well-maintained circulation.

Neuropathic Joint Lesions in Diabetes Mellitus. By C. CABELL BAILEY and HOWARD F. ROOT, Boston, Mass.

Painless destruction of the joints of the tarsus has been observed in fourteen diabetic patients at the New England Deaconess Hospital during the last few years. The lesion has been observed to progress and to result in a peculiar type of deformity of the tarsus, regardless of treatment. Careful study has eliminated syphilis and the Charcot joint, and syringomyelia. The condition has occurred in patients with diabetes of long duration, with inadequate diabetic control, at ages varying from 30 years to 60 years. Certain of the patients have had associated diabetic neuritis. One patient has come to autopsy and a complete examination of the joints of the foot and of the central nervous system is reported. The condition is not dependent, apparently, upon deficient blood supply. As a result of the diminished sensation, infections of the toes and skin later occur and sometimes become chronic. The etiology is not yet determined but seems to be of neuropathic type.

Further Observations on the Esophageal Electrocardiogram. By JAN NYBOER (introduced by Herman O. Mosenthal), New York, N. Y.

The esophageal electrocardiogram has frequently been employed in the study of arrhythmias, while Hamilton and Nyboer first emphasized its importance in the study of posterior myocardial infarction. These studies have been extended to include cases in which the standard leads show atypical QT patterns and in cases suspected of having multiple myocardial infarction. The observations clearly show that lesions of the anterior and posterior myocardial wall, respectively, may be demonstrated by multiple exploratory leads in the anterior and posterior ventricular regions.

In order to enlarge on the concept of the electrical field, typical cases of left ventricular hypertrophy, right ventricular hypertrophy, right bundle branch block, left bundle branch block, and digitalis effects have been obtained. Cases of bundle branch block, associated with or resulting from myocardial infarction, reveal patterns which are worthy of this esophageal, electrocardiographic study. On the basis of our limited experience, it appears that knowledge of the electrical field of the posterior heart region becomes definitely helpful in evaluating the normal and abnormal standard lead electrocardiogram.