PROCEEDINGS OF THE THIRTY-FIRST ANNUAL MEETING OF THE AMERICAN SOCIETY FOR CLINICAL INVESTIGATION HELD IN ATLANTIC CITY, N. J., MAY 1, 1939

READ BEFORE THE SCIENTIFIC SESSION

PRESIDENTIAL ADDRESS

By T. R. Harrison

If we assume that a presidential address has any useful function at all, it follows that this function is to try to benefit the organization to which the address is delivered. Such a purpose can best be served, not by praising the accomplishments of the past, but by considering the dangers of the future. Medical societies, as well as other cultural organizations, are like individuals in that they tend to grow, to reach maturity, to accomplish little or much—as the case may be—and then to decay. What are the causes of this institutional arteriosclerosis? Is it inevitable? Can its progress be delayed, arrested, or perhaps prevented entirely? By what means? Realizing that other and wiser physicians may prescribe differently for this important disease, my suggestions are as follows:

Since institutional arteriosclerosis is not limited to societies but tends to affect all cultural organizations, the problem should be approached in its broader aspects. A study of the decline of medical schools in the past suggests that there are two general groups of factors.

(1) *Extrinsic* causes. These include political, economic, and other influences which affect society as a whole and which cause a general cultural decline. The decay of the great medical faculties of Salerno, Montpelier, and Bologna can possibly be ascribed to such factors, which are also responsible for the present catastrophic decline of the medical centers in certain central European countries. These extrinsic causes are largely beyond our control. We are concerned with them as citizens rather than as physicians.

(2) *Intrinsic* causes. These include unfavorable conditions which develop within medical societies and which are therefore subject to control by the membership. Although there are numerous different conditions—such as nepotism, intolerance, and self-satisfaction—which tend to have an unhealthy effect, they can all be traced to one general cause—*a failure to select the best possible men.*

The importance of exhaustive effort to find the most capable individuals for chiefs of departments is generally recognized. Much attention is likewise paid to choosing the proper persons for the secondary places. However, assistants and instructors are often appointed rather casually, and too frequently the quality of agreeableness is emphasized to the neglect of more important capacities. This is entirely illogical. The professors of tomorrow must be chosen from the instructors of today. No man should be appointed to a permanent salaried academic position—be it ever so lowly—unless he already gives promise of becoming, in the future, material for positions of the highest rank. If the roots of the academic tree are properly cared for the fruit will take care of itself.

Even when external conditions are favorable medical culture can not flourish for long with mediocre personnel. When, as during the past ten years, and possibly for some decades in the future, the extrinsic causes of cultural decline are already operative, it is important that every precaution be taken against intrinsic decay. The only assurance lies in constant—almost agonizing—effort to choose the good man.

But this is not a simple matter. Some persons, in high positions, looking for an able man to fill a vacancy but lacking the patience of Diogenes and the illumination cast by his lantern, tend to become exhausted by the search. They then choose the next individual they encounter, saying, "God made him, and therefore let him pass for a man." A genius—like Gilman, or in the clinical field, Peabody—with an almost supernatural ability to pick the right man for the job, is a rarity. Are there any criteria whereby we with lesser gifts can be guided in choosing men? I believe there are.

The customary procedure in filling an academic position is to inquire concerning a prospective candidate from his present and past superiors. Since nearly everyone tries to appear at his best in the eyes of his chief, the professors and associate professors often have a false idea of a man's abilities. Why not inquire of his inferiors also? They see him as he is. The house staff of a teaching hospital can usually "size up" the members of the permanent staff as well and sometimes better than the chief can. No man should be seriously considered for academic advancement unless he has the respect—not only of his superiors but also of his inferiors. The old saying that "Young men think old men are fools; but old men know young men are fools" is only partly true, but in any case, young men usually know which other young men are fools.

Appointments are often made or refused on the basis of a man's school, his religion, or his social qualifications. I fail to see what significance these factors have. The "happy family" idea has been much over-emphasized. Even if one regards harmony as the prime *desideratum*, it will usually be found that truly unusual men get on well—while lesser men, jealous because they are deficient, tend to quarrel.

Much emphasis is placed on administrative ability but the term is usually not defined. Some consider that a good administrator is a man with a passion for unimportant details. If the word is to be used in this sense it should

not be confused with another quality—leadership. We should remember that "the greatest clerkes be not the wisest men." An administrator—as defined above—is often preoccupied with his own system of better doing things which are already being done; a leader is concerned with stimulating other men to do things which otherwise would be left undone. Even first-rate administration (as defined here) bears a close resemblance to puttering; first-rate leadership resembles nothing else—it is a unique and all-too-rare quality.

The good man is he who not only furnishes ideas but who when working with men of lower rank than himself does his own share and a little more of the actual labor. He says to his inferiors, "Come on," not "Go on."

The attitude of a man toward research, his interest in it, and his energy are just as important as his intelligence. All great investigators seem to have had one quality in common—they have labored while others rested.

We all know individuals with fine minds who accomplish little because they lack drive. Such men are like the cat which, "would eate fish and would not wet her feete." Critical, creative imagination—the most important quality in research—is not immaculately conceived by the mind alone; it is "by" energy "out of" intellect.

It is of major importance that a candidate should really love investigation. He should realize that research at its worst is:

"To loose good dayes, that might be better spent;
To wast long nights in pensive discontent;
To speed to-day, to be put back to-morrow;
To feed on hope, to pine with feare and sorrow.
. . . To fret thy soule with crosses and with cares;
To eat thy heart through comfortlesse dispaires;
To fawne, to crouche to waite, to ride to ronne,
To spend, to give, to want, to be undonne."

while at its best, research leads to "infinite riches in a little room."

The qualities which have been mentioned are only a few of the ones which mark the good man. They have been stressed because they seem to me especially important and because they are often overlooked. Many other qualities might be cited but in a final analysis most of them can be reduced to two traits of transcending importance. The first of these is wisdom. Such wisdom includes a broad knowledge of medicine in general and a deep understanding of certain fields of medicine. Aside from this purely intellectual quality there is an emotional trait which is perhaps even more important. This is a certain radiant energy which, operating internally, keeps the individual constantly working and which, operating externally, catalyses other men to similar action. For want of a better term we may, with apologies for the mixed metaphor, call this quality "contagious fire."

In a world of crumbling standards the safest assurance for the future of academic medicine lies in the thoughtful selection of the best possible young men. Our choosing should be tempered by the sober recollection that each corporal should with justice carry in his knapsack the baton of a marshal.

Contribution to the Etiology of Diabetic Retinitis. by JONAS S. FRIEDENWALD and (by invitation) MANUEL G. GICHNER, Baltimore, Md.

Patients with active hemorrhagic retinitis in diabetes have increased capillary fragility. The capillary fragility is improved, but is not as a rule brought back to normal by large doses of vitamin C. Saturation tests with ascorbic acid reveal a marked deficiency in the ability to excrete this substance in the urine following the injection of large doses by mouth. Absorption from the gastro-intestinal tract is apparently normal as is also the renal threshold. Hence the excretion deficit is to be attributed to abnormal utilization within the body. In a small group of cases the administration of vitamin B complex resulted in a return to normal of the capillary resistance, and also in a reappearance of the ability to excrete injected ascorbic acid.

Vitamin C Nutrition and Metabolism in Rheumatoid Spondylitis. JAMES F. RINEHART, San Francisco, Cal.

A detailed study of the nutritional status relative to vitamin C was made in a series of cases of rheumatoid spondylitis. In 32 cases the average fasting blood plasma vitamin C value was 0.12 mgm. per 100 cc. In 90 per cent of cases the initial value was below 0.40 mgm. per 100 cc. In a number of the cases, determinations of blood plasma ascorbic acid were made following administration of large oral doses of vitamin C (15 mgm. per kilogram). The curves were 'flat' indicating significant undersaturation of tissues.

Data gained from dietary histories indicate that although some of the cases were ingesting grossly inadequate amounts of vitamin C, this was not uniformly so. Many cases showed depleted vitamin C reserves in spite of a normally adequate dietary intake. In several cases the metabolic fault was striking. Possible factors responsible for this abnormality are considered.

The influence of known supplements of vitamin C upon the blood ascorbic acid sedimentation rate, capillary strength, weight, general condition, and arthritis in a group of cases followed for two months or longer is analyzed.

The capillary strength was determined initially in 27 cases. This was found to be almost uniformly lowered. In 11 of 14 cases followed for two months or more the capillary strength rose after administration of supplementary vitamin C. Eight of 11 cases gained weight. Twelve of 17 showed slowing of the sedimentation rate occurring within 4 months. Improvement in general condition and diminution of pain was almost regularly observed. The only other treatment was physiotherapy in a portion of the cases.

These data indicate that vitamin C deficiency is almost uniformly present in this form of arthritis. This deficiency may occur in the presence of a normally adequate vitamin C intake. The uniform finding of vitamin C depletion and the response to liberal vitamin C supplements noted suggest that the deficiency is contributory to the disease.

The Nature of Synovial Mucin. By KARL MEYER (by invitation) and M. H. DAWSON, New York, N. Y.

Although the importance of synovial "mucin" in the physiology of joints is generally recognized, its chemical nature has not been established. By a method similar to that employed by one of the authors (K. M.) in the isolation of chondroitin-sulfuric acid, a polysaccharide acid of high molecular weight has been obtained which possesses most of the viscosity of the starting material. This polysaccharide acid consists of equimolar parts of hexosamine, hexuronic acid, and acetyl, the latter apparently as N-acetylglucosamine. The polysaccharide occurs in synovial fluid either free or united to protein in salt linkage only.

In composition and rotation the polysaccharide acid appears to be identical with the polysaccharide acid of vitreous humor, umbilical cord, and the mucoid phase of Group A hemolytic streptococci. Further evidence of the identity of these polysaccharides is provided by the fact that they are hydrolyzed at the same rate by a specific enzyme.

The protein component of the carbohydrate-protein complex appears to be a globulin which forms an insoluble salt with the acid polysaccharide on acidification.

Immunological aspects of the polysaccharide acids obtained from various sources will be briefly considered.

Plasma Specific Gravity as an Aid in the Estimation and Maintenance of a Safe Fluid Balance in Artificial Fever. By HERBERT R. BROWN, JR., WILLIAM F. CLARK, and NATHANIEL JONES (by invitation), and STAFFORD L. WARREN, Rochester, New York.

Adequate storage and replacement of reserve water and electrolytes is necessary to safeguard the patient against dehydration resulting from increased losses of these substances during artificially induced fever.

Fluctuations in plasma specific gravity have been observed in 50 cases under various conditions (preparation for fever treatment, compensation during treatment, and sequelae of treatment).

There seems to be a good correlation between plasma specific gravity values and the clinical findings of adequate hydration, overhydration, and dehydration and collapse states.

During adequate hydration, plasma specific gravity fluctuates within the normal range defined by Van Slyke. Clinically the patient is in good condition (normal blood pressure, frequent urine excretion, moderately profuse sweating, absence of mania, somnolentia).

In states of dehydration accompanied by shock, blood pressure fall, anuria, lack of sweating, mania, and collapse, the plasma specific gravity rises well above normal levels.

In overhydration, plasma specific gravity falls below normal levels in keeping with the clinical evidence (blood pressure rise, polyuria, edema, excessive sweating, restlessness, *etc.*).

Plasma specific gravity values change significantly before the clinical symptoms of dehydration or overhydration are clearly evident, so that the hydration of the patient may be safely and quickly adjusted in the necessary direction.

Protective Antibodies in the Serum of Human Syphilitics. By THOMAS B. TURNER and (by invitation) WILLIAM L. FLEMING and NANCY L. BRAYTON, Baltimore, Md.

In a previous paper experiments were reported which showed that during the course of experimental syphilis rabbits developed protective antibodies against virulent *Treponema pallidum*, and that the presence of these antibodies was associated with a high degree of resistance to reinfection (Turner, T. B., J. Exper. Med.—In press). The present paper reports the results of protection tests made on the serum of 80 persons, 60 of whom had or had had syphilis, and 20 of whom were presumably non-syphilitic.

The technique of the test was the same as that used for testing rabbit sera. One part of a tissue emulsion rich in virulent *T. pallidum* was combined with 9 parts of whole serum, the mixture incubated for 6 hours at 37° C., and inoculated intracutaneously in 6 sites of one area in each of 4 normal rabbits. Sera were tested in groups of 4, one serum of each group being from a presumably non-syphilitic person. The same lot of spirochete emulsion, which had been preserved by freezing, was employed in all but one group of tests. Protection was manifested by failure of syphilitic lesions to develop at the sites of inoculation or by a prolonged incubation period as compared with the lesions in the control areas.

Of 60 sera from persons with syphilis, 53 showed definite protection; in 4 the results were equivocal, and in 3 there was no evidence of protective antibodies. Of 20 sera from presumably non-syphilitic persons, 16 showed no evidence of protection, in 2 the results were equivocal, and 2 showed definite protection. Of 11 syphilitics with negative Wassermann tests, the sera of 10 contained protective antibodies.

The bearing of these findings on the question of humoral immunity in syphilis and the relationship of protective antibodies to the ordinary diagnostic serological tests were briefly discussed.

The Bactericidal Effect of Sulfanilamide upon Pathogenic and Non-Pathogenic Staphylococci. By WESLEY W. SPINK, Minneapolis, Minn.

The purpose of this study was to show that sulfanilamide has a definite bactericidal effect upon staphylococci, and also to demonstrate certain factors influencing the effect of sulfanilamide upon bacteria. Twelve pathogenic and seven non-pathogenic strains were included. The influence of each of the following factors on the bactericidal action of sulfanilamide was observed: the nature of the culture media with special reference to ingredients, and pH; the strain of staphylococcus; the number of organisms in suspension; the concentration of sulfanilamide; the temperature at which suspensions of organisms and the drug were incubated; the length of time necessary for sulfanilamide to exert its effect.

Employing the usual type of veal infusion broth as media, high concentrations of sulfanilamide failed to kill

100 organisms. When sterile, human urine was substituted as a culture media; a marked bactericidal effect was obtained with low concentrations. The bactericidal effect was much more pronounced at an incubation temperature of 40° C. than at 37° C. When only one drop of veal infusion broth was added to 5 cc. of urine, the foregoing action of sulfanilamide was greatly inhibited. These observations indicate that peptone or peptone-like substances may inhibit the action of sulfanilamide, and that an elevation of temperature within human physiological limits is desirable for an optimum effect.

The Use of Sulfapyridine in the Treatment of Pneumonia. By J. MURRAY KINSMAN and JOHN WALKER MOORE, Louisville, Ky.

During the winter and early spring of 1939, we treated, in the Louisville City Hospital, 40 cases of pneumonia with sulfapyridine with a mortality rate of 5 per cent. The pneumonias have been of both the lobar and bronchial variety. Many different types of pneumococcus have been recovered from the sputum.

In every case, blood concentration curves have been obtained for both free and total sulfapyridine. Blood was taken at hourly intervals for 4 hours after the initial dose, and thereafter, once daily throughout the course of treatment and until the drug disappeared from the blood stream. Daily urines have also been examined quantitatively for the excretion of the drug in both the free and conjugated form.

The results of the blood and urine studies in general agree with the results of other workers. It appears that a blood concentration of the free sulfapyridine of anywhere from 1 to 12 may be effective in curing pneumonia. Absorption is very irregular. A few cases had recurrences of fever after the drug was discontinued and return of the temperature to normal when it was started again. No toxic effects on the blood were noted. Two patients had severe hematuria with complete recovery when the drug was stopped. Nausea was a very common side-effect. Empyema was not cured, even though the concentration of the sulfapyridine in the empyema fluid was much higher than in the blood.

Hemolysis from Sulfapyridine. By LOWELL A. ERF and COLIN M. MACLEOD (introduced by C. P. Rhoads), New York, N. Y.

The widespread and effective use of sulfapyridine in pneumonia has made important a knowledge of its possible harmful effects. Furthermore, observations of the hematological changes caused by chemicals of known constitution are useful for understanding the hematopoietic disorders of unknown etiology.

The urinary and fecal excretions of urobilin have been measured quantitatively, as an index of the rate of hemolysis, in 20 cases of pneumonia treated with sulfapyridine. As controls, 6 febrile cases of pneumonia, treated by the drug, have been studied similarly. The usual observations of the blood cells were made in all instances.

The results of the study are striking. The patients treated with large amounts of sulfapyridine showed unequivocal evidence of an increased rate of hemolysis. From two to ten times the normal amounts of urobilin were excreted; the greatest amounts by the patients receiving the most drug. Concurrently there appeared anemia, leukocytosis, and reticulocytosis; furthermore, in certain instances a diversion of urobilin from feces to urine gave evidence of hepatic insufficiency. When treatment with sulfapyridine was discontinued all evidence of abnormal blood destruction disappeared. Patients receiving moderate amounts of the drug excreted slightly increased amounts of urobilin, but when little drug was given no sign of abnormal hemolysis could be detected. Control cases without medication with sulfapyridine showed no increased excretion of urobilin.

It is concluded that sulfapyridine in large amounts causes an increase of the hemolytic process, although the disease for which the drug is given does not do so. The effect seems to be roughly proportional to the amount of drug administered.

Activity in the Central Nervous System During Anesthesia. By HENRY K. BEECHER (introduced by E. D. Churchill), Boston, Mass.

Investigation of the anesthesia process has been handicapped by lack of precisely measurable elements. The electrical activity of the central nervous system, and in particular that of the cerebral cortex, presents a suitable component for study. Measurement of the electrical activity there has been made possible by recent advances in electrophysiology. The application of the technics of this science to study of the central nervous system during anesthesia not only gives information leading to a more complete understanding of cortical action potentials but also presents fundamental information as to the characteristics of the anesthesia process itself.

When the frequency and voltage of the electrical waves and the pattern of the activity are considered in conjunction with the response to peripheral stimulation under the several agents at various levels of anesthesia, it becomes possible to make certain statements: The frequency of the cortical waves is characteristic for a given agent. It is a constant over a wide range of anesthesia depth. On the other hand, voltage of the waves is labile. Voltage is directly related to anesthesia depth. In one group of agents, but not in another, voltage can be altered by peripheral (sciatic) stimulation. Under deep anesthesia sciatic stimulation has no effect on voltage under any agent. The seventeen anesthetic agents studied can be sharply divided into two groups on the basis of six criteria: volatility, frequency of cortical waves, pattern, presence or absence of a secondary cortical discharge following peripheral stimulation, response of the voltage of cortical waves to sciatic stimulation, and type of flexion reflex. A consideration of these points leads to a mass of objective data regarding the central nervous system effects of various anesthetic agents and permits a general hypothesis to be stated as to the fundamental difference of action of volatile and non-volatile agents.

Basis of the Hematopoietic Activity in Pernicious Anemia of Desiccated Hog Ileum. By SMITH O. DEXTER, ROBERT W. HEINLE and HERBERT J. FOX (by invitation), and WILLIAM B. CASTLE, Boston, Mass.

Increased blood production in pernicious anemia has been observed by various workers to follow the oral administration not only of desiccated hog stomach, but also of similar preparations of the duodenum, jejunum, ileum and even the colon of that animal. From this evidence others have concluded that the so-called intrinsic factor is secreted by the intestine as well as by the stomach, or that the intestine plays an active part in the subsequent preparation or storage of an antianemic principle.

Still another interpretation is, however, possible, because these portions of the alimentary tract are normally exposed to gastric secretion from above. Their blood forming activity might therefore be due entirely to passive adsorption of intrinsic factor of gastric origin. If this were so, it might be more readily removed by prolonged washing than if actually secreted by the mucosa. Accordingly, a stream of cold running water was caused to distend and to pass through, in different experiments, several fresh specimens of the stomach, the duodenum and jejunum (3 feet), or the lower half (15 feet) of the small intestine of the hog. After 6 hours of such washing the entire mucosa was separated from the muscular layer and ground with approximately 400 grams of finely divided beef muscle per 100 feet of intestine. In another series of preparations of duodenum and stomach the mucosa was finely minced and suspended in a large volume of cold water which was continuously agitated by an inflowing stream. After 6 hours the mucosa was filtered off, excess water removed, and ground with finely divided beef muscle. The approximate proportions, 400 grams of beef muscle to the mucosa of each six stomachs, and 400 grams per 100 feet of duodenum, were used. The mixtures were then dried in a current of warm room air, defatted and pulverized. As controls, similar preparations of the various organs were made, except for the prolonged washing.

Observations on 12 patients with typical addisonian pernicious anemia were made. The hematopoietic activity of "unwashed" preparations of ileum, previously observed by others, was entirely confirmed. Its blood forming power, like that of the hog stomach, was, however, found to be readily destroyed by boiling, and thus shown not to be due to active material similar to that in liver. A washed preparation of hog's stomach retained its hematopoietic activity, but the lower half of the small intestine after washing possessed in three instances no detectable, and in one instance only slight blood forming activity. Washing did not remove the activity of the duodenal mucosa, but mincing and then washing rendered inactive the duodenal mucosa but not that of the stomach.

It is therefore suggested that the hematopoietic power of the "unwashed" ileum of the hog is due to the passive adsorption of gastric secretion. Whether the activity of the washed duodenum of the hog is due to an active secretion of intrinsic factor, as has been assumed by others, or to the inability of the washing process to get rid of a higher local concentration of adsorbed intrinsic factor, remains uncertain. Variations in the texture and thickness of the mucosa of the various organs cannot be excluded as a cause of the differences in hematopoietic activity, especially following the mincing and washing procedure.

A Newly Recognized Granulopenic Syndrome Caused by Excessive Splenic Leukolysis and Successfully Treated by Splenectomy. By B. K. WISEMAN (by invitation) and C. A. DOAN, Columbus, Ohio.

Theoretically, from the accumulated knowledge of splenic physiology there might be expected to occur a primary, more or less specific, granulopenic syndrome, comparable to congenital hemolytic jaundice or thrombocytopenic purpura, in which the spleen pathologically segregates and destroys leukocytes instead of red cells or platelets.

Practically, such a syndrome has been encountered during the past year in an acute, as well as in a sub-acute and chronic, form. The mechanism was established by direct sternal marrow studies revealing in each instance myeloid hyperplasia of qualitatively normal cells; by gross splenomegaly, with profound peripheral granulopenia; by ruling out associated liver cirrhosis (Banti's syndrome), chronic infection and other contributing organic, drug, or environmental factors; and finally, by the therapeutic test of splenectomy, which was followed by a prompt re-establishment of a normal peripheral white cell count.

Histologically each of the three spleens removed showed extreme clasmatocytosis with excessive phagocytosis of granulocytes.

Chemical extracts of the splenic tissue have been injected into rabbits and monkeys in an attempt to reproduce the syndrome experimentally.

The Experimental Production of Congestive Splenomegaly. Preliminary Report. By LOUIS M. ROUSSELOT (by invitation) and WILLIAM P. THOMPSON, New York, N. Y.

In an attempt to produce a congestive splenomegaly (Banti's syndrome) in dogs, various chronic hepatic irritants have been tried.

If a sterile suspension of 1 to 1.5 grams of SiO_2 particles, measuring 1 to 3 micra in size, is introduced into the dog's splenic vein, the particles promptly clear through the liver and appear in the hepatic lymph nodes. However, if, after several months, silica is again injected, the particles remain in the liver where they produce a slowly progressive, periportal, nodular fibrosis. A total of 6.0 grams, injected in divided doses, will result in a widespread cirrhosis, by the end of the second year. With the development of this hepatic lesion, portal hypertension and congestive splenomegaly appear; the splenic vein pressures rising to over 250 mm. of H_2O, the spleens increasing to from 4 to 6 times their normal size. Anemia and thrombocytopenia appear and, in the one animal autopsied, an esophageal varix was present.

Fatal Probable Riboflavin Deficiency in Man. By HENRY FIELD, JR., and (by invitation) EDWIN C. WISE, Ann Arbor, Mich.

Until recently, nothing has been known concerning the function of riboflavin in man. Sebrell and his coworkers have studied riboflavin deficiency in dogs. They reported sudden collapse and coma, promptly followed by death unless adequate doses of riboflavin were given. The outstanding necropsy finding was a yellow mottling of the liver and fatty infiltration of the liver and of the tubules of the kidneys.

We have observed patients who died unexpectedly and who, at autopsy, had similar fatty livers and kidneys. The dried liver of one patient has been found by biological assay to contain 10 Sherman units of vitamin B_2 per gram. The Vourquin-Sherman assay method is believed generally to measure riboflavin. The value found is of the order of magnitude found in experimental animals dying of riboflavin deficiency.

Fatty infiltration of the liver is a very common finding in patients dying of chronic disease. It was found to be much more marked in a series of autopsies of patients dying of ulcerative colitis than in a series of patients dying within 24 hours after accidents. It is suggested that a deficiency of the vitamins which are stored in relatively small amounts is an important factor in the death of such patients.

In Vitro *and* In Vivo *Studies on the Dissolution of Phosphatic Urinary Calculi with Citrate Solutions.* By FULLER ALBRIGHT and (by invitation) HIRSH W. SULKOWITCH, Boston, Mass.

This study was undertaken with the ultimate purpose of finding a solution which would dissolve phosphatic renal calculi on direct introduction of the solution into the renal pelvis. It was found that acid citrate solutions would dissolve phosphatic urinary calculi in a surprisingly short period of time in *in vitro* experiments. In order to study the quantitative effects of pH, of concentration of citrate, and of temperature it was found necessary to have a substance of uniform composition. Crystals of the mineral francolite were used for these solubility studies.

A case in which large bladder calculi were dissolved by a citrate solution introduced and withdrawn from the bladder by means of a constant tidal drainage apparatus will be reported.

Radioactive Iodine as an Indicator of Thyroid Physiology: Observations on Animal and Human Subjects. By S. HERTZ, A. ROBERTS, and R. D. EVANS (by invitation), and J. H. MEANS, Boston, Mass.

By means of artificially produced radioactive iodine, the authors were able to label various dosages of this element and study their fate in both animals and man. The distribution in tissues, excreta, and body fluids was determined. The quantity of iodine concentrated within the thyroid in various functional states, including Graves' disease, was investigated. The partition of the thyroid iodine among several chemical fractions was studied with the cooperation of Dr. William T. Salter, of the Huntington Memorial Hospital in Boston.

The rate of absorption and excretion of radioactive iodine can be taken as an index of that of ordinary iodine, since the radioactive isotopes differ in no chemical manner from stable isotopes. This method of study offers advantages of accuracy exceeding those of any chemical methods of iodine analysis so far applied to any clinical or biological problems.

Respiratory Metabolism of Human Muscle. By EDGAR S. GORDON, MARC J. MUSSER, and IRENE STARK (introduced by E. L. Sevringhaus), Madison, Wis.

Because older methods of investigation of the myopathies have failed to reveal the true nature of any of these diseases, a totally different approach has been made to this problem through a study of the respiratory metabolism of human muscle, as measured with the Warburg and Barcroft types of respirometer. Small sections of muscle for study were obtained at biopsy from the gastrocnemius. Normal muscle, used as control material, was obtained in the operating room from individuals undergoing surgery for a variety of conditions, in none of which was there any reason to suspect a disturbance of metabolism. This technique has made possible a study of the enzyme systems involved in the energy metabolism of muscle.

It seemed most logical first to repeat with human muscle some of the well established animal work. The important finding of Krebs on the *in vitro* action of insulin as a catalyst of intracellular respiration has been confirmed in diabetic human muscle. A failure to oxidize succinate has been found to occur in muscle from two patients with myasthenia gravis, but the exact mechanism of this defect has not been determined, and the phenomenon has not been observed in all cases of this disease. In one case of myotonia atrophica and in one case of amyotrophic lateral sclerosis, the addition of pyruvate as a substrate caused a marked increase in respiration, which does not occur in controls.

The effects of various anesthetics were established and found to be unimportant except with the use of pyruvate as substrate with cyclopropane anesthesia. These studies have provided suggestive evidence of chemical abnormalities in pathological muscle and have given some helpful indications for the planning of further investigations which are now in progress.

Migraine of the Vasodilating Type: Treatment with Histamine. By BAYARD T. HORTON and (by invitation) ALEXANDER H. MACLEAN and WINCHELL MCK. CRAIG, Rochester, Minn.

The results of treatment of 84 patients with migraine of the vasodilating type by "desensitization" with histamine are presented. In this study, we have considered migraine as a functional vascular disease. We recognized two types, the vasoconstricting and the vasodilating. The vasoconstricting type is usually familial, begins in early life and is characterized by severe headache, frequently of the hemicranial type, which usually is associated with nausea, vomiting, and ophthalmic symptoms. The

vasodilating type begins later in life, is usually of the hemicranial type, and is associated with evidence of vasodilatation, watering of the eye, and blockage of the nostril on the affected side. Nausea, vomiting, and scotomas are invariably absent.

During the past 18 months, we have observed 84 patients with migraine of the vasodilating type. Only patients who were refractory to other forms of treatment and who were having from 2 to 20 attacks a week were selected for study. They were under observation for 2½ to 4 weeks. Detailed observations and experimental studies were carried out. We were able to produce attacks of migraine of the vasodilating, erythromelalgic type experimentally by the administration of histamine and other vasodilating agents and to control the attacks completely by the administration of adrenalin and other vasoconstricting agents. In 2 cases, immersion of the hand of the patient in cold water at 4° C. for 1 minute caused a resultant rise in blood pressure which in turn brought about an abrupt cessation of the attack of pain. Patients were unable to distinguish between induced and previous spontaneous attacks. During the induced, as well as during the spontaneous attacks, a rise of 1 to 3° C. in surface temperature of the involved region was observed. These observations were made with electric thermocouples while the patient was under controlled environmental conditions.

The method of treatment consists in giving subcutaneously 0.05 mgm. of histamine twice a day for 2 consecutive days. On the third day the dose is increased to 0.066 mgm. twice a day, and by the fifth day 0.1 mgm. twice a day is well tolerated. The injection of 0.1 mgm. twice a day is continued for 2 to 3 weeks.

Sixty-five patients obtained definite permanent relief for periods of 2 weeks to 18 months. Several of these patients have suffered from a recurrence of their symptoms, but these recurrences promptly responded to another course of treatment with histamine. In cases in which treatment has been employed recently, we have been giving 0.1 mgm. of histamine subcutaneously at weekly intervals whenever possible in an attempt to prolong the period of freedom from attack. Ten patients received no benefit from administration of histamine for 2 weeks and 9 patients have not been heard from since their dismissal from our care.

In order to determine the rationale for the effect of histamine, the size of the wheal and flare following the intracutaneous injection of histamine of varying dilutions has been used as an index of the patient's response to the treatment by Brown and one of us (Horton). In 45 per cent of the cases studied, the flare that appeared in 100 per cent of the cases before treatment with histamine was begun could not be reproduced after treatment. Since formation of the flare is dependent on the axon reflex, the daily injections of histamine in some way have altered this reflex mechanism.

Guinea-pigs have been given relatively large doses of histamine subcutaneously twice a day for 2 to 3 weeks by one of us (Horton) and Essex, and later these animals have been given, intravenously, approximately twice the calculated lethal dose of histamine for guinea-pigs. Approximately 50 per cent of the guinea-pigs which had received previous injection of histamine recovered whereas only 13 per cent of the control guinea-pigs recovered. Hypertrophy of the adrenal glands occurred in the guinea-pigs previously treated with histamine.

Adrenocortical Function in Hypopituitarism. By D. J. STEPHENS, Rochester, N. Y.

Anatomical findings in hypophysectomized animals and in patients with hypopituitarism would indicate that impairment of adrenocortical function occurs in hypophyseal insufficiency and, if so, one might expect to find disturbances of electrolyte balance in pituitary disease. With this in mind, a study of the chloride excretion of a group of patients with hypopituitarism was made. The modification of the chloride depletion test recently described by Cutler, Powers, and Wilder was used. Six of seven patients with clinical evidence of well established hypopituitarism showed increased concentration of salt in the urine similar to that which has been found to be characteristic of adrenocortical insufficiency. Four of the six patients developed symptoms suggesting those of an addisonian crisis. These symptoms were relieved by the intravenous administration of sodium chloride and adrenal cortex extract. In two patients symptoms failed to occur, and the results of the test were favorably modified after the administration of extra sodium chloride and adrenal cortex extract.

The Assay of Desoxycorticosterone Acetate and its Use in the Treatment of Addison's Disease. By R. A. CLEGHORN and (by invitation) J. L. A. FOWLER, and J. S. WENZEL, Toronto, Can.

The minimal amount of desoxycorticosterone acetate in oil (Ciba) necessary to maintain the blood nonprotein nitrogen within normal limits has been determined on four adrenalectomized dogs. The standard diet used consisted chiefly of lean meat and contained approximately 2 per cent sodium chloride by dry weight. The hormone requirement varied from 0.031 to 0.17 mgm. per kgm. per dog per day.

Seven patients with Addison's disease have been successfully treated with desoxycorticosterone acetate. Four had previously been receiving sodium salts and an aqueous extract of adrenal cortex. It was found in four cases that 1 cc. of the desoxycorticosterone (5 mgm.) given intramuscularly on alternate days was a more effective maintenance dose than 5 cc. of the extract previously used. Blood chemical values were maintained within normal limits and the patients voluntarily stated that they experienced a greater sense of well-being and vigor while receiving desoxycorticosterone acetate than previously. Signs of excessive dosage were observed in one case.

The Treatment of Adrenal Insufficiency with Desoxycorticosterone Acetate (A Synthetic Adrenal Cortical Hormone). By GEORGE W. THORN and (by invitation) R. PALMER HOWARD and KENDALL EMERSON, JR., Baltimore, Md.

Ten patients with Addison's disease received daily injections of 5 to 30 mgm. of desoxy-corticosterone acetate.

Despite sodium chloride restriction this treatment resulted in marked clinical improvement and was associated with an increase in plasma volume, body weight and blood pressure, sodium and chloride retention, and an increased renal excretion of potassium. Withdrawal of treatment (48 to 96 hours) was followed by the onset of signs and symptoms of adrenal insufficiency and resumption of treatment resulted in rapid recovery.

Under local anesthesia, pellets (75 to 150 mgm.) composed only of crystals of desoxy-corticosterone acetate were implanted subcutaneously, in the infrascapular regions in six patients with Addison's disease. Treatment by this method resulted in marked clinical improvement, an increase in body weight and blood pressure, the maintenance of a normal concentration of serum electrolytes, and a positive sodium and chloride balance. The number of pellets necessary for maintenance was estimated from the daily requirement of desoxy-corticosterone acetate in oil. At intervals pellets were removed and weighed and the quantity of hormone absorbed was determined. The implantation of pellets obviated the necessity for daily injections and resulted in a considerable saving in hormone (30 to 40 per cent). A single implantation of pellets was found to provide adequate hormone therapy for several months.

Conclusions. The effect of desoxy-corticosterone acetate treatment is similar to that of adrenal cortical extract. The implantation of pellets of crystalline desoxy-corticosterone acetate appears to be feasible, and an economical and effective treatment for patients with Addison's disease.

The Effects on the Cardiovascular System in Man of Benzedrine (Amphetamine) and Paredrine. By M. D. ALTSCHULE and A. IGLAUER (introduced by S. L. Gargill), Boston, Mass.

The effects of amphetamine sulfate (benzedrine sulphate) and paredrine bromide given in doses of 10 to 70 mgm. on the cardiovascular system were studied in 15 normal human subjects. The drugs were given by mouth or by intramuscular injection. In three cases the effects of adrenalin were also studied.

Amphetamine (benzedrine) and paredrine caused a marked rise in systolic and diastolic blood pressures, the latter being somewhat more effective than the former. The cardiac output, pulse rate, pulmonary circulation time, venous pressure, and vital capacity were not changed. In several instances transitory slowing of the pulse occurred at the onset of the rise in arterial blood pressure due apparently to a vagal reflex. In such cases there was also a transitory slight fall in cardiac output.

The effects of adrenalin were quite different, consisting in a slight rise in systolic blood pressure, no change or a fall in diastolic blood pressure, marked increase in pulse rate and cardiac output, and marked shortening of the pulmonary circulation time.

These findings suggest that paredrine may be a useful drug in the treatment of certain types of shock in which stimulation of the myocardium may be undesirable. These include the shock of diabetic coma, overwhelming infection, and cardiac infarction. Paredrine is the drug of choice inasmuch as it has none of the stimulating effect on the cerebral cortex associated with the administration of amphetamine (benzedrine).

The Precordial Electrocardiogram in Myocardiol Infarction Complicated by Bundle Branch Block. By FRANKLIN D. JOHNSTON, FRANK N. WILSON and (by invitation) HANS HECHT, Ann Arbor, Mich.

It is well known that bundle branch block either in transient or permanent form often occurs after a coronary occlusion and that it may modify the ventricular deflections of the standard leads so profoundly as to completely mask the characteristic QRS and T-wave changes of infarction. This situation is especially apt to arise when left bundle branch block is present and under these circumstances precordial leads also fail to show the usual QRS changes of anterior myocardial infarction unless, as occurred in one of our cases, the infarct extends entirely through the lower end of the interventricular septum.

When right bundle branch block is present, recognizable QRS changes of anterior infarction are often seen in standard Lead I, and abnormally large Q deflections are found in serial precordial leads.

Quantitative Measurement of Cardiac Stroke and Valvular Leakage in Man. By ANCEL KEYS and H. L. FRIEDELL (introduced by C. J. Watson), Minneapolis, Minn.

Both systolic and diastolic areas of the heart can be measured on plates made with the multiple-slit roentgenkymograph. A method was devised in which roentgenkymographic plates were made simultaneously with acetylene-rebreathing measurements of cardiac output. From 21 experiments on 13 normal subjects we found stroke volume $= 0.64 \left(\text{area}^{\frac{1.45}{\text{diastole}}} - \text{area}^{\frac{1.45}{\text{systole}}} \right)$.

The coefficient of correlation between the two estimates of stroke volume was + 0.984. The mean discrepancy was ± 5.1 per cent; the maximum errors were + 10.7 and − 12.2 per cent. Similar results were obtained in myxedema and simple hypertension.

Nine patients with aortic or mitral regurgitation were studied. The gross output of the heart exceeded the net stroke output in all cases. The indicated valvular leaks ranged from 10 to 50 per cent of the gross stroke, and these values were closely parallel to the clinical findings. Repetitions showed that these estimates of leakage are relatively constant. All evidence indicates that our procedure accurately measures (*1*) total heart volume, (*2*) total heart stroke, (*3*), net circulation, and (*4*) the volume of blood regurgitated.

The Effect of Congestive Heart Failure on Erythropoesis and Blood Pigment Metabolism. By JOHN V. WALLER (by invitation) and HERRMAN L. BLUMGART, Boston, Mass.

Studies of the effect of congestive failure and its attendant anoxia on the red cells and pigment metabolism and the relation of erythropoesis and hemolysis to changes in the blood volume have been made in thirteen subjects. Before congestive failure beco mes pronounced, there is a

definite reticulocytosis, diminished excretion of urobilin, and an increase in the red cell mass as well as an increased plasma volume. The fragility of the red cells is increased during congestive failure; this increased fragility has been duplicated by tourniquet experiments in normal subjects.

With the onset of clinical improvement and reduction of the total blood volume, the loss of plasma predominates over the breakdown of erythrocytes and an increased hematocrit is regularly found. As the red cells undergo hemolysis, due in part to the observed increased fragility, the level of bilirubin rises, the excretion of urobilinogen increases, and the reticulocyte percentage becomes smaller. The urinary pigment excretion is greatest during the early phase of recovery when hepatic function is still impaired. As recovery progresses, the fragility of the red cells is lessened, urinary excretion becomes diminished, and pigmentary excretion is almost completely fecal. These studies afford insight into the factors which lead to jaundice in the various stages of congestive failure and its relation to changes in the blood volume. They also contribute significant information on the general problem of the effect of anoxia on erythropoesis and pigmentary metabolism.

Relation of the Adrenal Gland to the Pressor Substance in the Cortex of the Kidney. By BEN FRIEDMAN, B. S. OPPENHEIMER, and (by invitation) EUGENE SOMKIN, ENID TRIBE OPPENHEIMER, and BASIL BLUMENTHAL, New York, N. Y.

A thermolabile, protein-like pressor substance present in the cortex of the kidney has been advanced as a hypothetical chemical stimulus which may be responsible for the elevation of the blood pressure in animals with experimental hypertension due to renal ischemia. Since the integrity of the adrenal glands appears to be necessary for this type of hypertension (Goldblatt), it seemed of interest to determine the influence of adrenalectomy on the formation and action of the renal pressor principle.

The amounts of renal pressor material in a group of normal and adrenalectomized cats were compared. In another series similar comparisons were made in the same animal between one kidney prior to, and the ipsilateral kidney following removal of the adrenals. The concentration of renal pressor substance was not diminished, but rather somewhat increased by adrenalectomy.

Following ablation of the adrenal glands there was a progressive diminution in response to renal pressor principle, but not to other vasoconstrictor substances in unanesthetized dogs. The sensitivity to kidney extract returned gradually with the addition of cortin.

The results indicate that the adrenal cortex is necessary for the action of renal pressor material and suggest an explanation for the effects observed after removal of the adrenal glands in experimental renal hypertension.

Effect of Renal Extract (Renin) Upon the Flow of Blood Through Various Organs. By J. M. STEELE and (by invitation) H. A. SCHROEDER, New York, N. Y.

The effect of a watery extract of fresh hog kidney (renin), purified to free it of depressor substances, upon the flow of blood through various organs and tissues was studied in seven dogs. Simultaneous records were made of femoral pressure (Hamilton's intra-arterial manometer) and of blood flow (Schmidt's electrical stromuhr) through one renal artery. At the same time blood flow was also recorded in one other artery, either the splenic, mesenteric, femoral, carotid, or the other partially clamped renal artery. The effect of renin was compared also with that of tyramine and adrenalin.

Injections of renin were usually followed by an increase in flow through all of the arteries observed except the splenic. In this artery a decrease was observed in each of three instances in two animals. Flow of blood through the kidneys was not observed to decrease except in one instance when an extract known to contain depressor substances was injected. The arterial pressure fell at the same time. Subsequently the flow increased simultaneously with a rise in arterial pressure to more than the original level. This observation suggests that absence of depressor substances in the extract accounts for the divergence of these results from those of Merrill, Williams, and Harrison. In their experiments the renal blood flow was regularly found to decrease.

Increase in arterial tone following injections of renin occurs, as inferred by Landis, so uniformly through the body as to leave the distribution of blood flow undisturbed.

The Relative Hypertensive Effects of "Renin" on Dogs with Normal and Abnormal Renal Circulation. By LOUIS LEITER and (by invitation) LILLIAN EICHELBERGER, Chicago, Ill.

If "renin" is the pressor substance responsible for experimental renal hypertension, its administration should result in more prolonged hypertension in the dog with abnormal renal circulation than in the normal dog. Varying amounts of dog "renin" or pig "renin," free from depressor effects, were repeatedly injected into 4 trained unanesthetized dogs with clamps on one or both renal arteries. Normal unanesthetized dogs and dogs with uremia produced by bilateral nephrectomy or ureteral obstruction served as control groups. In some 20 sucessful experiments on the first group of dogs, the injection of "renin" in adequate amounts produced hypertensive plateaus, at 20 to 50 per cent above the pre-injection pressure levels, for 60 to 300 minutes. The effect of "renin" was of lesser duration in the normal controls. In the 9 uremic dogs, the results may be interpreted in various ways because of the multiple factors involved. Purified dog or pig "renin" may be injected into dogs at intervals for weeks or months without harming the animal or altering its blood pressure response.

The Action of Soaps upon the Virus of Epidemic Influenza. By THOMAS FRANCIS, JR., and (by invitation) C. CHESTER STOCK, New York, N. Y.

Certain organic acids such as oleic and linolic, at pH 8.0, inactivate the capacity of the virus of epidemic influenza to infect mice. Virus so inactivated still possesses, however, the capacity to induce active immunity in mice. Other fatty acids, more or less related fail to inactivate

the virus under similar conditions. The results suggest that the inactivating mechanism is related to certain specific groups or linkages in the constitution of the acids. The possible mechanism of this inactivation will be discussed.

READ BY TITLE

Effects of Large Doses of Irradiated Ergosterol in Patients with Chronic Arthritis. By S. E. DORST and (by invitation) G. M. GUEST, S. RAPOPORT, and J. WARKANY, Cincinnati, Ohio.

In previously reported studies, the administration of large doses of irradiated ergosterol in rabbits was found to be followed by increases of organic acid-soluble P in the blood cells, increases which were practically all accounted for in the diphosphoglycerate fraction. To study the effects of large doses of irradiated ergosterol in man, adult patients suffering with chronic arthritis were given this substance in doses ranging from 200,000 to 1,000,000 international units per day—doses similar to those used by various clinicians who have recommended this treatment in chronic arthritis. The blood was examined before and at varying intervals after the treatment was started, with the following determinations: cell count, cell volume, hemoglobin content and sedimentation rate of the blood cells; distribution of acid-soluble P in the inorganic, total organic, adenosinetriphosphate and diphosphoglycerate fractions; vitamin D content of the blood serum (by biologic assay). During the treatment, the vitamin D in the blood serum quickly increased to high values. In the absence of symptoms of intoxication the phosphorus changed slowly. It is suggested that, in individual cases, where doses of irradiated ergosterol are being increased to the maximum tolerated, the development of clinical signs and symptoms of intoxication can be anticipated from the increasing concentration of organic acid-soluble P in the blood cells.

Inability to Demonstrate a Platelet Reducing Substance in an Acetone Extract of the Spleen from Patients with Idiopathic Thrombocytopenic Purpura. By FREDERICK J. POHLE (by invitation) and OVID O. MEYER, Madison, Wis.

Recent investigations suggest that the spleen of patients with idiopathic thrombocytopenic purpura contains a substance capable of reducing the number of platelets in the circulating blood of laboratory animals. This substance has been called thrombocytopen.

In the present study the spleen was obtained postoperatively from three individuals with chronic idiopathic thrombocytopenic purpura. Splenectomy resulted in a clinical and hematological cure in each patient. An acetone extract was prepared from each of these organs (weights: 310, 265, and 70 grams) in a manner entirely similar to that previously described. The time allowed for extraction was 76, 59, and 34 days respectively. A portion of the extract obtained from each spleen was administered intravenously to three rabbits. One rabbit received 10 cc., another 25 cc., and a third 50 cc. of the material. There were no reactions. Platelet determinations were made with the aid of an isotonic diluting fluid by a direct method on the blood obtained from ear veins. Blood platelet counts were performed at frequent intervals during the 48-hour period prior to the injection and during a similar period after the injection.

Throughout each of the 3 sets of observations (9 experiments) the number of blood platelets remained essentially unchanged and within the limits of technical error. Therefore, it was not possible, by the methods employed, to establish the presence of a substance in the spleen of patients with thrombocytopenic purpura capable of reducing platelets in animals.

Immunological Studies on Patients Suffering from Bacterial Endocarditis. By EDWARD S. ORGAIN and MARY A. POSTON (introduced by David T. Smith), Durham, N. C.

This paper presents a study of the antibody responses (opsonins, agglutinins, bacteriolysins) in 9 instances of classical and 1 of suspected bacterial endocarditis, and a correlation of these serological findings with variations of the colony count of successive blood cultures over periods of observation and treatment of 1 to 8 months. Initial studies in each instance revealed uniformly little evidence of immune antibodies during the active bacteremic stage of bacterial endocarditis. Under treatment, immune antibodies developed coincidentally with the disappearance of the bacteremia. Complement fixing antibodies, determined in 3 instances, exhibited an inverse relationship to other antibodies.

The Organic and Inorganic Iodine of the Blood in Cases of Non-Toxic Goiter, Exophthalmic Goiter, and Primary Myxedema. By H. J. PERKIN (by invitation) and LEWIS M. HURXTHAL, Boston, Mass.

This work is a continuation of our studies presented at the Association for Clinical Investigation Meeting in 1938 (read by title).

The results show that the organic blood iodine in cases of myxedema is one-half that found in cases of non-toxic goiter. The organic blood iodine in exophthalmic goiter is twice that of non-toxic goiter and 4 times that found in myxedema.

Iodine medication in cases of exophthalmic goiter results in a decrease in the organic blood iodine. However, the organic blood iodine in cases of exophthalmic goiter is not proportional to the basal metabolic rate; nor is the decrease in organic blood iodine, due to iodine medication, proportional to the decrease in metabolism.

The results of this study have been based on fractional blood iodine analysis on 218 patients.

The Vasoconstriction Action of Epinephrine on the Digital Arterioles of Man Before and After Sympathectomy. By T. J. FATHERREE and A. W. ADSON (by invitation), and E. V. ALLEN, Rochester, Minn.

Sympathectomy cures Raynaud's disease of the feet routinely but frequently fails partially or completely when performed for Raynaud's disease of the upper extremities. Others have pointed out that sympathectomy for the lower extremities consists of preganglionic section, whereas

sympathectomy as ordinarily practiced for Raynaud's disease of the upper extremities consists of ganglionectomy, that is, postganglionic section. They have maintained that failure to cure Raynaud's disease in the upper extremities results because postganglionic sympathectomy increases sensitivity to circulating epinephrine much more than preganglionic sympathectomy performed for the lower extremities does. Our studies indicate that lumbar ganglionectomy (preganglionic section) does not increase sensitivity of the arterioles of the toes to epinephrine significantly. Both preganglionic section and postganglionic section of the sympathetic nerves to the hands increase the sensitivity of the digital arterioles to intravenous injection of epinephrine and in about the same degree. Therefore, what appeared to be a pleasant physiological explanation for the peculiar fact that Raynaud's disease of the feet may be cured routinely by sympathectomy while Raynaud's disease of the hands is not cured routinely by sympathectomy has been reexamined and found to be of very uncertain value.

The Preparation of Membranes of Graded Permeability from "Cellophane" and Their Use as a Means of Measuring Relative Molecular Size. By W. B. SEYMOUR (introduced by J. M. Hayman, Jr.), Cleveland, Ohio.

An elaboration of the method of McBain and Stuewer for increasing the permeability of DuPont "Cellophane" by immersion in zinc chloride solutions has been developed. This permits the preparation of membranes of graded permeability. The increase in permeability is proportional, within certain limits, to the concentration and the temperature of the zinc chloride solutions. The change in the membrane is probably in the nature of a physical rearrangement of the cellulose structure, no or very little imbibition of water taking place.

The advantages of cellophane over the collodion membranes used by others for measuring molecular size are that the former are prepared quickly and easily, and they do not absorb protein.

An estimation of the pore size is obtained by means of Poiseville's law. Membranes so calibrated have been used in ultrafiltering normal human plasma, acacia, oxyhemoglobin, and crystalline egg albumen. The results indicate that the size of the pores is relatively uniform, and that the molecules of oxyhemoglobin and crystalline egg albumen are nearly spherical and homodisperse; acacia solutions show polydispersion of molecules. Using plasma, membranes of proper size will allow the passage of about 40 per cent of the albumin fraction, holding back the remaining albumin and all of the globulin. The order of relative size of the above is: plasma albumin < egg albumen < acacia < plasma globulin < oxyhemoglobin.

Spherocytosis (and Increased Erythrocyte Fragility) as Indicators of Hemolytic Activity, with a Consideration of "Differential" Fragility. By WILLIAM DAMESHEK and (by invitation) STEVEN O. SCHWARTZ and KARL SINGER, Boston, Mass.

Our previous studies demonstrated that spherocytosis (and increased saline fragility) is not pathognomonic of congenital hemolytic jaundice but is common to various hemolytic syndromes. Present studies demonstrate that this phenomenon may be produced experimentally by various types of hemolytic agents either *in vitro* or *in vivo*. Distilled water, saponin, phenylhydrazine, "lysolecithin," or immune hemolytic serum produced spherocytosis of varying degree, dependent primarily upon dosage. Studies of the bone marrow and of diameters of both reticulocytes and mature red cells indicate that the spherocyte is a mature erythrocyte which has been morphologically altered outside of the bone marrow. Spherocytosis may thus be utilized as a morphological indicator of increased hemolytic activity. The degree of spherocytosis is, in general, proportional to the rapidity of the hemolysis.

Although all spherocytes, however produced, present increased fragility to hypotonic solutions of sodium chloride (a physicochemical phenomenon), their behavior to other lysins such as saponin and lysolecithin differs in different experimental and pathological conditions. In other words, although spherocytes are morphologically similar, they may differ physiologically, depending upon the type of lysin which has already acted upon the red cell. Preliminary observations in various disease states suggest that the reaction of the spherocyte to *various* substances ("differential fragility") may be helpful in the differentiation of the various types of hemolytic anemia.

Studies of the Circulation in a Group of College Athletes. By HAROLD J. STEWART and (by invitation) ROBERT F. WATSON, New York, N. Y.

In this study the following measurements were carried out on a group of 14 college athletes who, at the time, were members of a University football team: arteriovenous-oxygen difference, oxygen consumption, minute volume output, cardiac work, vital capacity, cardiac size, circulation time, venous pressure, arterial pressure, and heart rate. Similar observations were made of a control group of healthy young men of the same age group engaged in ordinary activities. The average values obtained for the athletes were as follows: arteriovenous-oxygen difference equals 63.9 cc. per liter; cardiac output (index) measured 2.12 liters per square meter of body surface area per minute; stroke volume equals 65 cc.; stroke volume per kilogram of body weight equals 0.80 cc.; left ventricular work per beat equals 1.06 grammeters per kilogram of body weight; venous pressure equals 9.2 cm. of saline; circulation time (decholin, arm to tongue) equals 15.4 seconds, and the cardiothoracic ratio equals 42.9 per cent. These values were compared with those for the control group and the only significant difference appeared in the stroke volume. This difference, however, is believed to be the result of a difference in the average size (weight) of the two groups. Electrocardiograms showed no variation from the normal in either group. It is concluded that the circulation in this group of college athletes, as measured by these methods, shows no appreciable variation from that in a group of normal young adult males.

The Mechanism of Elevation of the Blood Urea Nitrogen Following Hematemesis and Melena. By LEON SCHIFF and (by invitation) RICHARD J. STEVENS, SANDER GOODMAN, ELLEN GARBER, and ANNA LUBLIN, Cincinnati, Ohio.

The frequent elevation of the blood urea nitrogen following hematemesis and melena is confirmed in a series of 50 patients. In the past the following factors have been invoked to explain this increase: shock, dehydration, starvation, renal insufficiency, and absorption of blood from the gastro-intestinal tract.

Clinical data is adduced which excludes shock, dehydration, and starvation as essential factors in the production of this azotemia.

Studies consisting of urea, inulin, and phenol red clearances made both during and after the period of urea elevation showed no significant differences in renal function.

The administration of citrated human blood into the stomach, jejunum, or upper ileum was followed by an increase in the blood urea nitrogen. The rise was proportional to the amount of blood given. No rise followed introduction of blood into the colon.

Similar blood urea nitrogen curves were obtained after hematemesis and after the intragastric administration of large amounts of citrated blood.

These results indicate that the presence of blood in the upper intestinal tract (and presumably, its digestion and absorption) is the most important cause of the elevation of the blood urea nitrogen following hematemesis and melena.

Observations on Experimental Renal Hypertension. By LOUIS N. KATZ and (by invitation) S. RODBARD, F. S. STEINITZ, and L. FRIEDBERG, Chicago, Ill.

We have undertaken three lines of study on the nature of the chemical mediator responsible for renal hypertension, and the rôle of normal kidney in counteracting its hypertensive effects.

1. We found that removal of the ischemic kidney leads to the disappearance of the hypertension in less than 6 hours when a normal kidney is left *in situ*. In total nephrectomy, the hypertension postoperatively is more protracted (9 to over 50 hours, average 25 hours). This indicates that the normal kidney eliminates, destroys, or neutralizes the hypertensive effect of the ischemic kidney and supports the thesis that renal hypertension is dependent upon the ratio of ischemic to normal kidney tissue.

2. We found that when the dioxane derivative 933 F is injected in trained unanesthetized normotensive and hypertensive dogs, a similar depressor effect occurs in both. Hence, the chemical mediator of renal hypertension is probably not a sympathetico-constrictor substance like epinephrine, since 933 F tends to eliminate its pressor action. The pressor action of renin is not affected by 933 F.

3. We found that the pressure in the pulmonary artery of the dog was not elevated when hypertension is produced in the systemic circuit by renal ischemia. Since the cardiac output and circulating blood volume has been found to be little affected by renal hypertension, the chemical mediator appears to have little or no effect on the pulmonary vessels. It appears to have a selective constricting action on the systemic vascular bed.

The Properties of Blood Preserved for Transfusion. By ELMER L. DEGOWIN, JOHN E. HARRIS, and E. D. PLASS (introduced by H. M. Korns), Iowa City, Iowa.

Quantitative studies were made on blood stored at 5° C. in various types of preservatives. Hemolysis occurred in bloods preserved by any method but the rate of hemolysis varied greatly with the preservative used. The rate was fastest in blood plus sodium citrate and slowest when large amounts of isotonic dextrose solution were added to the anticoagulant. Blood mixtures kept in flasks from which air was excluded hemolyzed more slowly than when air was present.

The potassium ions migrated from the erythrocytes into the plasma at a constant rate which was a function of time. The maximum plasma concentration was attained in about 15 days; it was directly proportional to the number of erythrocytes in the mixture. The potassium concentration was independent of the temperature of storage, the amount of hemolysis present, the concentration of sodium, chlorine, or citrate ions, or the amount of dextrose present. By clinical trial, it was demonstrated that this amount of potassium in the plasma is not toxic for man.

The hydrogen ion concentration of various blood mixtures remained within the limits considered biologically safe for at least one month.

The prothrombin content of plasma as determined by the method of Warner, Brinkhous, and Smith was not seriously impaired by two weeks of storage.

The resistance of the erythrocytes to hypotonic solutions and to trauma was well retained in storage. Red blood corpuscles stored for 20 days or more retained their ability to respire as measured by the oxygen intake in Warburg micromanometers.

Renal Hyperparathyroidism: Metabolic Studies in an Adult with Severe Renal Insufficiency, Extensive Demineralization of Bone, and Pathological Calcification of Arteries. By CHARLES L. BROWN and (by invitation) I. W. GINSBURG, Philadelphia, Pa.

Metabolic studies were carried out on an adult 56 years of age with long standing renal insufficiency and a history of persistent albuminuria following scarlet fever at the age of 14 years. He had been in apparent good health until age 55 when weakness, dyspnea, pain in legs, and leg ulcers developed, and later, attacks of paroxysmal tachycardia.

There are extensive skeletal changes with x-ray appearance of generalized demineralization of bone and extensive pathological calcification of arteries, including the coronary and renal vessels. Biopsy of muscle showed chronic degenerative myositis and calcification of the media of the larger arteries.

Chemical examination of the blood reveals retention of nitrogen and phosphorous with depressed protein and normal calcium.

Skeletal changes have been followed by standardized roentgenological methods.

Metabolic study shows a negative calcium and negative phosphorous balance due to increased excretion by bowel.

The Rôle of the Protein Level Intake in the Production of Remissions in Macrocytic Anemias. By S. M. GOLDHAMER and (by invitation) A. I. FRITZELL, and F. MACKINNON, Ann Arbor, Mich.

Hematopoietic remissions produced by protein ingestion were studied in 3 cases of pernicious anemia and 1 case of "pernicious anemia" of pregnancy. Observations on the blood were made daily. Weights were recorded at 3-day intervals. All the patients were on known weighed diets which were varied at definite intervals. In addition, the patients received supplements of whole non-autolyzed yeast, or non-autolyzed yeast which was extracted by acidulated water at 80° C.

Improvement, as indicated by a reticulocyte response, an increase in red cells, or both, was observed in all instances where an adequate protein intake as compared to the body requirement was given. It is suggestive from the results obtained that the extrinsic factor is a protein or protein derivative, and its effectiveness is dependent at least upon the quantity. It appears, also, that non-autolyzed yeast contains only the extrinsic factor. Further, "spontaneous" remissions may be produced by adequate protein ingestion; hence, in the determination of the qualitative effectiveness of any antianemic substance, it is necessary to give subminimal amounts of protein in the diets.

Effect of Estrogenic Substance on the Fasting Blood Sugar in Diabetes. By CARL J. GESSLER, JAMES A. HALSTED, and RICHARD P. STETSON (introduced by Maurice B. Strauss), Boston, Mass.

A study was made of the effect of injections of large doses of estrogenic substance on the fasting blood sugar of 4 diabetic women who had passed the menopause. The particular objective was to determine whether the inhibitory effect of estrogenic substance on the anterior pituitary, known to be demonstrable on the excretion of gonadotropic hormone, might be extended to its diabetogenic factor. This effect would be theoretically more easily shown after the menopause, when the organism is lacking in ovarian estrogenic hormone, than before.

The patients were first regulated on diet (C151, P74, F92) and insulin. The insulin injections were then stopped. During the following control period, lasting from 9 to 14 days, the fasting blood sugar went up. Intramuscular injections of estradiolbenzoate (progynon B), in daily amounts of 50,000 international units, were then started. In 2 patients in whom the diabetes began at the time of the menopause, a significant lowering of the fasting blood sugar level was observed. In one of these patients the fasting blood sugar dropped from 267 to 131 mgm. per 100 cc. during the course of 18 daily injections. When injections were discontinued this effect persisted only a few days. In the third patient, in whom the diabetes existed a year before the menopause, no effect was observed. In the fourth patient, in whom the diabetes began 5 years before the menopause, there occurred a slight fall of blood sugar, possibly of no significance.

The Effect of Unequal Ventilation of Pulmonary Air Spaces on the Closed Circuit Measurement of Residual Air. A New Open Circuit Method. By ROBERT C. DARLING, ANDRE COURNAND, and JAMES S. MANSFIELD (by invitation), and DICKINSON W. RICHARDS, JR., New York, N. Y.

This paper demonstrates that residual air values in emphysematous subjects, by the usual closed circuit methods, are a summation of actual lung volume, plus a considerable error due to hypoventilation of stagnant air spaces. A new method is presented which largely eliminates this error.

In the usual closed circuit for residual air measurement, we have previously shown that homogeneous mixture of inert gases does not exist, as originally assumed. A correction was introduced by measuring alveolar as well as spirometer samples. This in turn assumes that alveolar air specimens are average lung samples.

To test this assumption, a "reversed" procedure was devised. The lungs were first filled with pure oxygen and the spirometer system with room air. If the previous assumption were correct, the residual air as calculated should be identical with that by the usual technique. If not, the second technique should give lower values. In actual experiments, the two figures were identical in some normals, but the second technique gave much lower values in emphysematous subjects.

By using an open circuit, in which pure oxygen is continuously inhaled and the expired gases collected, lung nitrogen can be washed out, and residual air then calculated as in the closed circuit method. Values (*a*) by this method and (*b*) by a "reversed" procedure similar to that used for testing the closed circuit, agree in emphysematous as well as normal subjects. Thus, any error due to untrue alveolar sampling is small.

As expected, values by the standard closed circuit are frequently higher than those by the open circuit.

The Iodine Content of the Blood in Diseases of the Liver and Biliary Tract: Clinical and Experimental Studies. By CARL H. GREENE and (by invitation) MAURICE BRUGER, New York, N. Y.

The concentration of iodine in the blood (method of Trevorrow and Fashena) was determined in 47 patients with diseases of the liver and biliary tract (acute hepatitis, obstructive jaundice due to stricture, stone, or carcinoma of the common bile duct, portal cirrhosis, and chronic cholecystitis). In those individuals where certainty existed that no iodine or iodine-containing compounds had been administered for several weeks prior to the analysis, the blood iodine fell within normal limits (3 to 8 micrograms per cent).

After the administration of iodine-containing compounds for cholecystography, the blood iodine increased and reached the maximum level approximately 24 hours later. Thereafter, the blood iodine remained elevated for a prolonged period particularly in patients with hepatic damage.

In 3 patients with obstructive jaundice, blood iodine of 470 micrograms per cent, 1167 micrograms per cent, and 488 micrograms per cent were obtained 20 days, 20 days, and 30 days respectively after the administration of the dye. In each of these cases, normal blood iodines were obtained prior to cholecystography. In a number of patients, iodine values of 10 to 40 micrograms per cent were observed shortly after the use of tincture of iodine on the skin for clyses, infusions, and transfusions.

Severe degrees of jaundice produced in cats by ligation of the common bile duct were not accompanied by significant elevation of the iodine content of the blood.

The elevated blood iodine in patients with diseases of the liver and biliary tract reported by previous investigators may be explained primarily by the antecedent administration of iodine, particularly of the iodine-containing compounds used in cholecystography. No clinical or experimental evidence has been found to indicate that the liver exerts a specific function in regulating iodine metabolism.

The Relation of Hypertension to Coronary Atherosclerosis. By DAVID DAVIS and (by invitation) MAX J. KLAINER, Boston, Mass.

The relation of hypertension to coronary disease was investigated in 507 cases; 101 of these were studied by the injection-dissection technique of Schlesinger.

Patients with essential hypertension showed an appreciably higher incidence of severe coronary disease than controls in each decade. Below the age of 50 the differences were as marked, or more so, than in the higher age groups.

On the other hand, a group of patients with severe hypertension associated with primary renal disease and finally uremia showed a lower incidence of severe coronary disease than controls in the same age groups.

The relation of the severity of hypertension to the degree of coronary atherosclerosis was further investigated in the patients with essential hypertension by considering both blood pressure levels and heart weights as indices of severity. Patients with severe hypertension showed the same incidence of coronary disease as those with mild hypertension. These findings: (*1*) the low incidence of coronary disease in patients with renal hypertension, and (*2*) the lack of relationship between the degree of hypertension and the severity of coronary disease in essential hypertension, are evidences that the hypertension *per se* is not a factor in the production of coronary atherosclerosis.

Iron Deficiency and Anemia Associated with Carcinoma of the Proximal Portion of the Colon. By R. L. CLARK, M. H. POWER, and FRANK J. HECK (by invitation), and E. G. WAKEFIELD, Rochester, Minn.

The type of anemia that occurs with carcinoma of the proximal portion of the colon has been observed to be the same as that produced by a deficient supply of iron for elaboration of hemoglobin. The abnormal demands made upon the iron supply of the body are increased in instances in which the lesion is situated in the proximal portion. Study of the concentration of iron in the serum has furnished additional confirmation of a deficiency of iron. In all cases of cancer of the right half of the colon, the concentration of iron in the serum was low. If severe anemia was present, a very marked decrease of the concentration of iron occurred. The anemia apparently can be arrested if a sufficient amount is absorbed. Recovery from the anemia following removal of the cancer was demonstrated to be dependent upon adequate absorption of iron. Administration and absorption of iron following resection of the involved segment of the colon resulted in a return of the normal concentration of iron and hemoglobin in the serum. In two cases the anemia accompanying carcinoma of the distal portion of the colon has been observed to be similar to that occurring in conjunction with carcinoma of the proximal position of the colon.

Carbohydrate Metabolism in Paget's Disease. By T. L. ALTHAUSEN and A. M. BASSETT (by invitation), San Francisco, Calif.

Decreased dextrose tolerance is commonly found in Paget's disease, and is usually ascribed to a diabetic tendency probably caused by a disturbance of the hypophysis.

Eighteen patients with Paget's disease were given our test for intestinal absorption consisting of oral administration of 40 grams of galactose followed by a blood galactose curve. This test gives normal results in diabetes mellitus. Among 18 patients with Paget's disease, increased intestinal absorption was found in 15. The average peak of the curve in the whole group was 57 mgm. per cent as compared to a normal peak of 19 mgm. per cent.

There was positive correlation between the galactose and dextrose tolerance curves. Impaired utilization of galactose was ruled out by intravenous administration of galactose. There was no correlation between the increase in blood phosphatase or the basal metabolic rate in Paget's disease and increased intestinal absorption of galactose.

Our data indicate that accelerated intestinal absorption rather than impaired utilization accounts for the decrease in sugar "tolerance" in Paget's disease.

Fractionation of the Serum Proteins and the Takata-Ara Reaction in Cirrhosis of the Liver. By JAMES A. DAUPHINEE, W. R. CAMPBELL, and (by invitation) M. I. HANNA, Toronto, Can.

In certain forms of liver disease, particularly hepatic cirrhosis, there is a definite alteration in the level and character of the serum proteins. This alteration consists in a decrease in the total protein which is accounted for largely by a decrease in the serum albumin. However, in a number of instances of cirrhosis there is a decrease in the albumin-globulin ratio not only because of a decrease in the albumin but also because of an actual increase in the total globulin.

The Takata-Ara reaction has also been found to be positive in many cases of cirrhosis and to be negative in a wide variety of other conditions with relatively few exceptions. These exceptions are commonly associated with an increase in the globulin fraction of the serum proteins.

By the use of the rapid and convenient sodium sulphite method of Campbell and Hanna for the separation of the serum protein fractions, the levels of serum albumin, pseudoglobulin I, pseudoglobulin II, euglobulin, and other proteins precipitated at a lower concentration than 15 per cent sodium sulphite have been investigated in cirrhosis of the liver and in other conditions. An attempt has been made to correlate these findings with the results of the Takata-Ara reaction.

Many cases of cirrhosis of the liver show a definite elevation of the serum globulin which is largely accounted for by an increase in the "euglobulin fraction." There is a close agreement between this elevation of the so-called "euglobulin fraction" and the positive Takata-Ara reaction, although the ratio of this material to the albumin portion may play some part. A peculiar feature noted in this series of cases is the frequency with which the Takata-Ara reaction appears to be correlated with fractions of serum protein intermediate in their behavior to sodium sulphite between euglobulin and fibrinogen. In certain other conditions where there is a similar change in the serum protein fractions the same correlation seems to exist, but this is not consistently the case.

Variations in the Acid-Base Balance of the Internal Jugular Blood of Man Induced by Voluntary Hyperpnea. By L. F. NIMS (by invitation), New Haven, Conn., and W. G. LENNOX, and F. A. GIBBS, Boston, Mass.

Samples of jugular blood were taken from 28 selected patients, before, during, and after short periods of voluntary hyperpnea. From some of the patients simultaneous arterial samples were taken from the femoral artery. The carbon dioxide content, the oxygen content, and the oxygen capacity of the blood was measured by means of the Van Slyke method and apparatus. To define the acid-base condition of the blood it is also necessary to determine either the pH or the carbon dioxide tension of the blood. In the present experiments the pH was determined with a glass electrode, and the carbon dioxide tension of the blood was calculated from the Henderson-Hasselbach equation.

As is well known, overventilation produces changes in the acid-base balance of the blood characterized by a shift to a more alkaline pH and a lowered carbon dioxide tension. This investigation adds somewhat to our knowledge of how these changes occur with time. The results also indicate that the brain has some control over the acid-base balance of the jugular blood. During the hyperpnea, for example, the pH change that occurs in the venous blood is only about half that which occurs in the arterial blood.

Immunological Observations of Patients with Pneumococcal Pneumonia Treated with Sulfapyridine. By MAXWELL FINLAND and (by invitation) WILLIAM C. SPRING, JR., and FRANCIS C. LOWELL, Boston, Mass.

The studies were carried out in the same manner as those by Finland and Brown in cases of Type III pneumonia. It was found that sulfapyridine exerts a greater bacteriostatic effect in whole blood *in vitro* on both Type I and Type III pneumonia in lower concentrations than sulfanilamide. In addition, a definite bactericidal effect was noted for large numbers of pneumococci of these types. With sulfanilamide, bactericidal action was demonstrated only in occasional patients when large amounts of the drug were added. In patients under treatment with sulfapyridine, the bacteriostatic and bactericidal effect of the blood corresponded to the *in vitro* results obtained when corresponding concentrations of the drug were added to the blood obtained prior to treatment. Actively acquired antibodies (agglutinins and mouse protection) appeared at the usual time irrespective of the febrile course. The optimum results were obtained when specific serum was given in combination with sulfapyridine or in patients treated with the drug alone when they had pneumococcidal activity or had evidence of the appearance of protective antibody at the time treatment was begun. In a number of cases of Type III pneumonia, recovery occurred although no evidence of type-specific antibodies could be demonstrated after treatment with sulfapyridine was discontinued.

The Blood Volume in Bright's Disease and Hypertension. By JOHN G. GIBSON, 2D, and ALFRED W. HARRIS (introduced by Henry A. Christian), Boston, Mass.

Blood volume studies in patients with Bright's disease were made by the method of Gibson and Evans (J. Clin. Invest., 1937, **16**, 301). Cases were grouped according to the clinical classification of Bright's disease of Christian (Interstate Post-graduate Assembly, 1931, pp. 71 to 74).

In a group of 16 hypertensive patients without congestive heart failure there was no significant variation from the normal in plasma, circulating red cell, or total blood volume, even in markedly plethoric appearing patients.

In 12 patients with chronic glomerular nephritis without edema and 10 patients with subacute glomerular nephritis with edema (nephrosis syndrome) total blood volume was definitely below normal due chiefly to a diminution in the circulating red cell volume, plasma volume being normal or slightly above. As azotemia progressed, plasma volume tended to increase and circulating red cell volume to diminish in a linear relationship to the decrease in the red cell count, but total blood volume remained below normal. In the anemia of nephritis the percentage reduction below normal in circulating red cell volume bore the same relationship to the red blood cell count found in both primary and secondary anemia.

In the 5 cases with congestive heart failure plasma, circulating red cell, and total blood volume, while not as high as the level found in congestive failure in valvular or chronic myocardial disease (J. Clin. Invest., 1937, **16**, 831) were definitely higher than the average volume values at comparable levels of anemia found in the group of nephritics without congestive heart failure. In one case cardiac compensation was accompanied by a marked decrease in plasma, circulating red cell, and total blood volume even though the red cell count was about 2 million during failure and subsequently.

Crystalline Insulin. By ALEXANDER MARBLE and (by invitation) ILMARI VARTIAINEN, Boston, Mass.

Although "crystalline insulin" (Solution of Zinc-Insulin Crystals) was released for sale in August 1938, the rapidity of action and duration of effect of this preparation have remained controversial. Insulin of crystalline type has been regarded by many as possessing a prolonged action.

In comparative studies carried out in both normal and diabetic individuals and in normal rabbits, the crystalline and amorphous types of insulin caused a prompt fall of the blood sugar which was almost identical in rate. Both types, therefore, must be regarded as rapidly-acting.

In normal rabbits the duration of action of the crystalline type was almost identical with that of the amorphous variety. In normal and diabetic human subjects the action of the former type seemed slightly prolonged. With the diabetic individuals there occurred on the average a slightly greater blood-sugar-lowering effect with insulin of crystalline type. Following a single subcutaneous injection on a day during which food was withheld, the lowest point in the blood sugar curve was reached, on the average, in 6 hours in the case of the amorphous, and in 7 hours in that of the crystalline variety. In the return toward the initial value, there was a lag of approximately two hours when the crystalline type was used.

Differences in values for sugar in blood and urine of diabetic patients during days of maintenance first on one type and then on the other type of insulin, were so slight as to be of relatively minor importance clinically although with some patients slightly lower values were obtained using the crystalline variety.

To simplify treatment, it is advisable to decrease rather than increase the number of types of insulin on the market. At the present stage of development it seems desirable to limit these to (*a*) a rapidly-acting insulin which, if commercially practicable, might be of the amorphous type, and (*b*) a slowly-acting variety, the protamine zinc insulin.

Periods of Crisis and of Stabilization in Addison's Disease. By JAMES A. GREENE and (by invitation) GEORGE JOHNSTON, Iowa City, Iowa.

Balance studies of sodium, potassium, and chloride have been made in a patient with Addison's disease. At first, while sodium was being stored, crises occurred frequently, although large amounts of sodium and cortical extract were administered. Later, as a sodium balance was established the crises promptly ceased. Sodium balance was then maintained without administration of cortical extract, and even after the sodium intake had been reduced about one-third for 24 days. A negative sodium balance was then produced by a greater reduction of sodium intake and was maintained for 11 days during which approximately 37 grams of the stored sodium was excreted, but crises did not develop.

The study shows that the patient was strikingly less sensitive to omission of cortical extract or reduction of sodium intake after sodium equilibrium had been established than during the period of sodium storage. In addition, the period of induced negative sodium balance, following that of sodium equilibrium, appears to be the best time for studying the effect of administration or omission of cortical extracts, or of alteration of sodium or potassium intake. The effect of orally and hypodermically administered cortical extract upon the storage of sodium is also reported.

The Association of Peptic Ulcer and Gallbladder Disease with Coronary Atherosclerosis: A Postmortem Study. By BERNARD J. WALSH (by invitation), and EDWARD F. BLAND and PAUL D. WHITE, Boston, Mass.

Because of recent interest in the combination of gallbladder and gastro-intestinal lesions with coronary arterial disease produced in dogs by the injection of acetylcholine (Hall) we have thought it important to compare the incidence in man.

Clinical Experiences with a Synthetic Estrogen, Stilboestrol. By EPHRAIM SHORR and (by invitation) GEORGE N. PAPANICOLAOU, and BENJAMIN F. STIMMEL, New York, N. Y.

The recent synthesis by Dodds and coworkers of an estrogenic substance, Stilboestrol (4,4′-dihydroxy-α, β-diethyl stilbene) has aroused considerable interest because of its powerful estrogenic activity, orally, as well as by subcutaneous use, and its chemical structure which differs greatly from the naturally occurring estrogens. Recent clinical trials in England have demonstrated its estrogenic activity in the human, its ability to produce the customary vaginal and endometrial changes, and the attendant relief of menopausal symptoms. Its low cost and oral effectiveness should make it a valuable therapeutic agent providing its use is without harmful features. The reports from England have mentioned an occasional transitory nausea by oral route, which was absent by subcutaneous injection.

Our experience with the use of this drug is as follows: Its estrogenic character and ability to relieve symptoms is confirmed. A large percentage of the patients, however, have experienced severe gastro-intestinal disturbance not only by the oral route but intramuscularly. This effect of the drug appears to be central in origin. Until its significance is known, great caution seems to be warranted in the use of this drug to replace the natural estrogens.

The Effect of Anterior Pituitary Injections on the Blood Acetone Bodies of Adrenalectomized Rats. By REGINALD A. SHIPLEY (introduced by Joseph T. Wearn), Cleveland, Ohio.

Fasting adrenalectomized rats have been tested for their blood acetone body response after injections of crude anterior pituitary extract by the analyses of samples of tail blood taken before and after injection. Graduated doses of extract were given to groups of both adrenalectomized and normal rats in order that the respective assay curves could be compared. The adrenalectomized rats were sensitive to the extract but their response was only one-half to one-third that of unoperated rats when a comparison was made on the basis of the size of dose necessary to produce a given response. These findings indicate that

the ketogenic activity of the pituitary gland is not necessarily mediated through the adrenal cortex.

Simultaneous blood and urine determinations were made in adrenalectomized rats receiving anterior pituitary extract. The results suggest that ketonuria fails to occur in these animals because the rise in blood acetone bodies is sufficient to exceed the urinary threshold.

Studies of Epidemics of Influenza which Occurred in 1939. By FRANK L. HORSFALL, JR., and (by invitation) MONROE D. EATON, RICHARD G. HAHN, and ELSMERE R. RICKARD, New York, N. Y.

Clinical studies were made of 174 cases in which the symptomatic syndromes were typical of mild epidemic influenza. The cases occurred in three localized epidemics in New York State during January, 1939. Throat washings were taken from 64 representative cases early in the disease, and 32 of the washings have been inoculated intranasally in ferrets. Although serial passages were made in ferrets, fever and nasal symptoms characteristic of epidemic influenza virus infection were observed in only 10, or 31 per cent, of the passage series. The difficulty that has been encountered in the isolation of the etiological agent from these cases of epidemic influenza contrasts sharply with the fact that serological diagnoses were made with ease. Studies of the acute and convalescent serum from the same cases have indicated that all but two did have epidemic influenza virus infection. Cross immunity tests in ferrets with two of the strains of influenza virus isolated from these epidemics have shown them to be antigenically different from strains isolated in previous years.

The Glucose Supply to Joint Cartilage. By ERIC G. L. BYWATERS (by invitation) and WALTER BAUER, Boston, Mass.

The glucose which joint cartilage has been shown (by manometric methods) to use reaches it by diffusion from synovial fluid. If the concentration here falls, glucose-deficiency will develop in the deeper layers of cartilage.

We have therefore investigated the entrance of glucose and other crystalloids into the joint cavity following intravenous injection and its removal therefrom, both in normal calves and in patients with knee effusions.

It has been shown that, whereas in normal joints there is a prompt rise to above venous level (as has been demonstrated in other body fluids), in certain diseased joints there is a very small, slow, and ill-sustained rise, reaching a delayed peak at one-fifth of the blood level. This is associated with a consistently low resting glucose level in the synovial fluid and with advanced pathological changes in the joint.

That this failure to reach blood level is due to utilization can be shown by the injection of glucose into these joints. The level rapidly falls to well below blood level and utilization can thus be measured. From a knowledge of the metabolic activity of cartilage, leukocytes, and synovial membrane, it can be shown that this sugar removal is due to an amount of synovial membrane comparable to that removed at synovectomy in similar cases.

Glucose deficiency may thus play some part in the impairment of cartilage seen in advanced rheumatoid arthritis, and hence synovial sugar determinations may indicate the proper time for the operative removal of this inflammatory tissue.

The Gravimetric Determination of Serum Proteins. By BERNARD M. JACOBSON, Boston, Mass.

In a few pathological sera there were noted discrepancies between the values for protein content afforded by gravimetric determination and the results of the commonly used method of nitrogen determination. These observations led to a systematic study of both normal and pathological sera. Total nitrogen was determined by the Kjehldahl procedure; the protein nitrogen was multiplied by the customary factor 6.25. The gravimetric determination was carried out by quantitatively precipitating the serum proteins with acetone, washing the precipitate with acetone and with ether, drying to constant weight, and finally ashing. This acetone precipitate was uncontaminated with lipoids or with significant amounts of non-protein nitrogenous substances. Precipitation of serum with trichloracetic acid, followed by washing of the precipitate with acetone, yielded protein values identical with those obtained by direct precipitation with acetone. On the other hand, considerably lower values were obtained by heat coagulation of the sera, for filtrates of such coagula contained much non-coagulable protein brought down by either acetone or trichloracetic acid.

In a large number of sera the total protein content was determined both gravimetrically and by means of the Kjehldahl method. In every instance the protein content obtained gravimetrically exceeded the value afforded by the nitrogen determination. This difference ranged from 0.11 to 0.72 gram of protein per 100 cc. of serum, or from 1.6 to 13.5 per cent of the Kjehldahl value. In four-fifths of all instances the difference exceeded 4 per cent of the Kjehldahl value.

The explanation of these discrepancies was furnished by the results of direct determination of the nitrogen content of the acetone precipitates. On an ash-free basis such precipitates contained from 14 to 15 per cent nitrogen, instead of the value of 16 per cent implied by the usual conversion factor of 6.25. However, the use of any other factor for all sera was found inaccurate, consequent upon the variable nitrogen content of the total proteins of different sera. Thus, for more exact determination of serum proteins the gravimetric method is recommended. The labor required by the gravimetric procedure is no greater than that involved in the Kjehldahl determination.

Peripheral Resistance and Vasomotor Reactions in Arterial Hypertension. By EUGENE A. STEAD, JR. and PAUL KUNKEL (introduced by Soma Weiss), Boston, Mass.

The nature of the arteriolar resistance and its distribution in the body remain the fundamental problems in the study of the etiology of arterial hypertension. Since the cardiac output is normal in this disease, the "average arteriolar resistance" at rest must be increased. It is essential, however, to obtain measurements on the specific state of the arteriolar resistance in various organs and tissues, and

to determine whether the peripheral resistance in any one organ can be reduced to normal by physiological vasodilating stimuli. Evidence that the peripheral resistance is uniformly high throughout the various organs and tissues and cannot be reduced to normal by physiological stimuli has been obtained by means of: (*1*) plethysmographic determinations of the blood flow in the foot and hand, with the vessels widely dilated by local heat of 43° C.; (*2*) plethysmographic determinations of the blood flow in the muscles of the forearm, with the vessels widely dilated by exercise; (*3*) indirect estimations of the blood flow through the brain by arteriovenous differences; (*4*) indirect estimations of the peripheral resistance in the brain by postural experiments after the administration of sodium nitrite. There was no significant difference in blood flow in any of the above organs between normal and hypertensive subjects. Therefore, as the pressure head is greater in hypertensive subjects, the peripheral resistance in hypertension must be uniformly increased in each of these parts; otherwise the blood flow would be greater than normal. Moreover, the finding of a constant increase in the arteriolar resistance in the skin, muscle, and brain in the presence of a normal cardiac output suggests a similar increase in vascular resistance in the abdominal viscera.

In two subjects with marked hypertension, the blood pressure was greatly reduced for a time by a course of malarial therapy. In one of these subjects, in whom hypertension had been known to be present for over 4 years, the blood flow in the dilated foot decreased when the blood pressure was lowered, indicating that the peripheral resistance was still high, even in the absence of hypertension. In the second subject, who was known to have had a normal blood pressure 2 years previously, the blood flow in the dilated foot did not change when the blood pressure was lowered, indicating that with the fall in blood pressure the peripheral resistance had become normal. Both of these subjects were afebrile and ambulatory when the blood flow determinations were made.

The vasomotor reactions in the hand and foot were similar in normal and in hypertensive subjects. A marked fall in pressure in two hypertensive subjects after malarial therapy caused no change in the vasomotor reactions. Postural studies and plethysmographic measurements of venous tone indicated that the response of the veins to sodium nitrite in normal and in hypertensive subjects was the same.

Further Clinical and Experimental Studies on the Ballistocardiogram. By ISAAC STARR, Philadelphia, Pa.

In the 1938 presentation emphasis was placed on the amplitude of the ballistic curves, which are a function of cardiac output. Since then we have been giving attention to the interpretation of the abnormalities in the form of the records which have been found in certain cases.

Impacts similar to those seen in disease may be derived theoretically by assuming abnormal curves of blood velocity in the aorta and pulmonary artery during a single systole.

Similar abnormal types of ballistic curves have been reproduced in animal experiments by asphyxia, by chloroform, and by directly damaging one side of the heart when the other was left intact.

Therefore it is concluded that the shape of the ballistic record is determined by the changes of blood velocity in the aorta during systole. When the heart is normal, maximum blood velocity is attained early in systole, when the heart is diseased, maximum velocity is attained late in systole. These conditions can be diagnosed by the ballistocardiogram.

If one side of the heart is weak, and the other strong, the ballistocardiogram is also characteristic.

The Functional Measurement of the Number of Active Glomeruli and Tubules in the Kidneys of Normal and Hypertensive Subjects. By H. CHASIS, H. A. RANGES, W. GOLDRING, and H. W. SMITH (introduced by James A. Shannon), New York, N. Y.

In 1924 Richards and Schmidt (Am. J. Physiol., 1924, **71**, 178) noted by direct microscopic observation that only a certain proportion of the glomeruli, or of the capillaries in individual glomeruli, were active at any one moment. This observation has been repeatedly confirmed, and it has been inferred from the behavior of glomeruli in the frog's kidney that there is similar intermittency of glomerular activity in the human kidney. Did such intermittency exist it would acquire increased significance in view of the possibility of a direct blood supply to the tubules in the human kidney via arterial-venous anastomoses (Spanner, Ergänzungsheft z. Anat. Anz., 1938, **85**, 81). The physiological importance of this point, and the clinical importance of determining whether there exists any tissue in the hypertensive kidney which is rendered ischemic by reversible vasoconstriction of renal arterioles has prompted us to measure the quantity of active glomerular and tubular tissue by saturation methods.

The total active tubular tissue in the kidney has been measured by elevating the plasma level of diodrast to a point where all the tissue receiving blood is excreting this substance at the maximal rate (diodrast-Tm, as described by Smith, Goldring, and Chasis, J. Clin. Invest., 1938, **17**, 263). The total active glomerular tissue has been measured by raising the plasma glucose to a point where the tubules are reabsorbing this substance at the maximal rate (glucose-Tm, as described by Shannon and Fisher, Am. J. Physiol., 1938, **122**, 765). If any glomeruli can be opened or closed by physiological means the fact will be revealed by an increase or decrease in the number of nephrons reabsorbing glucose, and therefore by a corresponding change in the value of glucose-Tm. At appropriate plasma levels of diodrast and glucose these measurements reveal the quantity of functioning tissue, and are independent of variations in renal blood flow or filtration rate.

Diodrast-Tm and glucose Tm have been measured in normal and hypertensive subjects under basal conditions, during renal ischemia induced by adrenin, neosynephrin, tyramine, *etc.*, and during sustained renal hyperemia.

Variations in the Codehydrogenase I and II Content of the Blood and Urine in Health and Disease. By RICHARD W. VILTER and SUE POTTER VILTER (by invitation), and TOM D. SPIES, Cincinnati, Ohio.

A method for the determination of codehydrogenases I and II, sensitive to 1 part per 200,000,000, has been devised and used in this investigation. The codehydrogenase values found in the blood and urine of 30 well-nourished members of the hospital staff were arbitrarily designated as normal. In contrast, the codehydrogenase in patients with pellagra in relapse, severe diabetic acidosis, lobar pneumonia, various malignant tumors, leukemia, and third degree burns was found to be 1/2 to 1/120th of normal values.

Repeated determinations were made before, during, and after therapy with nicotinic acid, riboflavin, or thiamin on samples of blood and urine from 10 pellagrins. The cozymase increased 400 per cent within 24 hours following the oral administration of nicotinic acid. Ten cases of lobar pneumonia showed 100 per cent increase in blood codehydrogenase within 6 to 24 hours after crises induced by serum or sulphapyridine; 10 cases of diabetic acidosis studied before, during, and after control by recognized therapy with insulin, fluids, and glucose, showed codehydrogenase values comparable to those found in pellagrins; 10 cases of malignant tumors before, during, and after x-ray therapy were studied. Before therapy, the tumor cases were found to have codehydrogenase values 1000 per cent greater than those found in the blood of 15 patients suffering from leukemia, both lymphatic and myeloid, who were followed in the hospital and at home for periods of time up to 5 months. The extremely low values for blood codehydrogenase found in the leukemic group of patients failed to respond to large doses of nicotinic acid, in contrast to the pellagrins, but could be increased 12,000 per cent, when yeast, nicotinic acid, and riboflavin were administered. Values of blood codehydrogenase 1/100th of normal were found, immediately following hospital admission, in three individuals with third degree burns.

Thus, the variations of codehydrogenase in the human body during severe infection, metabolic disorders, malignant tumors, leukemia, and burns have been determined and have been compared to a group of 30 healthy, well-nourished individuals who were used as controls.

The significance of these results will be discussed.

Factors Influencing Edema Formation in the Eyelids of Man. By GEORGE E. BURCH (introduced by J. H. Musser), New Orleans, La.

This presentation includes observations demonstrating marked distensibility of the tissues of the eyelids, greater in amount than that found for any other common edema site studied. Although the subcutaneous tissue pressure of the lower lids normally is about equal to that of the forearm, the loose areolar tissue and markedly "stretchable" skin renders the eyelids extremely distensible, to such an extent that with the accumulation of interstitial fluid they cannot benefit by the limiting influences of the skin and tissue pressure in curtailing edema formation. The linear rate of lymph flow in the superficial lid lymphatics was found to be greater with lid movement, blinking, and with the subject in the upright or sitting position than in the relaxed supine position.

This study was conducted on 80 living individuals, 50 normal and 30 with edema of the eyelids due to various causes. The subjects varied from 8 to 84 years in age and included males and females of the white and negro races in about equal numbers.

The mean subcutaneous tissue pressure, measured by a method previously described, for 21 normal lower eyelids was found to be 23.4 $\pm$ 0.7 mm. of water with a standard deviation of 5.1 $\pm$ 0.5 and minimum and maximum values of 16 and 32, respectively. For short periods of time the tissue pressure in the lids was not significantly affected by variations with respect to heart level or by loose closure of the eyes as in sleep. Subcutaneous injections of 1.0 cc. of normal saline (NaCl) into 10 lower lids produced practically no rise in tissue pressure, a moderate but significant rise in 9 atrophic breasts and 9 loose abdominal walls of multiparae and 8 prepuces, and a marked rise in the volar surfaces of 10 forearms and 10 pretibial areas. In 30 patients with various types of edema of the eyelids the tissue pressure was found to be only slightly elevated, the pressure in the lids, in spite of the edema, being lower than that in remote non-edematous areas, as the forearm and prepuce. The linear rate of lymph flow in the superficial lid lymphatics, measured by the McMaster method, of 50 eyelids in 20 normal subjects was increased over that in the relaxed supine position by sitting and by lid movement, blinking. The skin distensibility ("stretchability"), determined by a method previously described, of the 20 lower lids of 10 normal subjects, was found to be 1.23 $\pm$ 0.06 mm. per cm. of skin per 20 grams of force, with a standard deviation of 0.43 $\pm$ 0.05. The skin of the lids was found to be more distensible than the skin of any area studied, being approximately 3 times as distensible as that of the skin of the pretibial area, 2.5 times that of the volar surface of the forearm, twice that of the dorsum of the hand, 1.75 times that of the dorsum of the foot, and 1.2 times that of the abdomen.

The interplay of these factors favors the development of edema in the eyelids; and in systemic diseases equally affecting the interchange of fluid between the blood vessels and tissue spaces generally, as in acute hemorrhagic nephritis, the eyelids would be prone to an early development of edema, especially at night, with a tendency to recede during the day with activity.

Further Evidence for the Rôle of the Adrenal Cortex in Carbohydrate Metabolism: Relation of the Adrenal Cortex to Amylase Activity in Blood Serum and Liver of the Dog and Rabbit. By OLIVER COPE and (by invitation) ISRAEL KAPNICK, ADRIAN LAMBERT, T. DENNIE PRATT, and MAX G. VERLOT, Boston, Mass.

In the adrenalectomized dog, upon withdrawal of cortical extract, there is a sharp rise in amylase activity of the blood serum. The level of amylase activity reached in 24 hours, although not maximum, is equal to that seen in the hypophysectomized dog or in human pancreatitis. With the development of adrenal insufficiency there is a

further progressive moderate rise in activity until death. The final level reached is higher than that we have observed under any other condition. This rise in blood serum amylase activity is the most sensitive objective measure of adrenal cortical insufficiency yet observed in the dog. Following the removal of only one adrenal gland in four of seven dogs there was a rise in serum amylase activity returning to normal within a few weeks. After the removal of the second adrenal and the withdrawal of cortical extract, in all dogs the high level of serum amylase activity is reached 24 hours or longer before any changes are demonstrable in the hematocrit, nonprotein nitrogen, serum protein, serum sodium, potassium, or chloride. Doses of adrenal cortical extract (Eschatin) sufficient for maintenance of the adrenalectomized dog in apparent normal state, as judged by vigor, appetite, and the above laboratory data other than the amylase, are not sufficient to maintain the serum amylase activity within normal limits. Five to ten times the dose needed for ordinary maintenance is required to keep the serum amylase activity within normal limits after removal of the second adrenal or to return and maintain it within normal limits after cortical insufficiency has been allowed to develop.

The amylase activity of the liver in terminal insufficiency is increased over the normal. It is possible but not proven that the changes in the serum amylase reflect changes in liver function.

In the adrenalectomized rabbit the changes in the blood serum amylase activity are the reverse of those seen in the dog. The changes, however, are of a lower order.

In spite of the sensitivity of the amylase system of the dog to changes in adrenal cortical function it is not concluded that control of the amylase system by the cortex is the primary function of the gland. The difference in the behavior between the dog and the rabbit suggests that there may be some intermediary step as yet unsolved.

Effect of Orally Administered Cortical Extract upon Sodium and Chloride Balance in Addison's Disease. By JEROME W. CONN and FREIDA W. SILVERMAN (introduced by L. H. Newburgh), Ann Arbor, Mich.

Several reports indicate that adrenal cortical extract is effective when administered orally to adrenalectomized animals. We know of only one study (Thorne, 1938) in which the effect of oral administration of cortical extract in Addison's disease has been evaluated by means of electrolyte balance. Thorne found that 2½ times more extract was necessary by mouth than when injected.

In the present investigation, a severe case of Addison's disease was fed a constant diet for 55 consecutive days. The diet was maintenance in calories and contained 7.5 grams of sodium salts. Water intake was constant. The comparative effectiveness of parenterally and orally administered cortical extract, based upon sodium and chloride balance in addition to clinical manifestations were thus observed.

Conclusions

1. Adrenal cortical extract is physiologically effective when taken orally.

2. In terms of fresh gland, half as much extract was needed by mouth as when given parenterally to bring about sodium and chloride equilibrium.

3. When 7 grams of sodium chloride were added to the basic diet the amount of orally administered extract needed to maintain sodium and chloride balance was half of that required on the basic diet alone.

These results are in accord with reported observations on adrenalectomized animals.

Experimental Studies on Headache: Observations on Pain Pathways. By GEORGE A. SCHUMACHER (by invitation) and HAROLD G. WOLFF, New York, N. Y.

The purpose of the investigation was to determine what afferent nerves conduct the impulses interpreted as headache. Headaches were induced experimentally by injecting 0.1 mgm. of histamine phosphate intravenously. Normal subjects regularly develop bilateral headache under these circumstances. Patients who had partial or complete sections of the sensory root of the trigeminal nerve, with partial or complete hemi-analgesia of the face and anterior half of the scalp were investigated (operations performed by Dr. Bronson S. Ray). Also studied were patients who had sections of the upper cervical sensory roots with resultant occipital hemi-analgesia. Patients who had dorsal root or brain stem disease resulting in partial or complete analgesia on one side of the back of the head were likewise investigated.

It has been shown that histamine headache results from the stretch of cranial arteries. In order to be sure that the cranial arteries were being stretched adequately during these experiments photographic records of cranial artery pulsations were made during each induced headache.

Four patients who, as a result of incomplete section of the trigeminal sensory nerve root, had unilateral loss of sensation over the lower part of the face, had headache induced by histamine on both sides of the head, in the front and back.

Five patients who, as a result of complete section of the trigeminal sensory nerve root, had, in addition to hemi-analgesia of the lower half of the face, unilateral loss of sensation over the frontal, temporal, and parietal areas, did not have headache induced by histamine in these regions. However, they had headache elsewhere in the head, including the opposite fronto-parietal region and the back of the head.

The ligation of the middle meningeal and temporal arteries (necessary for trigeminal root section) did not explain the absence of "induced" headache. This was shown by the occurrence of the headache when the arteries were ligated as above, but the trigeminal root was only partially transected.

Two patients who had unilateral loss of sensation in the occipital region did not have headaches induced in this region by histamine. They did, however, have headaches elsewhere in the head, including the opposite occipital region and the front of the head.

Other data indicated that there were additional, though less important afferent pathways. In short, impulses from cranial arteries of the front of the head conducted through the sensory root of the fifth cranial nerve, were mainly

responsible for frontal, temporal, and parietal headache. The upper cervical sensory roots conveying impulses from cranial arteries from the back of the head were chiefly responsible for occipital headache.

The Effects of Heated Heterologous Kidney Extracts on Blood Pressure. By EUGENE M. LANDIS and (by invitation) W. A. JEFFERS, Philadelphia, Pa.

The injection of simple saline extracts of kidney tissue, both homologous and heterologous, is frequently followed by unpredictable results, ranging from sudden death of the injected animal to various combinations of pressor and depressor effects. Heated (55 to 56° C. for 20 minutes) and filtered extracts prepared from rabbits' kidneys consistently elevated the blood pressure of unanesthetized rabbits and did not contain depressor or lethal substances (J. Clin. Invest., 1938, **17**, 189).

This method was used to prepare similar 10 per cent extracts from the kidneys of rats, guinea pigs, rabbits, dogs, and man. The solutions obtained were entirely clear, yellowish or pink in color, and contained approximately 0.10 per cent albumin and 0.12 per cent globulin. These extracts were preserved in ampules by freezing and desiccation *in vacuo* (Cryochem process); later they were redissolved, centrifuged, and immediately injected into unanesthetized rabbits and into rats, guinea pigs, rabbits, and dogs under light nembutal anesthesia. Dosage was adjusted so that the animals received equivalent amounts of fluid and of solid extract according to body weight.

In this group of animals the pressor effects of the respective extracts were not species-specific, since each extract raised the blood pressure to some degree in all 4 species. However, the potency of the extracts differed according to species in that extracts of rabbits' kidneys were most highly active throughout while those of human kidneys were often almost inactive, with rat and guinea pig extracts in an intermediate position as to potency. The average sensitivity of the 4 species also differed in that the guinea pig was most responsive, and the rabbit least responsive, with rat and dog intermediate.

The results obtained with fractional ammonium sulphate precipitation, followed by suitable dialysis, indicate that heating to 55° C., while diminishing depressor and toxic effects, also precipitates or destroys at least some of the pressor substance, particularly in the extracts from kidneys of dog and man.

A Double Alternating Pressure Chamber to Provide Adequate Lung Ventilation Without Discernible Lung Movement. By ALVAN L. BARACH, New York, N. Y.

Instead of a rhythmical increase and decrease in the volume of the lungs, which characterizes normal respiration, Thuneberg (1926) suggested that a change of one-sixth of the barometric pressure applied to an individual within a chamber would result in adequate pulmonary ventilation without movement of the chest wall. The principle depends on the physical law that the number of gas molecules present in a gas container varies with the pressure under which the gas is kept in the container, provided the volume and pressure remain constant.

We constructed a small room in which an alternating pressure of 110 mm. Hg was produced 25 times a minute, using a large air compressor and a special valve mechanism. Animal and clinical studies showed that pressure in the positive cycle was applied to the outer chest wall earlier and was of slightly larger extent than that which was transmitted through the bronchi and alveoli to the inside surface of the chest. Continuous cessation of discernible lung movement was accomplished by placing the body of the patient in an inner chamber, with the head protruding. Pressure to the outer chest wall was then delayed until the lungs were suitably filled with air. Under these circumstances, no discernible chest movement took place while the lungs were being ventilated. The accomplishment of continuous lung rest has been shown to be clinically feasible and is accompanied by no appreciable alteration in the oxygen or CO_2 content of the arterial blood, the venous pressure, or the circulation time.

A Common and Important Error in the Measurement of Auriculoventricular Conduction (P–R Interval). By PAUL D. WHITE and (by invitation) STEPHEN A. FOOTE, and C. EDWARD LEACH, Boston, Mass.

In the course of routine electrocardiography we have discovered that an error is sometimes possible in the measurement of the P–R(Q) interval and therefore in the estimation of the auriculoventricular conduction time, which may result in an erroneous diagnosis of partial heart block with the clinical implications that attend such a diagnosis.

It has been the custom, almost universally, to measure the P–R(Q) interval in Lead 2, and usually to consider the longest P–R(Q) interval as the correct P–R interval measurement. This has probably been done because the P waves and often the QRS waves are larger and better marked in Lead 2 than in the other leads. However, an error can arise when the QRS in Lead 2 begins with an iso-electric phase which can be discovered only by the comparison of the QRS waves in the three leads.

Thus, the Q wave in Lead 1 may neutralize an R wave in Lead 3, when these waves are of the same amplitude, time, and duration, or they may partially neutralize each other, thus erroneously adding to the P–R(Q) interval in Lead 2. Also R in Lead 1 and Q in Lead 3, a still more common combination, may considerably neutralize each other to produce an iso-electric level in Lead 2.

It is important to bear in mind the possibility of this error and to measure the P–R intervals in Leads 1 and 3, as well as in Lead 2. Actually the shortest P–R interval is the correct P–R interval no matter what lead we study provided the P wave begins simultaneously in the three leads. We suggest that if the interval from the beginning of the P to the end of the S is found equal in the three leads, the shortest P–R(Q) interval should be taken as the correct measurement of auriculoventricular conduction time.

The Clot Promoting Activity in Hemophilia of Berkefelded Normal Human Plasma Free from Fibrinogen and Prothrombin. By EUGENE L. LOZNER, ROBERT KARK, and F. H. L. TAYLOR (introduced by George R. Minot), Boston, Mass.

Previous investigations have shown that platelet free normal human plasma is effective in accelerating clot formation of hemophilic blood both *in vivo* and *in vitro*. The activity of such plasma has been shown to be associated with the globulin fraction of the plasma proteins. Among the known constituents of this globulin fraction are fibrinogen and prothrombin. Using precipitation and adsorption methods it has been possible to make preparations from citrated normal plasma free from these proteins. After the removal of either prothrombin or both prothrombin and fibrinogen from citrated normal human plasma it was found that the remaining fluid promoted the clotting of hemophilic blood *in vitro*. When similar preparations were injected intravenously into patients with hemophilia, the coagulation time of their blood approached normal limits. Repeated injections maintained the shortened coagulation time of the patient's blood. The effects of the injections were entirely similar to those of unmodified normal human plasma or whole citrated blood.

The Significance of Changes in Synovial Fluid Mucin in Joint Disease. By MARIAN W. ROPES (introduced by Granville A. Bennett), Boston, Mass.

Knowledge of the characteristics and functions of mucin is essential for an understanding of the physiology of joints and determination of the origin and removal of mucin.

Synovial fluid mucin is composed of protein and polysaccharide elements the structure and mode of combination of which are not established definitely. The physicochemical properties indicate some functions of mucin. The high viscosity and resulting lubricating power of synovial fluid are due to mucin. The high base binding power of mucin explains the observed effect on distribution of calcium between plasma and fluid. Osmotic pressure studies indicate the significance of mucin in the exchange of water.

Changes in mucin in pathological fluids are of diagnostic value. In traumatic fluids the unit concentration is normal (0.85 gram per 100 cc.). In fluids from specific infectious and rheumatoid arthritis the unit concentration decreases in accord with the degree of inflammation. Despite the decreased mucin concentration the unit concentration of glucosamine remains high indicating mucin breakdown. The characteristic precipitation of mucin is lost and the viscosity of the fluid decreased in accord with the severity of the arthritis. The findings indicate that the entrance of mucin is increased in inflammation and that the destruction of mucin is increased in severe infectious joints.

The similarity of these changes to those produced by "mucinase" (isolated from B. Welchii) suggests an enzymatic nature of the changes in pathological fluids. No mucinase has as yet been demonstrated in pathological fluids.

The Mechanism of Uric Acid Elimination by the Kidney. By FREDERICK S. COOMBS (by invitation) and JOHN H. TALBOTT, Boston, Mass.

Simultaneous inulin, creatinine, and uric acid clearances were done in normals and in 20 patients with gout. The patients were divided arbitrarily into three groups: (*1*) no disturbance of inulin clearance; (*2*) mild disturbance; (*3*) severe disturbance. Subcutaneous and osseous tophi were observed in subjects of each group.

Previous work has shown that inulin excretion may be taken as a measure of glomerular filtration. It is assumed that in man, uric acid is excreted in the glomerular filtrate and is not a product of tubular activity. Our data indicate that normals and gouty patients of the first group have a uric acid clearance of approximately 10 per cent of the inulin clearance. This means that 90 per cent of the uric acid is reabsorbed from the glomerular filtrate. Patients with a moderate disturbance of inulin and creatinine clearance have a similar uric acid clearance and tubular reabsorption. A progressive decrease in the excretion of phenolsulphonephthalein and the ability to concentrate urine above 1.020 is noted, however.

The third group shows severe impairment of inulin and creatinine clearance, phenolsulphonephthalein excretion, and ability to concentrate urine. Tubular reabsorption of uric acid is about 70 per cent. An approximately normal uric acid clearance results in spite of diminished glomerular activity. In this group only are nitrogenous products retained in the serum and the blood pressure elevated. Advanced glomerular and tubular dysfunction is presumed.

Clearance studies were repeated in several patients following the administration of cincophen, colchicine, and salyrgan. No effect upon the inulin and creatinine clearance was noted. Diminished tubular reabsorption and increase in uric acid clearance was observed in patients without severe renal impairment following the administration of 45 grains of cincophen or 2 cc. of salyrgan. Patients with advanced gouty nephritis show minimal changes in uric acid clearance. Colchicine in therapeutic amounts produced no change in uric acid clearance.

It is concluded that gouty patients show no selective inferiority for excretion of uric acid. In advanced gouty nephritis a profound disturbance of glomerular filtration is observed without concomitant diminution of uric acid excretion. This is thought to be due to failure of reabsorption in the renal tubule. Cincophen and salyrgan, similarly, prevent uric acid reabsorption in the tubule. The pathogenesis of the increased concentration of uric acid in body fluids of patients with gout is believed, therefore, to be a function of increased formation or decreased destruction and not impaired elimination.

Hypoaminoacidemic Crises in Young Children with the Nephrotic Syndrome. By LEE E. FARR and (by invitation) DOUGLAS A. MACFADYEN, New York, N. Y.

In young children with the nephrotic syndome, the incidence of acute febrile episodes with peritoneal symptoms was markedly increased in that group with plasma albumin below one gram per 100 cc. contrasted with nephrotic children having a higher plasma albumin con-

centration. During these acute episodes there was a very rapid fall in the plasma albumin concentration with a rapid rise to its previous level after recovery. This change was independent of the proteinuria. Neither the apparent clinical severity of the illness nor the effect on the plasma albumin level was directly related to the presence of blood stream or peritoneal infection. A characteristic pattern was always followed in onset and recovery. These facts pointed to a disturbance of protein metabolism. Using the specific determination for amino acids developed by Dillon and Van Slyke, which was adapted for blood by MacFadyen and Van Slyke, we have followed the cell and plasma amino acids of five children with the nephrotic syndrome over a period of months. This work revealed a hitherto unknown disturbance of plasma amino acids which was a prolonged lowering of their concentration with occasional periods of critical fall and rapid recovery to pre-existing levels. The crises occur independent of infection. The acute disturbances were very closely correlated to the onset of, and recovery from, severe and typical clinical manifestations. These were identical with those noted in the acute illness usually accompanied by fatal pneumococcal peritonitis so often observed in these children. Recovery from the nephrotic syndrome was accompanied by a gradual return of the plasma amino acid levels to a normal value. We have termed the acute episodes hypoaminoacidemic crises.

Ultrafiltrate Magnesium Studies in Hyperthyroidism. By L. J. SOFFER and (by invitation) D. A. DANTES, E. B. GROSSMAN, and H. H. SOBOTKA, New York, N. Y.

The following report concerns itself with the study of magnesium metabolism in clinical and experimental hyperthyroidism. The total and ultrafiltrable blood magnesium was determined in 20 normal individuals. It was found that the percentage of the total magnesium bound, presumably to proteins, varied from 3.1 to 22.1 per cent. In 5 patients with neurocirculatory asthenia, the percentage of bound magnesium varied from 9.1 to 20.6 per cent. In 30 patients with hyperthyroidism, where the basal metabolic rate varied from 30 to 106, the percentage of bound magnesium varied from 21.5 to 60.0 per cent. It is evident, therefore, that in hyperthyroidism there occurs an increase in the amount of circulating magnesium which is bound. The increase in the bound magnesium occurs at the expense of the ionized form, since the total blood magnesium remains unaltered in hyperthyroidism.

There is apparently no relationship between the amount of bound magnesium and the level of the basal metabolic rate.

In 12 patients the bound magnesium in the blood was determined before and after the administration of iodine. Before the administration of iodine the non-filtrable magnesium varied between 21.5 and 49.8 per cent of the total while after administration, the percentage of bound magnesium varied from 6.0 to 34.5 per cent.

In 11 patients similar determinations were made before and after operation. Whereas before operation the percentage of bound magnesium varied between 26.0 and 49.8 per cent, after operation it varied between 0 and 23.0 per cent—a return to a perfectly normal value. In 10 instances studies were conducted before and after the administration of iodine, and after operation. It was found that, after the administration of iodine, there occurred some drop in the amount of bound magnesium which further dropped to normal levels after operation.

The next step was to determine how the magnesium was bound. From 50 to 200 mgm. of thyroglobulin was injected intravenously in one dose into 5 dogs. Total and ultrafiltrable blood magnesium was determined at intervals of 15 minutes, 1.5, and 24 hours. In each instance the increase in bound magnesium varied between 75 and 100 per cent over the control level. This increase occurred within 1 to 5 hours after the injection. The injection of equivalent doses of thyroxin and horse serum produced no change in the percentage of bound magnesium. This would suggest that the thyroglobulin plays some part in binding the ionized magnesium.

Studies of Cutaneous Capillary Blood Pressure in Man. By L. W. EICHNA (by invitation) and JAMES BORDLEY, III, Baltimore, Md.

A critical study has been made of two methods for determining human capillary blood pressure: (*1*) the *indirect* pressure-capsule method of Danzer and Hooker, and (*2*) the *direct* microinjection method of Landis. To test the accuracy of these methods the capillary pressure in the nail-fold was determined at various subdiastolic levels of venous pressure.

In each of 30 capillaries studied by the direct method, when the venous pressure in the arm was raised the capillary pressure promptly rose to exceed the increased venous pressure. This was observed in 18 subjects, with normal, high, and low arterial pressure.

In over 200 capillaries studied by the indirect method no significant rise in the capillary pressure reading was observed when the venous pressure was raised. For example, with venous pressures as high as 50 mm. Hg, capillary pressure was frequently recorded as low as 10 mm. Hg.

In 9 experiments in which a single capillary was studied by both methods, the same discrepancy was noted: the directly determined capillary pressure always exceeded venous pressure, while the indirectly determined pressure showed no correlation with venous pressure.

That the capillary pressure actually rises to exceed venous pressure is indicated by the fact that in all experiments capillary blood flow continued in the presence of increased venous pressure. It is believed therefore that the direct method gives accurate results; the indirect method inaccurate results.

Bacterial Endocarditis (Acute and Subacute) Superimposed on Syphilitic Aortic Valvulitis. By ALBERT L. BRAUNSTEIN and STUART R. TOWNSEND (introduced by John T. King, Jr.), Baltimore, Md.

Though syphilitic aortic valvulitis and vegetative bacterial endocarditis are well established separate clinicopathological entities, the concomitant occurrence of the two processes on the same valve has been regarded as extremely rare and very little has been written on this

subject. To our knowledge only 11 proved cases have been reported. We have had occasion to study several such cases at postmortem examination. A thorough search through our autopsy protocols has revealed, moreover, that among 4936 routine autopsies there have occurred 9 cases in which bacterial endocarditis was primarily engrafted on previously syphilitic aortic valves. This represents 15.5 per cent of all our cases of bacterial endocarditis (58 cases) and an incidence of 3.37 per cent in all our cases with syphilitic aortic valvulitis (267 cases).

An analysis of the clinical and pathological data of our own cases, as well as those found in the literature, reveals that both acute and subacute types of endocarditis are superimposed on syphilitic aortic valves (6 acute and 14 subacute). Clinically, in the *subacute cases* the only constant findings suggestive of bacterial endocarditis were progressive anemia and daily intermittent fever. The occurrence of chills, chilly sensations, subjective sense of fever, petechiae, embolic phenomena, and nephritis was markedly reduced. The predominating signs and symptoms were those referable to syphilitic aortic insufficiency with myocardial failure. At autopsy the vegetations were small and were located on the ventricular surfaces of the valve cusps and *not along the occlusal margins*. There was also a great tendency toward healing of the vegetations. No evidence of rheumatism was present in any case. In 4 cases *Streptococcus viridans* was recovered either antemortem or postmortem. Blood cultures were not taken in most of the instances because the diagnosis of bacterial endocarditis was not suspected clinically.

In the *acute instances*, evidences of septicemia were usually obvious and myocardial failure was also quite striking. At autopsy there were no distinctive findings.

From our findings we conclude that with obvious signs of bacterial endocarditis in the presence of syphilitic aortic insufficiency the bacterial process most likely exists on a valve other than the aortic. However, one may suspect the presence of bacterial endocarditis on a syphilitic aortic valve when, in the presence of aortic insufficiency, there exist a gradually progressive anemia and daily intermittent temperature rises which cannot be explained by any other findings.

Simultaneous Electrograms and Mechanograms from the Intact Human Subject. By CARL A. JOHNSON and GRANT LAING (introduced by J. A. Capps), Chicago, Ill.

By a special method the authors have been able to take simultaneous mechanograms and electrograms from the esophagus and stomach of normal unanesthetized intact human subjects. The mechanograms showed the changes due to the contractions of the organ under observation. The electrograms showed changes due to the action of the heart as well as other changes which will be discussed. The possible importance of the electrical changes in relation to smooth muscle contractions as well as the possible importance of these changes to clinical medicine are discussed. Results of other experiments in which changes in the conventional electrocardiogram were produced by inflation of the stomach by means of a stomach balloon will be shown.

The Effects of Adrenal Cortical Extract and Potassium on the Electrolyte Balance in Addison's Disease. By K. A. KLINGHOFFER (by invitation) and P. H. LAVIETES, New Haven, Conn.

The salt intake of a patient with Addison's disease was so limited that he was in slight negative balance. Large doses of adrenal cortical extract repeatedly converted the negative balance to a positive one, the effect persisting for less than 48 hours. No other result of the administration of the extract was consistently observed. Lowering the potassium of the diet had no demonstrable effect, nor did the subsequent increase to normal.

The Fermentation Stimulating Effect of Vitamin B_1 and Related Substances in the Urine of Human Subjects. By J. ALLEN KENNEDY and HELEN FRANK (by invitation), and JOHN B. YOUMANS, Nashville, Tenn.

The amount of vitamin B_1 and related substances excreted in the urine as determined by the stimulation of yeast fermentation is reported for a series of normal subjects and patients suspected of vitamin B_1 deficiency. The possible significance of substances causing acceleration of fermentation other than thiamin, as degradation products of B_1, and a measure of vitamin B_1 metabolism *in vivo* is discussed.

Subleukemic Splenic Reticulosis. By C. H. WATKINS and H. Z. GIFFIN, Rochester, Minn.

In 1934 we reported two cases of subleukemic splenic reticulosis, emphasizing the close similarity of this condition to splenic anemia. Since that time we have seen six similar cases. These patients have been treated conservatively by roentgen therapy with control of the condition in four of the cases. A summary of the clinical findings, differential diagnosis, and treatment is given.

Variations in the Serum Cholesterol Following Pneumonia. By KENNETH B. TURNER and (by invitation) ALFRED STEINER, New York, N. Y.

The relative stability of the serum cholesterol level for the individual has been established. Acute infection is known to produce a hypocholesterolemia, but the behavior of the serum cholesterol in the convalescent period is less well known.

In the present study the serum cholesterol of 20 patients with pneumonia was followed for 60 to 300 days after the onset of the illness. During the febrile period there was a hypocholesterolemia as had been expected. This was largely due to a marked decrease in cholesterol ester. For a variable time during convalescence, wide fluctuations occurred in the serum cholesterol with, in general, a hypercholesterolemia. This was due to an increase in both free and ester cholesterol, and was not associated with a fall in the basal metabolic rate or demonstrable disturbance in liver function. Finally, the serum cholesterol became stabilized at a constant level assumed to be normal for the individual.

The possible implication of these findings in relation to the development of atherosclerosis is discussed.

A Vitamin C Saturation Test with a Modification to Compensate for the Error Due to Impairment of Renal Excretion. By JOHN LUDDEN (by invitation) and IRVING S. WRIGHT, New York, N. Y.

Impairment of renal function has been demonstrated to retard the excretion of vitamin C in the urine. This has resulted in erroneous low values following intravenous or oral vitamin C saturation tests. Analyses of urine specimens obtained at 1.5, 3, 5, and 24 hours after an intravenous dose of 1 gram of cevitamic acid revealed a definite correlation between, (*1*), the percentage of the 5-hour output excreted during the first 1.5 hours, and (*2*), the percentage of the 24-hour output excreted during the first 5 hours.

A careful study of the data showed this correlation to hold for patients in a wide range of saturation levels and with various degrees of renal insufficiency.

A formula has been devised where by using the excretion figures of vitamin C for 1.5 and 5-hour samples after the test dose it is possible to predict the 24-hour output with an average error of 3.4 per cent. A patient with known renal insufficiency can be correctly evaluated as to vitamin C saturation through the use of this procedure. In our experience parallel blood and urine studies clarify the interpretation in certain instances. In certain aged individuals following the intravenous test dose it has been noted that there may be a retardation of vitamin C excretion in the absence of other laboratory evidence to suggest renal insufficiency including urea clearance and other commonly used kidney function tests.

The Urinary Excretion of Sex Hormones in Normal Children. By IRA T. NATHANSON and LOIS E. TOWNE (by invitation) and JOSEPH C. AUB, Boston, Mass.

Assays of the urinary estrogens, by bio-assay and of the urinary androgens by the colorimetric method were determined one or more times on 87 children under 14 years of age. There was a steady rise in the excretion of these hormones until puberty. This varied directly with the chronological age, but also with the physical maturity of the individual. There was no evidence of a cyclic excretion of the androgens in either sex. There might be daily variations in the androgen excretion but it did not appear to be of sufficient magnitude to be of physiological significance.

There was no evidence of a cyclic excretion of the estrogens in males nor in the younger females below 10 years of age. In the preadolescent years, however, there was evidence of a definite cycle of urinary estrogen excretion some time before menstruation occurred. This has been substantiated by repeated observations on the same individuals.

These normal control figures may be used as standards for the future study of the excretion of these hormones in endocrine abnormalities in childhood.

Stimulation of Skeletal Growth in Young Boys with Anterior Pituitary-like Principle. By W. O. THOMPSON and (by invitation) N. J. HECKEL, Chicago, Ill.

In boys showing marked genital growth during the administration of the anterior pituitary-like principle from the urine of pregnant women, acceleration of skeletal growth has been observed. When the treatment was discontinued, the rate of skeletal growth decreased. In general, the rate of skeletal growth appeared to bear a direct relationship to the amount of genital growth. A series of 30 treated patients varying in age from 1 to 15 years has been compared with a series of 24 untreated patients of the same age group.

Experimental Induction of "Fastness" to Sulfapyridine in Pneumococcus Type I. By COLIN M. MACLEOD and GIUSEPPE DADDI (introduced by O. T. Avery), New York, N. Y.

By serial transfer in serum broth containing increasing concentrations of sulfapyridine, "fastness" to the drug has been induced in a strain of Pneumococcus Type I. "Sulfapyridine fastness" is demonstrable *in vitro* as well as in experimental infections of mice.

The "sulfapyridine-fast" strain of Pneumococcus Type I retains the morphological characteristics of the parent strain and is gram-positive. No alteration in virulence or specific immunological characteristics have been demonstrated in association with the acquisition of "sulfapyridine-fastness." The change in the organism appears to be a relatively permanent one.

Iodinated Protein in Human Athyreosis. II. The Production of Physiological Activity by Simple Iodination of Serum Protein. By J. LERMAN and W. T. SALTER, Boston, Mass.

In a previous report hydrolyzed iodoprotein was shown to relieve 6 cases of human athyreosis. In terms of iodine, this material had the activity of diiodothyronine, *i.e.*, about one-thirtieth that of whole thyroid. Recently 4 other patients have responded clinically and metabolically to oral administration of serum protein, which had merely been iodinated. The original serum proved, of course, to be inert. These iodoprotein preparations contained 15 to 20 per cent iodine. It is not known definitely in what form the iodine is bound. Part of it certainly exists as diiodotyrosine; presumably a part exists as iodohistidine. In terms of iodine, the relative potency of this material was only one-five hundredth that of whole thyroid.

However, peptic digestion (as with natural thyroid) yielded a "thyroxine-like" fraction (active) and a "diiodotyrosine-like" fraction (inert). The active peptone, tested in three myxedematous patients and in two thyroidectomized rabbits, contained almost the entire activity of the parent iodoprotein.

This evidence that thyroidal activity can arise in serum protein through simple iodination suggests several problems: (*1*) Does thyronine (thyroxine minus all 4 iodine atoms) exist preformed in serum protein as an essential amino acid, awaiting iodination? (*2*) Does the process of iodinating the protein also change molecular configura-

tion so as to produce physiological activity? (*3*) Can the thyroidless organism synthesize iodothyronine molecules from other iodinated residues? The proper interpretation of this chemical process may contribute to a better understanding of thyroid activity.

Observations on the Inulin Clearance as a Measure of the True Glomerular Filtration Rate in Normal, Hypertensive, and Nephritic Individuals. By BENJAMIN F. MILLER (by invitation), ALF S. ALVING, and (by invitation) M. J. CARL ALLINSON, Chicago, Ill.

Present evidence indicates that in mammals the renal excretion of inulin equals, or closely approximates, the glomerular filtration rate. However, for man the evidence is less conclusive.

It is axiomatic that the clearance of any substance measuring only the glomerular filtration rate must be independent of the concentration of the substance in the plasma. Shannon and Smith have shown that in normal man the inulin clearance satisfies this criterion at plasma levels higher than 50 mgm. per 100 cc.

The methods used in previous investigations have not allowed accurate determination of inulin at very low plasma concentrations. Also, no critical evaluation of inulin excretion as a measure of filtration in the diseased human kidney has yet been made. Employing a new method for the estimation of inulin we have determined its clearance at a range of 1 to 7 mgm. per 100 cc. of plasma and have compared it with the clearance at 40 to 80 mgm. per 100 cc. in normal subjects, hypertensive and nephritic patients. The inulin clearance values obtained at low plasma concentrations agree very closely with clearances at the higher levels, indicating that exceedingly little or no tubular reabsorption or tubular excretion of inulin occurs in the kidney of such individuals.

Observations on Effort Pain in Normal Individuals, the So-called "Stitch in the Side" with a Consideration of the Mechanism. By RICHARD B. CAPPS, Chicago, Ill.

Although the so-called "stitch in the side" pain is extremely common, there is almost no information concerning it in the literature. Apparently, no systematic attempt has been made to observe its characteristics or to suggest a mechanism. This study is an attempt to throw some light on the problem.

Data collected by questionnaire or by asking individuals to recall their symptoms from months or years previously are notoriously unreliable in a problem of this kind. Consequently, this report is based primarily on personally observed attacks. Ninety-six such attacks have been observed in 52 different individuals. There were 43 males and 9 females. Only 2 were not healthy. Ages ranged from 15 to 63 years.

Stitch pain was produced by both mild and strenuous exertion, often only postprandial. The pain was usually located in either the right or the left upper quadrant, although a number of other loci were seen less often. Occasionally, the location varied in the same individual in different attacks. The relation to respiration was very inconstant. Bending over frequently gave relief.

Several possible mechanisms are discussed, especially the possibility of a diaphragmatic origin.

The Response of Blood Vessels in Forearm and Hand to Various Stimuli. By EUGENE B. FERRIS, JR., and (by invitation) DAVID I. ABRAMSON, Cincinnati, Ohio.

Although blood flow in the hand, as studied by plethysmography, is known to be unstable, it has under certain conditions been used as an index of peripheral blood flow. We have made a comparative study of the effects of various stimuli upon limb volume and blood flow in the hand and forearm.

Our results indicate that: (*1*) Some stimuli cause a significant reduction in limb volume and blood flow in the hand, without notable changes in the peripheral circulation. (*2*) Blood flow to the forearm, under similar circumstances, is not affected although the volume often decreases. (*3*) Stimuli which cause a significant rise in heart rate or arterial pressure generally induce an increase in limb volume and blood flow in the forearm and a decrease in the hand. (*4*) The reduction in limb volume in the hand appears to be due partly to constriction of veins and partly to constriction of arterioles, whereas evidence of arteriolar constriction was never seen in the forearm. Such a dissimilarity in vasomotor reaction in the two areas is thought to be due to the presence of arteriovenous anastomoses in the skin of the palm and finger tips, and to their absence in the skin of the forearm. (*5*) The blood flow through the forearm is a more accurate index of peripheral blood flow than that through the hand.

Studies of Circulation and Respiration in Anxiety Neurosis and in Psychoneurosis with Anxiety Features. By MANDEL E. COHEN (by invitation) and JACOB E. FINESINGER, Boston, Mass.

Studies are in progress on circulatory function in a series of 75 patients whose diagnoses are anxiety neurosis and psychoneurosis with anxiety features. This study includes, in addition to clinical and routine laboratory observations, venous pressure, blood volume, circulation time, basal metabolic rate, minute respiratory volume, and alveolar carbon dioxide measurements. Studies of the arm to carotid circulation time (cyanide method) show a mean value of 12.6 seconds as compared with the normal value of 15.6 seconds. This indicates that the blood flows more rapidly in this group of patients than in normal individuals. Despite the rapid circulation, the oxygen consumption, as evidenced by the basal metabolic rate, is not increased (mean − 3 per cent). In a few observations of anxiety attacks, the ventilation was markedly increased (30+ liters per minute).

Changes in the Blood and Nervous System of Pigs Associated with Deficiency of Substances Contained in Yeast. By M. M. WINTROBE and (by invitation) M. SAMTER, and H. LISCO, Baltimore, Md.

Young pigs were weaned at 10 to 23 days of age on a diet consisting of casein, sucrose, lard, cod liver oil, a mineral mixture, ascorbic acid, and yeast. When satisfactory growth had been established the quantity of yeast given

some of the animals was gradually reduced and it was replaced by thiamin chloride, riboflavin, and nicotinic acid in various combinations.

Anemia did not develop in the pigs given 3 or more grams of yeast per kgm. of body weight, but it occurred in all but one of those given smaller amounts. It was characterized by the presence of macrocytes, polychromatophilia, Howell-Jolly bodies, and nucleated red cells, and in some instances a significant increase in mean corpuscular volume was observed. In 4 of the animals in which such therapy was attempted, administration of yeast was accompanied by partial or complete relief of anemia. Hyperplasia of the bone marrow was observed at autopsy in the anemic animals.

In all of the pigs given suboptimal amounts of yeast, ataxia developed and changes in the nervous system, particularly in the posterior columns of the spinal cord and sensory nerves, were observed. The ataxia is demonstrated in motion pictures.

The Experimental Production of Anemia in Dogs by the Injection of Sodium Iodoacetate. By J. S. WENZEL and J. L. A. FOWLER (by invitation), and J. A. DAUPHINEE and R. A. CLEGHORN, Toronto, Can.

In the course of some investigations to determine whether iodoacetate poisoning in dogs resembled adrenal insufficiency it was found that a marked anemia developed following subcutaneous injection of the sodium iodoacetate. No striking similarities between iodoacetate poisoning and adrenal insufficiency were observed in dogs, in contrast to Verzar's observations on rats. The anemia which occurred within 10 days of the start of the bi-daily injections seems to be associated with a very marked increase in the destruction of red blood cells and increased activity on the part of the bone marrow. Death occurred as early as 10 days after the start of the injections in 2 instances, with a hemoglobin below 16 per cent. Evidence has also been obtained which indicates that this toxic action of iodoacetate is inhibited by the administration of methylene blue.

Blood and urine electrolyte studies on these animals will be made the subject of a future communication.

The Esophageal Electrocardiogram in Coronary Thrombosis. By JAN NYBOER (introduced by Herman O. Mosenthal), New York, N. Y.

Hamilton and Nyboer (1938) showed that the absence of the auricular "intrinsic waves" of Lewis from exploratory leads taken below the esophageal auricular border determines the position of the electrode in relation to the posterior ventricular wall in human subjects. Further study shows the validity of this method with particular reference to posterior myocardial infarct localization.

In such cases there is usually a significant Q-wave associated with R–ST segment or T-wave changes in the tracings taken at the esophageal ventricular level. These were not found in normal subjects, and resemble changes found in exploratory leads over the anterior wall in cases of anterior myocardial infarction. Among these, one case is presented in which the diagnosis was established by the esophageal lead 17 years after the dramatic episode, although healing had taken place, and standard leads at this time remain equivocal.

Other factors modifying the QRS and T-wave complexes in the esophageal ventricular region are also considered.

Immunological Aspects of Hemolytic Mechanism in Paroxysmal Nocturnal Hemoglobinuria. By THOMAS HALE HAM and JOHN H. DINGLE (introduced by Laurence B. Ellis), Boston, Mass.

In a preliminary report (Ham, T. H., New England J. Med., 1937, 217, 915) certain features of the mechanism of hemolysis were described for patients with chronic hemolytic anemia with paroxysmal nocturnal hemoglobinuria (Marchiafava-Micheli syndrome). The fundamental abnormality resided in the red blood cells; a thermolabile factor essential for hemolysis was demonstrated in plasma (heparin) and serum from five patients and from all normal subjects of compatible blood groups; the patient's plasma and serum did not hemolyze normal erythrocytes. The degree of hemolysis *in vitro* and *in vivo* was influenced by variations in the acid-base equilibrium.

These features suggested that an immunological reaction might be responsible for the hemolytic mechanism. No antigenic difference was observed between the abnormal and normal human erythrocytes when employed to immunize rabbits. No antibody or hemolytic substance has yet been isolated from one patient's red blood cells or stroma when treated by 10 per cent sucrose, 10 per cent salt solution, dilute acid and alkali, and by ether and saline. No hemolytic antibody was absorbed from the serum of one patient and of normal subjects by sheep cells or by human erythrocytes and stroma. However, the serum factor essential for hemolysis was found identical in behavior to *human* complement since all procedures and reagents which inactivated, destroyed, reduced or inhibited the serum complement, or any of its four "components," as measured by sensitized sheep cells also reduced the hemolytic activity of the serum for the patient's erythrocytes. For hemolysis of patient's erythrocytes fresh animal serums did not restore the thermolabile components of heat inactivated human serum but fresh guinea pig serum did restore the component of human serum inactivated by ammonium hydroxide.

Vitamin A Deficiency in Diabetes Mellitus. A Photometric Study. By J. G. BRAZER (by invitation) and A. C. CURTIS, Ann Arbor, Mich.

Biophotometric studies on a series of 20 juvenile diabetics were compared with similar studies on a series of 20 interns and staff members used as normals. A definite reduction in the biophotometer readings was noted in the group of diabetics.

Carotenemia was present in all the diabetics studied. It has been shown by others that the conversion of carotene to vitamin A is altered in diabetes mellitus. In substantiation of this failure to convert the provitamin carotene to vitamin A in diabetes mellitus, 7 diabetics were given 60,000 units of carotene daily for 7 days, with substantial increases in their blood carotene levels but no improvement in their biophotometer readings. When

60,000 units of vitamin A were given as halibut liver oil, for a period of 7 days, the biophotometer readings showed return of function to near normal levels. Two patients receiving carotene and vitamin A supplements in similar amounts for 14 days reacted like the groups above.

Patients whose biophotometric readings were improved by the administration of vitamin A developed rapid retrogression of their biophotometric readings after the vitamin was discontinued.

Our findings suggest that juvenile diabetics are deficient in vitamin A as measured by the biophotometer in spite of high blood provitamin levels. This deficiency confirms previous work done by others that diabetics are unable to convert carotene to vitamin A.

The Histamine Content of the Blood in Allergic Disease. By THERON G. RANDOLPH (introduced by Francis M. Rackemann), Boston, Mass.

Code's modification of Barsoum and Gaddum's method of determining the histamine content of blood is being used with results as follows:

1. No striking differences in the blood histamine values between normal and allergic individuals have been observed.
2. No significant increase of histamine has been found in patients suffering attacks of hay fever or asthma as compared with the same patients between attacks.
3. A few patients with very high percentages of eosinophils in their blood have been studied but failed to show any increase of histamine in the whole blood.

So far, these results are contrary to the findings of McDonald and of Code and so upset the theory that asthma depends fundamentally upon the activity of histamine. However, the work is still in progress and further data may lead to other conclusions.

Adaptation of Climate in Relation to Serum Volume. By F. WILLIAM SUNDERMAN and (by invitation) H. C. BAZETT and J. C. SCOTT, Philadelphia, Pa.

Seasonal variations in the serum and blood volumes have been detected in the same individuals. These variations appear to be more marked in individuals of middle age and onward. Using an air-conditioned room it was observed that there was a gradual increase in serum volume when individuals were maintained during winter months in a hot room (33.3° C. during the day and 31° during the night), and a decrease in serum volume during summer months in a cold room. At the time of increased serum volume the concentration of serum proteins was approximately normal, the total serum protein in the circulation was therefore greater. The change in serum volume was usually correlated with a corresponding change in body weight. Infra red photographs indicate that superficial veins are not constricted fully in response to mild cold for 2 or 3 days afterwards when adjustments in blood volume have occurred. There are cardiovascular changes correlated with changes in the serum volume—thus for instance, the cardiac output was reduced on standing when the subjects were adapted to cold while the reduction was very slight when the same subjects were adapted to heat.

The Formation of Methemoglobin and Sulfhemoglobin During Sulfanilamide Therapy. By J. S. HARRIS and H. O. MICHEL (introduced by W. C. Davison), Durham, N. C.

Nine hundred and sixty blood samples from 476 patients receiving sulfanilamide were examined for free sulfanilamide content, methemoglobin, and sulfhemoglobin. In the 277 patients who had methemoglobinemia and in the 37 patients who had sulfhemoglobinemia at some time, as demonstrable by the hand spectroscope, quantitative spectrophotometric determinations were made.

The percentage of bloods which showed methemoglobin was highest in the group that had high sulfanilamide content. The average methemoglobin value of all bloods was proportional to the sulfanilamide concentration. Methemoglobinemia did not depend upon sex, but was somewhat more frequent and more pronounced in the very young. The average methemoglobin concentration tended to diminish with increasing duration of therapy at constant blood sulfanilamide levels up to 8 mgm. per cent, but at higher sulfanilamide concentrations there was a tendency for the methemoglobin to increase with time. After a single dose of sulfanilamide, the maximal methemoglobinemia occurred several hours after the blood sulfanilamide had reached its peak.

Sulfhemoglobinemia was more frequent after long courses of sulfanilamide, but did not bear any relationship to age, sex, or the concentration of sulfanilamide or methemoglobin in the blood.

On the basis of these findings, it is postulated that an active substance is normally produced in the course of sulfanilamide metabolism which causes the production of methemoglobin and sulfhemoglobin. We have demonstrated the formation of such an active substance when surviving tissues react with sulfanilamide *in vitro*. The statistics presented are found to agree with the concept that methemoglobinemia depends upon the balance of the following reactions: formation of the active agent, oxidation of hemoglobin under the influence of the active agent, and reduction of methemoglobin by the body.