# PROCEEDINGS OF THE TWENTIETH ANNUAL MEETING OF THE AMERICAN SOCIETY FOR CLINICAL INVESTIGATION HELD IN WASHINGTON, D. C., APRIL 30, 1928

Death has laid a heavy hand upon our Society in the past year, and we have lost three of our number who were constant participants in our programs and activities.

## Dr. Charles F. Hoover

Dr. Charles F. Hoover, Professor of Medicine in Western Reserve University, was a man long trained in the best traditions of European Medicine. He was an individualist, very conscientious in his University studies, in which he assumed work that many others would have delegated to assistants. But in spite of this he was a constant investigator of disease. These traits all made him a teacher whom his students will long remember, and a confrère who commanded the respect of his colleagues.

## Dr. Karl K. Koessler

Dr. Karl K. Koessler, Clinical Professor of Medicine in the University of Chicago, was a person who brought a mind well trained in chemistry to bear on medical subjects. He was hard working, enthusiastic, original and stimulating. We all looked forward to his communications to our programs with unusual interest. We are the poorer for his going.

## Dr. Francis W. Peabody

Dr. Francis W. Peabody, Professor of Medicine in Harvard Medical School, lived a life such as makes it impossible for any words of eulogy to amplify. During our careers we sometimes are so fortunate as to know well a man like Francis Peabody. In him were combined the qualities which lead to success without exciting in his colleagues any emotion but that of admiration. In planning and establishing the Thorndyke Memorial Laboratory he made a unique

contribution to the field of Clinical Investigation. At the same time he was encouraging coöperative efforts in other departments of his University. He was always helping others; his advice was sought by many. One wonders how he found time to do so much. And in the last year he faced the inevitable with a courage that has stimulated all who knew him to carry on in a way they would not have done had he not lived. His place cannot be filled.

*Observations on the Etiological Relationship of Achylia Gastrica to Pernicious Anemia.*

By W. B. CASTLE (by invitation) and EDWIN A. LOCKE, Boston, Mass.

The action of liver in benefiting cases of pernicious anemia promptly and throughout the duration of the liver diet suggests the possibility of a deficiency etiology for the disease. The deficiency would, however, seem not to be of the usual dietary type, for liver is ordinarily absent from the diet of unaffected normals. The high incidence of a marked reduction of hydrochloric acid and pepsin in the stomach, sometimes discovered before the development of the disease, and not affected by the general improvement of the patient on a liver diet, suggests that the achylia may possibly play an intermediary rôle in causing the deficiency. An obvious possibility, especially in view of the probable polypeptid nature of the effective principle in liver extract, is a deficiency of the gastric digestion of protein.

To test this idea, the contents of the stomach of a normal man recovered one hour after a meal of 300 grams of rare Hamburg steak was administered daily to each of ten patients with pernicious anemia. The material as obtained from the normal stomach was treated with strong hydrochloric acid to pH 2 to 3, incubated six hours, then neutralized with sodium hydroxide to pH 5, and given by stomach tube to the fasting patient. In eight of the ten patients so treated clinical improvement, a characteristic rise of the reticulocytes and a progressive increase of the red blood cells was observed, comparable to effects ordinarily seen with small doses of liver in similar patients. In one of the eight cases benefited the effect may have been initiated by a transfusion, and in one of the two cases showing no clinical improvement there was a slight increase in the reticulocytes at the expected time.

The daily administration of mixtures of 300 grams of Hamburg steak with commercial pepsin or with 150 grams of the mucous membrane of the pig's stomach, incubated like the gastric contents, was found ineffective in three of these ten cases, and in two others. In three cases of this series, and in two other cases, 200 to 300 grams of Hamburg steak daily were given without effect. In another case, mixtures of Hamburg steak and hydrochloric acid gave no benefit. In view of Elders' work these controls must nevertheless be multiplied.

At present a definite conclusion is impossible; but these observations suggest that the secretions of the normal gastric mucous membrane alone, or through their action on food proteins, can produce some substance capable on oral administra-

tion of definitely benefiting certain cases of pernicious anemia. It is then possible that the achylia gastrica of the pernicious anemia patient is operative in the production of a deficiency causing the disease through a failure of the patient's stomach to produce the substance apparently formed during digestion in the normal stomach.

*Liver Fractions in Pernicious Anemia.* By R. WEST and (by invitation) E. G. NICHOLS, New York City, N. Y.

We have shown that a 60 per cent alcoholic extract of liver is efficacious in raising the blood count in patients suffering from pernicious anemia.

The alcoholic extract was next evaporated to dryness in vacuo, dissolved in water, saturated with solid ammonium sulphate. The precipitate was found to be inert, and the filtrate active. The ammonium sulphate was removed by adding alcohol up to 70 per cent to the filtrate and the resulting filtrate evaporated to dryness. A patient placed on 1.6 grams of this material a day showed a prompt response, the reticulocytes rising to 190,000 per cubic millimeter.

At this point the Committee on Pernicious Anemia of the Harvard Medical School had the Eli Lilly Company furnish us with material which was being manufactured by them according to the method of Cohn and his collaborators.

We first prepared some material by this method in our own laboratory, and cleared it with basic lead acetate. The lead acetate filtrate, after removing the lead, was precipitated with Kahlbaums phosphotungstic acid, and the precipitate decomposed in 75 per cent acetone with hot baryta. On feeding 4.5 grams daily of this material to a patient there was a marked response, reticulocytes rising to about 200,000.

Subsequent material was prepared from the Eli Lilly extract, through lead and phosphotungstic acid. The decomposed phosphotungstic precipitate was fractionated by Kossel's silver method. The two precipitates ("Histidine" and "Arginine" fractions) were combined, decomposed with $H_2S$, and fed with no response in doses of 620 mgm. daily for ten days.

The silver filtrate ("Lysine" fraction) was reprecipitated with phosphotungstic acid, the precipitate decomposed and fed to a patient in doses of 240 mgm. daily. The reticulocytes rose to 140,000 per cubic millimeter and the red cells 800,000 in ten days, the red cells starting at 1,600,000. A second patient has shown a similar response on this fraction.

The last fraction gives a buret reaction, a diazo reaction, a weak Hopkins-Cole reaction, N 11.9 per cent, $NH_2N$ 20 per cent of total N, traces of sulphur and no phosphorus. Negative results have been obtained with pure choline, and a mercuric sulphate precipitate of a 60 per cent alcohol extract of liver, also a probable negative with glutathione.

We wish to thank Dr. Minot and Dr. Cohn for placing the extract and their results at our disposal, and Dr. H. D. Dakin for invaluable advice.

*The Effect of Hyperthyroidism on the Total Blood Count.* By HARRY BLOTNER, REGINALD FITZ, and WILLIAM P. MURPHY, Boston, Mass.

A few years ago Thompson showed that the plasma volume is diminished in myxedema. We attempted to study the converse of his work by studying the plasma volume in hyperthyroidism. We at once became interested in the behavior of the red cell count. It appeared that the ordinary method for counting red cells is relatively inaccurate; the blood count is expressed in corpuscles per volume of blood without taking into consideration differences in total blood volume which may occur, or differences in individual body size and shape. We made, therefore, total red blood counts expressed in trillion red cells circulating per square meter of surface area. When so expressed, patients with a low metabolic rate appear to have a low total red blood count which increases in almost direct proportion to an increasing metabolic rate. Patients with hyperthyroidism have a high total red count. The rising total red count which parallels a rising metabolic rate in thyroid disorders is very similar to the rising red count found in pernicious anemia cases under treatment with liver. It appears, therefore, that the rate of metabolism may have an appreciable effect upon the total red count. Our data bring to mind the possibility that the factor of stimulation of the metabolism of the blood forming tissues may be one possible factor in the beneficial effect of liver in pernicious anemia, although before this point can be particularly stressed, further observations are necessary.

*The Chloride, Base and Nitrogen Content of Gastric Juice After Histamine Stimulation.* By W. SCOTT POLLAND and A. M. ROBERTS (by invitation) and A. L. BLOOMFIELD, San Francisco, Calif.

See published article, JOUR. CLIN. INVEST., 1928, v, 611.

*Histologic Studies on the Small Peripheral Arteries and Arterioles in Ambulatory Cases of High Blood Pressure.* By J. W. KERNOHAN and E. W. ANDERSON (by invitation), and N. M. KEITH, Rochester, Minn.

Tissues taken at autopsy from cases of malignant hypertension showed, as the significant histologic picture, a diffuse arteriolar lesion. This suggested further study of the smaller vessels in tissue obtained from ambulatory patients with high blood pressure. The biopsy material was obtained from the pectoral muscle. The histologic study of the arterioles in this tissue form the basis of this report. All cases show marked thickening of the walls of the smaller arteries and arterioles, especially hypertrophy of the muscular elements of the media and also hypertrophy of the internal elastic lamina. Perivascular fibrosis is not constant. There seem to be different degrees of hyperplasia of the lining endothelium of these vessels but the hyperplasia is not particularly constant in cases of malignant hypertension. This finding agrees with that previously reported in autopsy cases. An attempt has been made to relate the microscopic findings in these cases with the ophthalmoscopic examination of the retinal arteries, the appearance of the nail-fold capillaries and other clinical findings.

*Obliterative Bronchiolitis Occurring with Advanced Kidney Disease.* By ERNEST G. STILLMAN and (by invitation) WILHELM E. EHRICH and JOHN F. MCINTOSH, New York City, N. Y.

Three cases of advanced kidney disease which died in uremia have shown at autopsy serositis of body cavities, and patches of fresh bronchopneumonia. In addition, older lesions are observed, showing three different stages of an organizing process in the bronchioles and alveoli. In the first case, degenerated exudate is surrounded and penetrated by young connective tissue cells, apparently not more than fourteen days old. In the second, the bronchioles and adjacent alveoli are filled with young connective tissue, rich in fibroblasts. The lumen is often entirely filled. These lesions are two to four weeks old. In the third, the connective tissue is more mature. It is not accompanied by round-cell infiltration.

In the third case, the condition was observed in x-ray pictures before death. It appeared as recticular markings in the hylus region. The appearance is striking and characteristic. It has been observed in two other cases of advanced nephritis.

The pathologic picture differs materially from that of bronchiolitis obliterans following the infectious diseases, and the inhalation of poisonous gases. It has not been previously described. It may be referred to the same underlying cause as the organizing pericarditis and pleurisy of uremia, and probably has the same prognostic significance.

*The Relation of Urea to Nitrogen Metabolism.* By J. P. PETERS and (by invitation) DAVID D. MOORE, New Haven, Conn.

In the course of certain studies of nitrogen metabolism in chronic nephritis with edema in which both stools and urine were analyzed, it was found that, when large doses of urea were administered for diuretic purposes, the extra nitrogen thus given could not be entirely recovered. The doses of urea given varied from 20 to 80 grams daily and the amount of unrecovered nitrogen was very large. The lost nitrogen could not be explained by increases of non-protein nitrogen in the blood which were minimal. Furthermore, there was no evidence in subsequent periods of the sweeping out of previously retained nitrogen.

In order to determine whether its ability to spare nitrogen was characteristic of nephritis, a normal individual was given a diet containing 75 grams of protein and 3000 calories daily for 24 days and in addition during the second 7 days was given 40 grams of urea daily. Stools and urine were analyzed throughout for nitrogen. During the first period perfect nitrogen equilibrium was secured. During the second period 42 grams of nitrogen were not recovered. At the end of this period nitrogen equilibrium was restored within 48 hours and maintained for a total of 10 days. The non-protein nitrogen of the blood and the weight of the subject did not vary significantly in the course of the experiment.

Experimental evidence that urea could be utilized by the body has been presented frequently. In these experiments, most of which were carried out on

animals, urea has been substituted for nutritive nitrogenous foods. In our experiments it has been added to an already adequate diet. Addis was unable to recover all the urea administered to normal individuals within 48 hours after it had been given, although the urea excretion had apparently returned to the normal level.

If such large quantities of urea can be retained in the body without affecting the non-protein nitrogen of the blood, current theories which claim that urea is equally distributed throughout the fluids of the body, are untenable. Furthermore, one should expect nitrogen thus retained to be swept out in subsequent periods if urea is, as has been generally believed, an obligatory waste end product of metabolism which must be excreted.

Other studies aimed to determine more accurately the fate of urea are being undertaken.

*An Analysis of the Adrenalin Reaction and Its Relation to the Blood Chemistry etc.* By WILLIAM F. PETERSEN, Chicago, Ill.

The effect of adrenalin on the blood pressure has been studied in 100 so-called normal individuals, as well as in some 75 patients and the results of the systolic blood pressure correlated with blood chemistry (calcium, potassium, phosphate, sugar, etc.) as well as with the basal metabolism, the albumin-globulin ratio and the physical examination of the patient. In addition, the reaction of the skin to pharmacological substances has been followed in the same patients. The range of the reaction for the normal, as well as for the exaggerated reactions of the vagotonic and sympaticotonic individuals has been determined.

*Physiological Factors Influencing Inorganic Salt Secretion.* By RAY FARQUHARSON, and WILLIAM SALTER, (by invitation) and JOSEPH C. AUB, Boston, Mass.

Four patients were studied to determine the effects of exercise, change of diet and ingestion of acid and base upon their inorganic salt secretion.

We determined the calcium, phosphorus and total base of urine and feces, the ammonia, titratable acid, chlorides, sulphates and nitrogen in the urine, and the serum calcium, phosphorus, carbon dioxide and protein. The diet was then varied from a neutral to an acid diet and periods with alkalies, ammonium chloride and acid phosphates were given. The effect of rest in bed was also studied.

The results demonstrate the extent of physiological changes which may occur in the organism with respect to inorganic salt secretion. The importance of such observations as a basis for the study of abnormal conditions is obvious.

*Pleural and Pulmonary Lesions in Rheumatic Fever.* By JOHN R. PAUL, Philadelphia, Pa.

The study reported below is essentially a pathological one based upon material from a series of 28 autopsies, performed upon patients who died in the active stages of rheumatic fever. The basis of selection of these cases was the

finding of pathological evidences of rheumatic activity, including the presence of the Aschoff nodule in the myocardium. We will mention but four of the many lesions which the lungs have shown, i.e., (1) atelectasis, (2) rheumatic pleurisy, (3) vascular lesions, and (4) an unusual type of hemorrhagic bronchopneumonia.

1. Pulmonary atelectasis: Varying degrees of atelectasis involving the dependent portions of both lungs but particularly the left lung proved to be an almost constant findings. We have concluded, as have many others, that the physical signs elicited from these chests such as dullness to percussion, suppression of breath sounds and even bronchial breathing are often not due in these cases to large areas of consolidation but rather to pulmonary atelectasis, for which a number of factors seem to be responsible. Primarily, we have the accumulation of pleural fluid, generally as a result of an active although possibly insignificant pleurisy. More important, however, is the presence of an enlarged pericardial sac which often exerts pressure upon the left lower lobe and may play a rôle in retarding the movements of the left diaphragm. The combination of these factors and perhaps others, often results in complete atelectasis of the left lower lobe.

2. Pleurisy: This was noted in 60 per cent of our cases. The lesions resembles rheumatic pericarditis although as a rule it is less extensive and far less serious. It has been said to represent an extension of the pericardial lesion to the pleura although in two of our cases severe pleurisy was found in the absence of pericarditis. It generally gives rise to the accumulation of pleural fluid rich in fibrin, recalling the picture usually seen in tuberculous pleurisy with effusion. We do not find a thickened hyalinized pleura as in the end stages of the latter. Studies of the cellular content of these fluids may show wide variations, but as a rule polynuclears are scarce whereas mononuclear and particularly desquamated endothelial cells are numerous. Of the many bacteriological studies we have made, all have proved to be essentially negative.

Histogically the picture of the pleural lesion resembles that of the pericardium; and is characterized first by swelling of the endothelial cells, secondly, by further evidence of metaplasia and thirdly, by cell death.

3. Vascular lesions: These are also specific manifestations of the disease and have been described by Pappenheimer and VonGlahn. They were detected in 30 per cent of our cases. The lesion is essentially a panarteritis with primary involvement of the vascular endothelium and may be widespread throughout the lungs.

4. Hemorrhagic bronchopneumonia: This was a frequent finding in patients under twenty years of age and was noted in more than half of the cases. It is characterized by the presence of multiple hemorrhagic foci in the lung. Grossly and histologically the picture recalls that of the hemorrhagic stage of an early lobular pneumonia in which red blood cells and fibrin are found within the alveoli. We have, however, repeatedly failed to demonstrate bacteria in association with these hemorrhagic areas, thus differentiating the picture from the usual type of

early bronchopneumonia. In spite of our negative bacteriological studies it may be relatively non-specific, representing a pneumonia occurring in a lung in which there is marked circulatory stasis; but its focal nature has suggested that it may be a purpuric manifestation.

Frank early lobular pneumonia of proven bacterial origin has been a relatively uncommon finding in our series.

*A Study of Prolonged Auriculo-ventricular Conduction in Rheumatic Fever.* By ROBERT L. LEVY and (by invitation) KENNETH B. TURNER, New York City, N. Y.

A comparison has been made of the incidence of prolonged A-V conduction in rheumatic fever and in other diseases. The material is taken from a general medical service during a ten year period. The following points are made: (1) prolonged A-V conduction is an important criterion in the recognition and differential diagnosis of rheumatic carditis; (2) prolonged conduction may afford evidence of the presence of myocardial lesions long after the clinical signs of rheumatic disease have subsided; (3) in four cases, prolonged conduction has been found during or shortly after an attack of acute tonsillitis, in the absence of other evidence of rheumatic infection; (4) in certain instances, there appears to be a definite relationship between variations in conduction time and salicylate medication. In these cases, salicylate apparently exerts a favorable effect upon the lesions in the heart muscle.

*Observations on Goitre in Laboratory Rabbits.* By ALAN M. CHESNEY, and (by invitation) BRUCE WEBSTER and THOMAS A CLAWSON.

A high incidence of goitre has been observed in a series of 486 rabbits which were used for the study of experimental syphilis and have been under observation for varying intervals from September 1924 until the present time. The frequency and extent of the condition have been such as to warrant the use of the term "endemic goiter." The animals were fed upon a standard diet of oats, cabbage and hay, and were not given water to drink. The development of the goitre was not related to any particular breed of rabbits, but was definitely related to the time the animals had been caged. It developed in non-syphilitic as well as in syphilitic rabbits.

The enlargement of the gland was diffuse and involved isthmus as well as both lobes. The glands were vascular and histologically showed marked hyperplasia with relative scarcity of colloid. In a few, foci of lymphocytic infiltration were observed. Many of the animals died in a cachectic state, without signs of terminal infection and in these the absence of body fat was striking.

The heat production in the goitrous animals was found to be 16 per cent below that of "normal" rabbits on the average. Some animals showed a rising metabolic rate prior to death. The administration of Lugol's solution by mouth in doses of 1 minim per day was followed by a prompt rise in the metabolic rate,

rapid loss of weight and death within a few days. Examination of the glands of these animals suggested that newly-formed colloid had been laid down in the acini. Similar reactions were not obtained when iodine was administered to normal rabbits.

*Dilution of Blood and Cerebrospinal Fluid in Fever.* By FRANK FREMONT-SMITH, and (by invitation) MARY ELIZABETH DAILEY, and GILES W. THOMAS, Boston, Mass.

Comparative studies of human plasma and cerebrospinal fluid, started in 1924, demonstrate that the low concentration of chloride in the cerebrospinal fluid in acute meningitis is a reflection of the marked diminution of plasma chlorides found in these cases. Further studies show that the plasma chloride is diminished in many of the acute infections, including pneumonia, typhoid fever, septicemia, acute tonsillitis, acute rheumatic fever, malaria, etc., and that low spinal fluid chloride occurs in such cases in the absence of meningitis. Thus diminution in spinal fluid chloride in meningitis reflects the low plasma chloride values regularly accompanying the onset of many acute infections. During the past few months the acute febrile response to intravenous injection of typhoid vaccine has been studied ten times in a group of five patients. Blood and spinal fluid were obtained fasting, immediately before the vaccine injection, and at the height of febrile reaction. The following determinations were made on the serum and spinal fluid: Specific gravity, total solids, freezing point, chloride protein, sugar, non-protein nitrogen. At the height of these fevers there has occurred in the serum consistent and significant diminution in specific gravity, total solids, chloride, protein and in the total osmotic pressure (as shown by the freezing point) while the spinal fluid has shown similar but less marked changes.

These changes indicate a dilution of the blood plasma and of the cerebrospinal fluid at the onset of the acute febrile reactions to typhoid vaccine injections and are analogous to the changes found in many acute infections. The results are consistent with the increased plasma volume in fever, recently reported by Soule, Buckman, and Darrow.

A discussion of the mechanism involved in this dilution, and its clinical significance is offered.

*The Occurrence of Pneumococcidal-promoting Properties in the Serum of Type I Lobar Pneumonia Following Immune Serum Therapy.* By O. H. ROBERTSON and (by invitation) RICHARD H. P. SIA, Chicago, Ill.

The present work consists of an extension of former studies in which it was found that the blood serum of both animals and human beings recovering from pneumococcus infection acquires the property of promoting the destruction of virulent pneumococci by rabbit serum and leucocytes when added to such a mixture in relatively small amounts. In the case of experimental animals this change in the serum was shown to be associated with increased immunity. Following

the injection of specific antipneumococcus serum in cases of lobar pneumonia due to Pneumococcus Type I, the serum was found to acquire these same properties. A striking difference, however, was observed between the spontaneously recovering and the treated cases in respect to the curve of the titer of pneumococcidal-promoting substances. In the former cases the appearance of these bodies was followed promptly by recovery; in the latter the disease frequently persisted for some days in spite of the presence of a high concentration of immune substances in the serum. This phenomenon is discussed.

*The Relation of the Hyperglycemia to the Renal Threshold in Older Diabetics and Its Clinical Significance.* By ALBERT A. EPSTEIN, New York City, N. Y.

In the resting or fasting stage of the normal individual the blood sugar level is maintained by two factors, namely, sugar mobilization and sugar utilization. After feeding, the sugar level rises and the curve which the hyperglycemia follows is small in amplitude and of short duration.

In the resting stage of the diabetic the blood sugar level depends upon three factors, namely, sugar mobilization, suger utilization, and sugar excretion. After feeding, the level of the blood sugar rises sharply and the hyperglycemia is of long duration.

*There is a distinct difference in the curves of the blood sugar levels of early and late diabetes.* This difference is ascribed to a change in the renal threshold for sugar. The relation of the renal threshold to the blood sugar level is of two-fold character. On the one hand, interference with the excretion of sugar (renal impermeability) causes a progressive rise in the blood sugar level; on the other, readjustment of the level of carbohydrate utilization in which the kidney participates (renal tolerance) leads to an elevation of the blood sugar which remains constant and represents a condition in which a balance between the rate of sugar mobilization and sugar utilization throughout the body has been established.

The differences which early and late cases of diabetes show in their reaction to insulin with respect to the blood sugar level indicate that the persistent hyperglycemia in older or late diabetics is the result of a conservative process and represents an altered state in carbohydrate metabolism. Recognition of this fact is important in the interpretation of the blood sugar findings in the different stages of diabetes and in the application of insulin in its therapy.

*On the Significance of the Respiratory Quotient after Carbohydrate Ingestion.* By WALTER R. CAMPBELL and (by invitation) S. SOSKIN, and E. J. MALTBY, Toronto, Canada.

With the respiration calorimeter of Macleod we have confirmed on dogs the differences recently reported in the "respiratory quotient" after administration of glucose and dihydroxyacetone. After administration of 25 grams glucose the respiratory quotient rises gradually to a maximum value of one, then gradually decreases, while after dihydroxyacetone it rises sharply to a maximal value often

exceeding unity in the first half hour or hour and then declines to the initial value. In each case oxygen consumption increases in the first or second hour but the average consumption for four hours is identical with that of the control periods. The greatest difference between the two sugars is the large increase in $CO_2$ excretion immediately following dihydroxyacetone administration. This indicates hyperventilation.

With the administration of dihydroxyacetone, fructose and sucrose to man the $CO_2$ combining power of the plasma falls markedly, due to lactic acid production. The lactic acid production and consequent release of $CO_2$ from the blood and tissues and the later destruction of lactic acid accounts for the rapid rise in R.Q. and its later fall. The so-called respiratory quotient, therefore, is of no value in confirming utilization of these sugars. Glucose, maltose, lactose, and glycerine cause no change in the $CO_2$ combining power or blood lactic acid and the $CO_2/O_2$ ratio represents more nearly a combustion ratio.

*A Comparison of the Thresholds of Ketosis in Diabetes, Epilepsy and Obesity.* By EUGENE F. DU BOIS, and (by invitation) WALTER S. MCCLELLAN and HENRY J. SPENCER, New York City, N. Y.

Many observations have been made during the past decade with the calorimeter of the Russell Sage Institute of Pathology to determine the food materials metabolized and the appearance and degree of ketosis. Recently detailed studies were made of six men. Two artic exploreres and one laboratory worker, took exclusive meat diets, one for 90 days, one for 53 days and one the laboratory worker for 10 days. Also one obese man was observed for 118 days, one epileptic for 84 days, and one diabetic for 99 days. The latter group received only small amounts of carbohydrate in the diet.

The average respiratory quotient of 24 basal observations was 0.761 and of 16 observations following food was 0.751. It is doubtful if any group of subjects has been observed in such a steady state of metabolism for such long periods.

The threshold of ketosis, as determined for periods of 3 to 30 days, was found to be at an FA/G ratio of 1.5 (Woodyatt) for all except the obese man whose threshold was approximately at an FA/G ratio of 2.4. When studied for the actual short periods in the calorimeter the threshold was at a ratio of 1.0 for the general group and for the obese man no definite level was observed. The obese man never exceeded an excretion of 0.5 grams of acetone bodies per day.

Individual variations in acetone excretion were noted, due, possibly, to varying amounts of protein and fat eaten, or to the nature of the fat taken or to an adaptation evidenced by a decreasing ketosis over long periods.

The FA/G ratios for periods plotted against the acetone excretion, excluding the data of the obese man, suggest the existence of a logarithmic curve. If any adaptation occurs over long periods a logarithmic curve will not be found.

*Metabolic Disturbances in White Snake Root Poisoning.* By H. A. BULGER, and F. M. SMITH (by invitation) and D. P. BARR, St. Louis.

It is now well established that the disease known as "milk sick" is caused by the injection of milk from cows feeding on white snake root (*Eupatorium urticalifolium*). Preliminary experiments on animals poisoned by this plant have indicated that such studies present a new field for the investigation of ketosis and of fat and carbohydrate metabolism. They also suggest the cause of certain clinical features of "milk sick" and indicate rational treatment of this mysterious malady. We have found that it is ordinarily impossible to produce more than a slight ketosis in rabbits. When poisoned with white snake root they developed a marked acetonemia and acetonuria. Hypoglycemia was a prominent feature of the intoxication in these rabbits; most animals died with hypoglycemic convulsions. Another prominent feature was a lipemia which may be extreme. Glucose followed by a high carbohydrate diet apparently restored the animals to health. The fatigue and rapid recurrence of symptoms following exertion in "milk sick," the coma and occasional convulsions suggest a relationship to hypoglycemia.

*The Isolation and Purification of a New Reducing Urinary Compound.* By HILDING BERGLUND and (by invitation) GRACE MEDES and ANNE LOHMANN, Minneapolis, Minn.

*The Circulation in the Pneumonic Lung as Studied by Means of Temperature Measurements during Diathermy.* By CARL A. L. BINGER, and (by invitation) RONALD V. CHRISTIE, and WILHELM EHRICH, New York City, N. Y.

Previous studies have shown us that the lung of the normal dog can be heated only slightly (0.4°C.) above the systemic temperature. The cooling mechanism which dissipates the heat and prevents its localization in the lung was found to depend upon the pulmonary circulation rather than upon ingress and egress of air through the trachea and bronchi.

In this study an experimental pneumonia was produced in dogs by the insufflation of pneumococci and of *B. Friedlaenderi.* The temperature of the consolidated and normal lobes was measured by thermocouples while high frequency currents were passed through the dogs' thoraces. It was found that the pneumonic lobe was heated slightly (1° to 2°C.) above the systemic temperature and the temperature of the normal lobes. The change was of the same order of magnitude as seen in lungs with obstructed pulmonary arteries.

The experimental data were correlated with the gross and histologic appearance of the lungs, which furnished an explanation for the heat retention on the basis of an impaired circulation. This appeared to be due to the pressure of the intra-alveolar exudate which resulted in an ischemic state in which the alveolar capillaries were empty of blood. The impairment of the circulation was further substantiated by post-mortem barium-gelatin injection preparations, which showed

in several specimens that the region in which the vascular tree remained poorly injected corresponded to the area of consolidation.

*Hypercalcemia in Cases of Polycythemia Vera.* By GEORGE E. BROWN, and (by invitation) GRACE M. ROTH.

The variation in the calcium content in normal subjects is relatively narrow. Lowered values have been found in certain diseases; increased values are rare, but have been reported by Coates and Raimont in gout and have been confirmed by Horowitz.

In fourteen cases of polycythemia vera the serum calcium varied from 11.1 to 18.1 mgm. for each 100 cc. of blood. The average value was 14.3; in six cases the values were 15 mgm. or more. The calcium content of the whole blood averaged 5 mgm. for each 100 cc. of blood, a normal value.

Following treatment with phenylhydrazine hydrochloride, a decrease occurred in the percentage and total calcium content of the serum in every case. In no instance did the calcium decrease below the accepted normal level. Determinations of the sodium, potassium, magnesium, phosphate and chloride in the serum and whole blood were made in five cases. Abnormally high values for the serum potassium were obtained in two cases, which dropped to a normal level after treatment.

The explanation of the hypercalcemia is not clear. It may be secondary to or compensatory to the increase in the concentration of the serum potassium. The apparent increased calcification in the peripheral vessels and the susceptibility to thrombosis in cases of polycythemia vera may be related to increased calcium content.

*The Effect of the Digitalis Bodies on the Velocity of Blood Flow of Normal Subjects and of Patients with Cardiovascular Disease.* By SOMA WEISS, Boston, Mass.

The immediate and late effects of strophanthin and digitalis on the circulation were studied on seven normal persons, and on fifteen patients suffering from cardiovascular disease. Strophanthin of tested physiological potency (0.14 mgm. = 1 cat unit) was administered intravenously from two to twenty-four hours previous to the circulatory measurements. Tested tincture of digitalis was administered by mouth, and evidence of digitalis effect was reached within twenty-four to forty-eight hours after the first dose. The velocity of pulmonary and peripheral venous blood flow was measured before and after the administration of digitalis by the "radioactive method" described.

The patients studied exhibited both regular and totally irregular cardiac rhythm and before the administration of digitalis, they rested in bed until no evidence of spontaneous improvement could be noted. The degree of circulatory failure varied considerably.

In normal subjects the velocity of pulmonary and venous blood flow showed no definite change as a result of the administration of strophanthin or digitalis.

With the exception of three patients, the velocity of the pulmonary and of the venous blood flow after strophanthin or digitalis was either unchanged or increased in all the patients with cardiovascular disease. Although the average cardiac rate showed a reduction (10 per cent) the average velocity of pulmonary blood flow increased 35 per cent and that of the peripheral venous blood flow by 40 per cent. In all the patients in whom digitalis caused a definite improvement in the clinical behavior, the velocity of blood flow was definitely increased. The other three patients showed a slowing (20 per cent) of the pulmonary flow, with no change in the velocity of the venous blood flow. Proportionate to the slowing in the pulmonary blood flow there was a reduction in the pulse rate.

The observations by others that digitalis decreases the minute volume output, and the finding that it has no effect or that it increases the velocity of blood flow can be reconciled only if digitalis decreases the cross sectional area of the vascular bed, under which condition unchanged velocity would inevitably yield a decreased minute volume. Blood volume studies in addition to the measurements of the velocity of blood flow were performed on several patients in order to clarify this problem.

*The Initial Effect of Moderate Undernutrition upon the Weight Curve in the Obese.* By MARK FALCON-LESSES, (by invitation) and L. H. NEWBURGH, Ann Arbor, Mich.

The initial effect, upon the weight curve in the obese, of the shift from a maintenance diet to one of moderate undernutrition is the production of a tri-phasic curve. The three phases occur as follows: (1) The first phase is one of excessive weight loss lasting from two to seven days. (2) The second phase is one of weight maintenance and failure to lose weight, despite the sub-maintenance calories—lasting five to fifteen days. (3) The third phase is one of excessive weight loss lasting two or three days. This tri-phasic curve does not occur if the caloric value of the diet is excessively sub-maintenance but it has been produced in every obese person so far studied.

The first phase seems intimately connected with the katabolism of glycogen, since it occurred when the subjects were in nitrogen balance and the weight losses were much too great to be accounted for by the katabolism of fat.

The second phase is one of hydration due to the retention of water as shown by water-balance studies.

The third phase is one of dehydration, apparently due to the loss of the excess water stored up during the weight-holding period. At the end of the third phase, the weight is exactly where it should be as calculated from the theoretical weight loss.

*The Rôle of Carbohydrate in Obesity. With Special Reference to the Treatment of Obesity Complicated by Hypertension and Cardiac Disorders.* By BURGESS GORDON, and (by invitation) C. W. NISSLER, Philadelphia, Pa.

Various factors such as hereditary influences, habits of living and types of food consumed were studied in a group of 328 obese patients. The data suggest that although the tendency to overweight may be present, the customary intake of food is important. It appears that the total intake at meal time varies between 575 and 3000 calories. This intake, however, is usually augmented by additional food between meals. In estimating the amount of food consumed during a period of one week the average daily intake was found to be increased about 15 per cent above the portion tabulated on certain days. This variation, suggested in the daily recording of food and symptoms, is due apparently to fatigue, hunger and weakness. The symptoms were noted, especially during exercise, on days when a small amount of carbohydrate was consumed.

The possibility that hypersecretion of the pancreas or some disturbance in the storage and utilization of carbohydrate may account for certain hypoglycemic-like symptoms was suggested in the following hypothesis: The excessive intake of starch to satisfy the natural desire for food or to relieve hypoglycemic-like symptoms results in stimulation of the pancreas. The continued over-secretion of the pancreas tends to cause further hypoglycemia, which results in the greater intake of carbohydrate and thus the body weight is increased.

A group of male patients exercised on a stationary bicycle from one to five hours, showed a fairly constant lowering of the blood sugar (limits, 130 to 80 mgm.) In some instances mild hypoglycemic-like symptoms occurred, which were relieved by the administration of dextrose. The response of the blood sugar in a small group of women was inconstant. Hyperglycemia was noted in some instances, although the patients experienced fatigue, hunger and weakness. The favorable effect following the administration of dextrose, suggested the possibility that reducing substances other than dextrose may have been mobilized in the blood stream.

In view of the difficulty of understanding the relation between the level of the blood sugar and the onset of various symptoms, the so-called dextrose moderately low caloric diet was devised. The regime is as follows: during a period of six days the patient tabulates accurately the occurrence of symptoms and the food consumed at meal time and between meals. The total intake of carbohydrate at meal time is then reduced about one-third (no change is made in the usual consumption of fat or protein). Dextrose in 2 to 4 gram doses is administered between meals to relieve all symptoms. In a majority of patients weight is lost effectively and the occurrence of symptoms is decreased, suggesting that the sugar regulating mechanism may have been restored to normal. In a small group of obese patients with circulatory disorders a reduction of the blood sugar and improved circulation was noted. Although this could be attributed to the loss of weight, it seemed, in some instances, that dizziness, weakness and other phenomena may have been due in part to some disturbance in the storage and utilization of carbohydrate.

*Experimental Leukocytosis and Leukopenia.* By PAUL REZNIKOFF, New York City, N. Y.

Recent investigations of Minot, Murphy and Cohn indicate that erythrocytic stimulation by chemical means is possible. Doan and his coworkers have presented evidence that myelocytic stimulation may also be induced by nucleoproteins and nucleotides. They obtained a preliminary leukopenia with nucleoprotein which they ascribed to the activity of the spleen but with nucleotides an immediate leukocytosis occurred.

In the experiments reported here, nucleoprotein from liver and thymus (Dr. John A Mandel), nucleic acid from yeast and thymus (Dr. Mary V. Buell, Dr. P. A. Levene), and adenine sulphate and guanine hydrochloride (Mr. Kenneth Blanchard, Dr. Henry Jackson, Jr.) were injected intravenously into rabbits. When solutions of these substances in phosphate buffers were introduced, a leukopenia occurred, at first of the myelocytic forms and then, of the lymphocytes. The myelocytic leukopenia was of short duration and was succeeded by a marked and sustained polynucleosis. Increases in total cell count from 20,000 to 79,000 have been obtained with no apparent ill effects. Solutions of phosphates caused a marked lymphocytic leukopenia. This did not occur with NaCl or aqueous solutions containing no inorganic phosphate. During the state of polynucleosis a marked shift to the left took place, indicating increased young cell formation or marked chemotaxis.

*The Development of the Ethyl Iodide Method for Determining the Cardiac Output of Man; a Test of the Method by Estimations of Flow through Dogs' Lungs Perfused at a Known Rate.* By ISAAC STARR, JR., and (by invitation) CLARENCE JAMES GAMBLE, Philadelphia, Pa.

In anesthetized dogs, the ethyl iodide content in mixed venous blood does not change materially during rebreathing. The ethyl iodide content estimated from rebreathed air and the coefficient of distribution agrees with that found by analysis of mixed venous blood taken before rebreathing started. The content in arterial blood agrees with the value calculated from alveolar air. This permitted the measurement of flow by ethyl iodide while perfusing dogs' lungs at a known rate, satisfactory agreement resulting in five of six experiments.

In normal persons breathing ethyl iodide the arterial content (by analysis) is correctly estimated from alveolar air collected automatically. The ethyl iodide content in rebreathed air remains constant or falls very slowly during rebreathing for 1½ minutes, therefore we believe the content in mixed venous blood can be estimated as in dogs.

The technique for the determination of blood flow in man is that of Henderson and Haggard, followed by rebreathing for thirty seconds, and determining the subject's distribution coefficient, (average normal blood = 6.1). Consecutive estimations on subject G. reclining on three days = 3.9; 4.1, 4.0, 4.1; 4.0, 3.9, 3.9. On S. (on three days) 5.3, 4.9, 4.1; 3.4, 4.6, 3.3; 3.0, 2.9, 3.5 liters per minute.

*The Erethitic and Kolytic Types of Temperament and Their Relation to the Process of Excitation and Inhibition.* By J. RAMSAY HUNT, New York City, N. Y.

The purpose of this study is to emphasize the fundamental importance of the processes of excitation and inhibition, in determining questions of temperament and psychological type, and to show that there is an excitatory or *erethitic* (Erethizo—"Excite," "provoke") and an inhibitory or *kolytic type* (Kolyo—"Prevent," "check") based on the predominance of one or other of these functions in the psychic sphere.

In human beings, while the processes of excitation and inhibition share in all neural functioning, it is perfectly evident that some individuals are more excitable and others are more inhibitable, in their relations to environmental and other forms of stimuli.

In any psychological organization of the excitable type this tendency would be increased by use, and habit formation, and the same would hold true for the inhibitable type.

The *erethitic temperament* is an active one, characterized by great activity of mind and body. Such types are easily excited, very responsive, impulsive, highly emotional and quick tempered. They are many sided and have many interests and their psychic trend is objective rather than subjective. They are mercurial, inclined to be rash and hasty in action. The psychic tempo is rapid and there is a slight tendency to distractibility. The general trend of this type is toward expression, and they are, as a rule, accessible and sociable.

The *kolytic temperament*, on the other hand, is more calm and controlled, with a tendency to passivity of mind and body. Such individuals compared with the erethitic appear cold, apathetic and indifferent. They are self-centered, often heavy and plodding, but when more energetic manifest a quiet concentration of power. They are slow tempered, self-centered and reflective with a tendency to subjectivity. The psychic tempo is slow.

The pathological extremes of these two types are mania and melancholia of the manic depressive psychosis.—On the one hand is mania, with its high degree of excitability of mind and body, the flight of ideas, exaltation of mood, and increase of psychomotility. At the other end of the scale is melancholia, with retardation of thought and action and depression of mind.

Certain general characteristics which are associated with the erethitic and kolytic types may also be recognized in the types of Jordan, Jung and Kretschmer, and the question arises whether the same fundamental processes are not represented in all, although the approach has been from an entirely different point of view.

*Studies in Cerebral Circulation: Vasodilator Mechanism.* By STANLEY COBB and (by invitation) H. G. WOLFF.

By direct examination of the cerebral vessels (pial) of the cat through a tightly sealed window, so constructed as to permit the removal of air and the injection

of fluids, accurate measurements of the vessels by micrometry and photography have been made. It has been determined that the cerebral vessels may show changes in diameter consistent with mere passive expansion or collapse, following abrupt rise or fall in arterial pressure. In addition, the arteries show changes exactly opposite in direction to these passive changes. These can be brought about by stimulation of constrictor or dilator nerves, and by alteration of the chemical and physical (osmotic tension) constitution of the blood.

It was concluded that the cerebral circulation is not altogether *passively* regulated, i.e., from a distance by splanchnic or general systemic vasoconstriction and dilatation. It is also dependent upon an active vasomotor mechanism for cerebral vessels, and by changes in the physical and chemical characteristics of the blood.

In addition to vasomotor, osmotic tension and drug actions, other dilator mechanisms have been studied. It has been determined that cerebral artery vasodilatation follows: (1) reduction in the quantity of arterial blood circulating through the brain (severe hemorrhage, clamping the carotid arteries, circulatory failure and increased intracranial pressure); (2) reduction in the oxygen content of the arterial blood circulating through the brain (carbon monoxide); (3) increase in carbon dioxide content of the arterial blood circulating through the brain; (4) intravenous injection of acid or acid producing substances (lactic acid, acetone).

Hypothetically, these experimental changes in the quantity and quality of the blood create a physiological emergency. They were always associated with cerebral vasodilatation.

*The Adaptation of the Circulation to Hyperthyroidism and to Hypothyroidism.* By HERMANN L. BLUMGART and (by invitation) SAMUEL L. GARGLE, Boston, Mass.

The purpose of the investigation was to learn in what manner and to what degree the circulation of blood is accelerated to enable the transport of larger quantities of oxygen to the over-active tissues of thyrotoxic patients. Ten thyrotoxic patients of different types have been studied. The basal metabolic rates range from plus 11 to plus 50 per cent. The speed of blood flow through the lungs was considerably faster than the average normal (10.8 seconds) in every patient studied. In some patients the velocity of blood flow was more than twice the normal. The velocity of venous blood flow from the arm to the heart was likewise greatly increased. The extent of increase of the velocity of blood flow and of the basal metabolic rate were in general, proportional. The vital capacity was reduced in all subjects even in the absence of any signs of congestive failure, an observation in accord with other studies. The conspicuous strain under which the heart labors even under basal conditions in maintaining such an increased velocity of blood flow is undoubtedly an important factor in causing frequent occurrence of heart failure in thyrotoxic states.

In hypothyroidism quite the reverse conditions are present. With lowering of the basal metabolic rate there is proportionate slowing of the blood flow. In one patient whose basal metabolic rate was minus 24 per cent, the velocity of blood flow was less than one-half the average normal speed of blood flow. Repeated measurements on this patient at various metabolic levels following thyroid medication showed corresponding speed of blood flow.

*The Arterial Supply of the Congenital Polycystic Kidney and Its Relation to the Clinical Picture.* By GEORGE BAEHR and (by invitation) SAUL A. RITTER, New York City, N. Y.

Although the clinical course of patients with congenital bilateral polycystic kidneys may be uneventful until late in adult life, occasional attacks of lumbar pain are commonly experienced, some of which may be followed by persistent hematuria. By injecting the arterial supply with a mixture of barium sulphate and gelatin according to a method devised by L. Gross and studying the injected organs by means of stereoroentgenograms after clearing the specimens with methyl salicylate, the explanation for the attacks of pain and hematuria becomes evident. The pain and hematuria are apparently caused by rupture of arteries of various sizes which in the polycystic organ come to lie in the walls of the cysts, and which often stretch across the lumen of the cystic cavities enveloped merely in a thin falciform fold of the cyst wall. Rupture of these overstretched arteries into a cyst cavity may be produced by trauma or as a result of arterial hypertension and local arteriosclerotic changes in the vessel wall. Rupture of a hemorrhagic cyst into a calyx produces hematuria. Rupture upon the surface of the kidney may result in a perirenal hematoma.

Sometime during adult life,—as early as the third decade or as late as the sixth decade, but usually the former,—sclerosis of the arterioles and small arteries of the kidney and perhaps other organs makes it appearance. This pathological process begins to manifest itself clinically in an arterial hypertension and cardiac hypertrophy. The earliest disturbance in renal function is usually a polyuria, nocturia and a fixation of specific gravity of the urine. Eventually, nitrogenous constitutents gradually increase in the blood and the terminal clinical picture of a dry uremia develops.

Except for the attacks of pain and hematuria, this sequence of events is indistinguishable from that observed in patients suffering from primary arteriolar sclerosis (malignant hypertension) and in patients in the late stages of chronic glomerulo-nephritis who have survived the period of nephritic edema. We believe we have demonstrated by means of arterial injections and microscopic study, that the clinical course of patients with congenital bilateral polycystic kidney is essentially the result of the same obliterative process in the arterioles and small arteries of the kidneys.

*Effect of Some of the Purin-base Diuretics upon the Coronary Flow.* By N. C. GILBERT and (by invitation) G. K. FENN, Chicago, Ill.

Previous experimental work has shown the purin-base diuretics to have a vasodilator effect upon the coronary arteries, and to increase the coronary flow. This has not been completely confirmed by all investigators, and the objection has been made that the doses used were larger than the human therapeutic doses.

Because of the beneficial therapeutic results, further experimental work was done upon the intact animal. Under different methods of anesthesia a modified Morovitz cannula was inserted into the coronary sinus and the volume flow measured by means of a piston recorder tracing on a revolving drum. The doses used were low average human equivalents, and fractions of these: Theobromine sodium salicylate and acetate 0.01 gm. per kilogram, theocine sodium acetate 0.0032 gm. per kilogram, caffeine sodium benzoate 0.0066 gm. per kilogram and euphyllin 0.0014 gm. per kilogram. A definitely increased coronary flow was obtained with each of these, in the presence of a decreased systolic and diastolic pressure. Except when an extreme vasodilatation was already present, the increased coronary flow was apparently constant, with these drugs. In the case of the theobromine salts, the increased flow resulted in some cases with one-eighth of the above doses. In the case of euphyllin, theocine, and caffeine, results with less than one-half of the above doses were uncertain. The effect of anesthetics used on coronary flow was considered. Chloretone was shown to have an extreme vasodilator action.

*Studies on Experimental Auricular Fibrillation Produced by Multiple Stimuli.* By ARTHUR D. HIRSCHFELDER, Minneapolis, Minn.

Auricular fibrillation can be produced in the exposed heart of the dog by stimulating either auricle with a single make and break shock thrown in rapid succession into three neighboring parts of the auricular wall. This is accomplished by means of three separate currents sent in rapid succession through four electrodes composed of blunt pointed copper wires about three millimeters apart, applied to the wall of the auricle.

The primary circuits to the three induction coils are made and broken by passing the current through a rapidly revolving drum covered with a perforated paper. As each perforation passes a spring wire which completes the circuit, the current is made and broken. Three perforations are located in an oblique row to insure sequence. A single cycle of three separate stimulations sets up circus movements which invariably produce auricular fibrillation. Fibrillation produced in this way often lasts much longer than that produced by ordinary faradization and frequently lasts from ten minutes to more than half an hour. Duration seems independent of cardiac weakness. Lasting fibrillation seemed to occur most commonly in slow hearts and in pilocarpinized animals. Stimuli to the auricle applied during sympathetic stimulation or after adrenalin following atropin, gave rise to fibrillation lasting only a few seconds. Further experiments are in progress.

*Heart Rate Studies with the Cardiotachometer.* By ERNST P. BOAS, and (by invitation) MORRIS M. WEISS, New York City, N. Y.

An instrument, named the Cardiotachometer, has been devised, by means of which the total number of heart beats may be counted over long periods of time while the subject under test is actively moving about. The action current of the heart is led off through two chest electrodes, green soap serving as an electrolyte, into a specially constructed amplifier. Leaving the amplifier, the current actuates a sensitive relay, which, in turn, operates an electromagnetic counter, and simultaneously records on a moving tape.

Patients are kept under test for from 20 to 24 hours. Normally during sleep the heart rate is 10 to 20 beats a minute lower than when the subject is at rest, but awake. In patients with functional tachycardias, the rate drops considerably during sleep, but does not sink to the same low level, which suggests that even during sleep the vegetative nervous system of these individuals is hyperirritable. Patients with rheumatic myocarditis and myocardial insufficiency show very little drop in rate during sleep. Patients with auricular fibrillation, whether digitalized or undigitalized, show a marked variability in ventricular rate during the day, and a considerable drop in rate during sleep.

The possible clinical applications of the cardiotachometer are manifold. Many physiological problems, such as the response of the heart to exercise, drugs, and other stimuli can be studied. As an accessory in many physiological and clinical examinations, such as basal metabolic rate and minute volume flow determinations, it is invaluable. It will for the first time give us an actual count of the total number of heart beats under the conditions and activities of every day life. It will be of particular value in determining the clinical significance of the simple tachycardias.

*The Effect of the Administration of Liver to Patients with Various Types of Anemia.* By CYRUS C. STURGIS, RAPHAEL ISAACS and (by invitation) MILLARD SMITH, Ann Arbor, Mich.

It has been observed that patients with pernicious anemia respond to the administration of liver by an increase in the hemoglobin and erythrocytes, which is preceded by a rise in the reticulocytes of the peripheral blood. It is important to determine if this is a specific reaction peculiar to pernicious anemia and if other tyes of anemia are benefited by liver therapy.

A few patients of a large series are presented as they have been studied intensively and the observations made are of special interest. The effect of liver feeding in the following patients was noted. One patient with *Dibothriocephalus latus* anemia made a complete recovery, although the parasite was not removed until the blood returned to normal. The response in this patient was entirely similar to that observed in a patient with pernicious anemia as there was increase in the number of reticulocytes and a return of the red blood count to normal after ½ pound of liver had been fed daily for two months. One patient with the anemia

of myxedema showed no improvement with the liver treatment; studies of the blood were made following the use of dried thyroid gland, and the red blood count observed to return gradually to normal limits. One patient with cancer of the prostate gland showed a striking increase in the reticulocytes and a rise in the erythrocyte count. It is entirely possible that this patient had cancer of the prostate gland and pernicious anemia. In a second patient with cancer of the prostate gland there was no respone to liver therapy. Two patients with leukemia showed no improvement. Liver was of no benefit in preventing the development of the anemia following the inoculation of patients with the malaria plasmodium for the treatment of general paresis.

*Whole Blood Immunity in Lobar Pneumonia.* By R. L. CECIL, and (by invitation) D. R. RHOADES, and W. D. SUTLIFF, Washington, D. C.

The pneumococcidal power of whole, uncoagulated blood has been measured. The method in brief consists in determining the number of pneumococci which 0.5 cc. of human blood will kill in 24 hours. Heparin is the anticoagulant used.

The number of pneumococci killed varied as follows:

(a) In ward patients with minor complaints and without a history of lobar pneumonia: from none to 10,000.

(b) In patients convalescing from lobar pneumonia: from 100,000 to 10,000,000.

The following changes were observed in lobar pneumonia:

1. In the acute stage pneumococcidal power is normal or less than normal.

2. When bacteriemia is present before the crisis, no pneumococcidal power is present.

3. Shortly before or at the time of crisis the pneumococcidal power of the whole blood becomes greater than normal.

4. The pneumococcidal power of the whole blood reaches its highest point after the crisis.

5. The simultaneous occurrence of bacteriemia (250 colonies of pneumococcus Type I per cubic centimeter of blood) and pneumococcidal power of high degree was encountered in a patient who developed acute pneumococcal endocarditis following Type I lobar pneumonia.

6. Felton's antipneumococcus serum was administered to pneumonia patients with normal or subnormal pneumococcidal power. Tests of these patient's blood made 24 hours after the injection of serum usually showed whole blood immunity fully as great as that found after spontaneous recovery from the disease.

*The Skin Temperature in Diabetes.* By HOWARD F. ROOT, Boston, Mass.

The temperature of the skin of 19 diabetics was determined by a method consisting of two copper constantan junctions, one located in a constant temperature bath—a Dewar flask—and the other applied to the skin. The resulting current, which is measured on a galvanometer, is proportional to the difference in temperature between the two junctions.

The measurements were made at the Carnegie Nutrition Laboratory in the afternoon. The subjects lay clothed on a suspended balance under one layer of blanket while their insensible perspiration was determined during one hour. The temperature measurements were then made under the clothing at various points, the room temperature being almost constantly at about 20°C.

The results show that diabetics have a considerable variation in skin temperature. Comparison with normal individuals is difficult owing to the lack of data. If the girl scout figures of Benedict are used, the diabetics have a somewhat lower surface temperature. Even under blanket covering, as great a variation in temperature was shown by case no. 2052, aged 23 years, as was found in the subject Miss L. after 2½ hours exposure to 14°C. In general, patients with more severe diabetes, who were thin, had very low skin temperatures in the lower extremities. No close correlation between skin temperature and metabolism or insensible perspiration was apparent, although it was notable that when the surface temperature of the extremities was low the insensible perspiration was also low.

*The Vitamin B Content of Malignant Tissue.* By HENRY JACKSON, JR., and (by invitation) C. I. KRANTZ, Boston, Mass.

It has been claimed by Burrows that cancer is due to a local excess of vitamin B in the tissues. If this be so, cancerous tissue should have a high vitamin B content. To test this point, human cancer was dried under precautions necessary to preserve its vitamin B content. Transplantable mouse carcinoma and normal mouse liver were similarly prepared. Rats of suitable age for testing the presence of vitamin were then fed on basic diets entirely free of vitamin B but adequate in other respects. Weighed amounts of dried human cancer, mouse cancer and mouse liver were fed to three series of these rats. A fourth series on vitamin free diet plus weighed amounts of Harris' vitamin B served as controls. From the weight curves obtained it would appear that human cancer contains very little vitamin B and mouse cancer contains considerably less than does normal mouse liver. These findings do not lend support to the theory that cancer may be due to a localized excess of vitamin B.

*The Effect on Epileptic Seizures of Varying the Composition of the Respired Air.* By WM. G. LENNOX, Boston, Mass.

In certain patients with epilepsy having very frequent minor seizures, we have found that seizures may be induced by having the patient breath an atmosphere containing a low percentage of oxygen. They may also be induced by overventilation. Both factors together will induce seizures more quickly than either alone. The opposite condition of breathing pure oxygen (or air under increased tension), or an atmosphere containing a high percentage of $CO_2$ will tend to inhibit seizures, a combination of the two conditions being more effective than either alone. These considerations, when combined with observations by Wolff and Lennox on the effect of similar procedures on the caliber of pial vessels, and with

previously reported studies of the effect of changes in acid-base relationships on epileptic seizures, permit a clearer analysis than has yet been possible of the physiological processes in the brain which contribute to seizures.

*Toxemia of Intestinal Obstruction, and Ileus: Clinical Deductions Regarding its Nature and Treatment.* By CHARLES S. MCVICAR and (by invitation) JAMES F. WEIR, Rochester, Minn.

Inhibition of gastro-intestinal motility, whether due to organic or functional causes, is attended with grave consequences. Death ensues if an organic obstruction persists and is equally a danger if functional inhibition is not relieved. Animal experimentation has advanced knowledge with regard to this, and is directly responsible for the discovery that the toxic condition preceding death is associated with characteristic disturbances in the chemistry of the blood, namely nitrogen retention, alkalosis and hypochloremia. Estimations of the chemical changes in the blood enable one to measure the severity of the toxemia and to estimate progress in treatment. Animal experiments have as a rule been directed to the determination of the cause of death and while this is eminently desirable it is equally important that studies be made of earlier clinical manifestations and morbidity.

It was observed that the toxic manifestations of motor inhibition were associated with diminished urinary output, and routine treatment now consists in maintaining adequate fluid intake to compensate for the loss of fluids by vomiting or by lavage of gastric contents. It has been found that the intravenous route of administration is most satisfactory, since the oral route is precluded by vomiting, clysmata are soon rejected or lost because of incontinence, and subcutaneous administration is exceedingly uncomfortable if sufficient amounts are given. For intravenous injection a solution is used containing 10 grams of sodium chloride and 100 grams of glucose to a liter of freshly distilled sterile water. It was found that the intravenous administration of sodium chloride solution was not invariably followed by diuresis, and the glucose was added to insure urinary excretion.

As clinical experience enlarged it became evident that cases could be grouped arbitrarily into: (1) fatal cases with marked disturbances in the chemistry of the blood and anuria; at necropsy renal injury may be demonstrated; (2) severe toxemia also associated with marked changes in the chemistry of the blood and oliguria which, however, respond to intensive treatment and the patients recover without any discoverable evidence of renal injury; (3) mild toxemia with diminished urinary output and characteristic but moderate changes in the chemistry of the blood; the patients respond quickly to treatment; (4) clinical manifestations of motor inhibition, namely, vomiting and gastric retention with a low output of urine but without disturbance in the chemistry of the blood. The last group is of special interest because if the earliest clinical manifestations of ileus may be recognized before changes occur it follows that the toxic syndrome is not due to a disturbance in the chemistry of the blood. It was found, moreover, that in the

routine management of patients with proved acute organic obstruction of the intestine, diagnosis was made and surgical treatment instituted before any disturbance occurred in the chemistry of the blood. It was further found that such disturbances may occur following operations within the abdomen which do not involve the intestine, for example, following cholecystectomy. In such cases there was always motor inhibition, shown by gastric retention, and this was associated with a low output of urine. A case was also encountered of very severe toxemia occurring in a patient who had hysterical vomiting. Treatment of the toxemia arising from motor inhibition has been equally satisfactory whether the cause was organic or functional, although prompt relief of organic obstruction is indicated as soon as the clinical condition of the patient permits. These observations seem to warrant the conclusion that the toxic condition described cannot be due to hypochloremia since the clinical evidences of toxemia may precede a drop in blood chlorides or indeed any disturbance in chemistry. Nor can the cause of the toxemia be ascribed to starvation since an adjustment in the clinical condition and a restoration of the chemical constituents of the blood to normal may be accomplished without the administration of food.

The factor in treatment which seems of greatest importance is the administration of water. When water is administered intravenously, sodium chloride is the electrolye of choice to insure isotonicity. This salt is the one selected in nature to accomplish the transporation of water within the animal organism. Apart from this function we are not convinced that sodium chloride exerts a specific influence in the control of the toxemia of intestinal obstruction or ileus.

*On the Production of Glucose from Fat in Diabetes Mellitus.* By A. ALMON FLETCHER, Toronto, Canada.

The work of A. V. Hill, of Best, Dale, Hoet and Marks and of MacLeod, Choi and others suggests that not only can muscle burn glucose in the absence of insulin but that glucose is the sole source of energy for muscle during its activity. That is to say, these experiments indicate that fat and protein must be converted into glucose before utilization by muscle and presumably this conversion takes place in the liver.

If this is so, the amount of new glucose so formed will depend largely on the administered diet, and in diabetic patients receiving large amounts of fat and minimal amounts of carbohydrate and protein most of this new glucose must come from fat.

Observation has been carried out on patients with diabetes mellitus to determine if this process of neoglucogenesis could be stimulated by the withdrawal of insulin to an extent where the new glucose would exceed the total glucose combustion. This would be the case if the excretion of glucose in the urine became greater than the amount of glucose which could theoretically be formed from all other sources. That is, when the urinary glucose became greater than G ($0.58 \times P + 0.1 \times F + CHO$ where P represents the urinary nitrogen $\times$ 6.25 and F and CHO, the total fat and carbohydrate of the diet).

This degree of new glucose formation has been observed in two patients. The diet in each case was high in fat and low in protein and carbohydrate. In one case, a diabetic of moderate severity, the process was stimulated by thyroid extract, and over a period of ten days the glucose excreted in the urine exceeded G by 128 grams. In the other case, one of diabetes of ususual severity, insulin could be discontinued for only twenty-four hours while the patient was receiving such a diet. During this period of twenty-four hours the glucose excretion exceeded G by amounts as great as 100 grams on two occasions. Respiratory quotients were observed as low as 0.67.

In both patients the observations were terminated by the development of extreme ketosis and acidosis, the carbon dioxide combining power falling to 19 or 20 volumes per cent. The development of severe ketosis under these conditions suggests that these figures represent the maximum power of new glucose formation in diabetes mellitus.

*Hypoglycemic Reactions in a Diabetic without Insulin.* By HOWARD F. WEST and BERTNARD SMITH, Los Angeles, Calif.

This report concerns observations on the case of a boy who developed diabetes at the age of fourteen with coma. He was seen first by the authors when in deep coma in April, 1924, one year after onset of diabetes. The second period of coma was the result of discontinuing insulin and routine diet. For the subsequent two years he ran a typical diabetic course, requiring from forty to fifty units of insulin per day while on a diet allowing 90 grams of carbohydrate per day with some variations in fat from time to time to avoid overweight. In October, 1926, following acute ketosis (pre-coma) due to irregularities in diet and insulin, he developed sensitiveness to insulin which was discontinued. For the following two months he was subject to severe and typical hypoglycemic shocks though the carbohydrate value of his diet was increased to 170 grams per day with supplementary feedings of carbohydrate food at times of severe reactions. During this period his blood sugar varied from 19 mgm. per hundred to 668 mgm. in an entirely erratic and unpredictable manner.

After a period of about three months he became stabilized and remained in good condition on a diet allowing 170 grams of carbohydrate without insulin. In November, 1927, following an acute respiratory infection he again developed acute ketosis and glycosuria. Insulin was again required for control. After three weeks of treatment he again developed sensitiveness to insulin and for several weeks after insulin was discontinued he was subject to frequent hypoglycemic reactions with occasional periods of unconsciousness and convulsions in spite of high carbohydrate intake with frequent feedings. He again became stabilized and is now in apparent good health and free from glycosuria on a diet allowing 180 grams of carbohydrate per day without insulin.

The only significant physical findings during the hypoglycemic periods were an enlarged and tender liver, moderate edema and, on occasion, traces of bile in the urine.

Details of blood sugar and inorganic phosphate curves and respiratory quotient studies are to be published at a later date.

*Experimental Toxic Necrosis of the Liver.* By ROBERT N. NYE, Boston, Mass.

The intravenous injection into rabbits of bacteria-free filtrates of a certain strain of *Streptococcus scarlatinae* has resulted, with proper dosage, and with a properly aged filtrate, in death. The outstanding pathology consists of well defined areas of necrosis in the liver, comparable to the lesions occasionally found in human beings at autopsy, following death complicated by sepsis. Frequent mitoses in the adrenals and the tubular epithelium of the kidneys are indicative of damage to these organs. This "toxin" is relatively thermo-stabile and can be neutralized by scarlet fever antitoxin. It was found in only one of five strains of *Streptococcus scarlatinae.* It seems likely that these findings explain many of the human toxic necroses of the liver and may even account for some cases of acute yellow atrophy.

*Changes in Renal Function, Hemoglobin, and Circulatory System in Different Types of Nephritis.* By D. D. VAN SLYKE, J. F. MCINTOSH, and EGGERT MÖLLER, (by invitation) and EDGAR STILLMAN.

Over 200 cases of Bright's disease have been studied in the Rockefeller Hospital. The functional changes in these cases have been followed by determining the number of cc. of blood the urea content of which is excreted in one minute, when the urine output is at the average normal rate of 1 cc. per minute. This figure calculated by the formula of Austin, Stillmann, and Van Slyke is spoken of as the Standard Blood Clearance. The average normal adult excretes at a rate to remove the urea from 54 cc. of blood per minute.

1. At a certain stage of developing renal deficit, the urea clearance frequently indicates a functional decline which is not shown by the phthalein excretion.

2. A stage of hyperfunction in urea excretion frequently follows the functional deficite of acute nephritis.

3. Progressive anemia usually parallels failure of function in glomerular nephritis, and is a grave prognostic sign in chronic cases, as already noted by Brown.

4. Parallelism between failure of function and cardiovascular changes in glomerulonephritis is often absent. Two cases of glomerulonephritis have reached the stage of uremia, entirely without hypertension, arteriosclerosis, or other circulatory derangement.

5. A renal deficit is not uncommon in genuine nephrosis. The deficit often becomes more pronounced as the cases progress.

*Weight Prediction from Stature and Pelvic Breadth Is Better than from Stature and Age.* By H. GRAY, Chicago, Ill.

The theory that body weight can be predicted from height together with some body diameter more accurately than in the usual way from stature and age, was

recently tested by means of correlation coefficients. Before the Society for Experimental Biology and Medicine on December 20, it was shown that correlation of weight with age is inferior to its correlation with the diameter of the pelvis, and that the multiple correlation of weight with stature and bi-cristal diameter was better than with stature and age. Since, however, the dependability of the multiple correlations depends on the distributions being linear, this paper tests linearity by means of $\eta$.

*The Leucocytes in Pernicious Anemia—Physiology, Pathology and Clinical Significance.* By RAPHAEL ISAACS, Ann Arbor, Michigan.

Throughout the relapse in pernicious anemia there is a leucopenia, with the appearance of abnormal and atypical white blood cells in the peripheral circulation. There appears to be considerable anisocytosis of the polymorphonuclear cells as well as of the red blood cells. But few leucocytes appear in the saliva, although there may be increased gastric leucopedesis, often with an excess of eosinophilic cells. On the day following the beginning of liver or liver extract treatment, there may be a great increase in the number of cells in the saliva, showing 2 to 3 days before the percentage of reticulated red blood cells in the peripheral circulation changes, and lasting from 1 to 6 days. The excretion of white blood cells then decreases and the number in the peripheral circulation increases, on the average, from the fifth to seventh day (second to fourteenth). The leucocyte count in the peripheral blood reaches a maximum of 10,000 to 15,000 per cubic millimeter in about 4 weeks (2 to 6 weeks). The hemopoietically active substance in the liver appears to affect the immature leucocytes in the hyperplastic bone marrow, and the excess leucoblastic tissue is very rapidly decrease, the clearing out process starting with remarkable rapidity in some cases. The remission is initiated with an increased excretion of the leucocytes through the mucous membranes. The increase of the blood leucocyte count to normal is an early sign of a good prognosis.

*Further Studies on the Function of the Intestinal Musculature.* By DAVID M. COWIE, Ann Arbor, Mich.

We have confirmed, the work of Alvarez and his co-workers on the rate, amplitude, tone, vascular and metabolic intestinal gradients as demonstrated with excised segments of rabbit's intestine by the von Conheim, Magnus, and the Trendelenberg methods.

An attempt has been made to classify the curves produced by the contraction of intestinal segments in oxygenated Locke's solution. The various curves seem to fall definitely into primary, secondary and tertiary groups, each succeeding group depending upon the primary group as a basis.

The phenomena in longitudinal muscle tracings due to changes in circular muscle tone and rhythm have been differentiated.

Visual observations and records of contractions of circular muscle have been compared demonstrating in the excised intestine, segmenting contractions, peristaltic waves and peristaltic rushes.

Evidence seems to have been produced that circular muscle contraction always precedes or initiates longitudinal muscle relaxation by about one-fifth of a second.

From these studies, it seems that it may be important in examining the action of drugs and organic extracts to distinguish effects on the contraction or relaxation of the separate muscle layers. Those substances causing increased contraction of longitudinal muscle such as liver extract, cause a decrease in circular muscle tone and contraction. Those substances which cause a marked fall in longitudinal muscle tone, cause an increase in circular muscle tone and contraction.

It has been further fairly well established that great care should be exercised in choosing intestinal segments for experimental work. Certain concentrations of chemicals, drugs and organic extracts, act differently on segments taken from various levels of the gut. For example: A very weak solution of bile (1–2000) will cause a prompt fall in longitudinal muscle tone of the duodenum and upper ileum, while it may take a concentration of 1–300 to cause a fall in longitudinal muscle tone of the lower ileum. Calcium lactate may cause a fall in tone of longitudinal muscle from duodenum and upper ileum while it causes a very marked increase in tone of longitudinal muscle from the lower ileum and colon. The reverse conditions usually obtain with circular muscle.

*The Influence of Medicinal Iron, as Compared with Food Iron, upon the Iron Reserve.* By CHARLES SPENCER WILLIAMSON, Chicago, Ill.

This investigation was undertaken to see if the administration of medicinal iron, as this term is generally understood, has any effect in increasing the available iron reserve. By available iron reserve, we mean, of course, that part of the iron in the body, outside of the circulating blood, which is capable of being converted into hemoglobin. Two large groups of white rats were fed on a standard diet, adequate in all respects. One group received in addition medicinal iron over a considerable period of time.

The hemoglobin was determined at the beginning of the experiment, and again just before bleeding. The animals in both groups were then bled. One-fourth of the total amount of blood was removed and both groups were then placed on the standard diet without iron. The hemoglobin was determined at short intervals spectrophotometrically. Both groups behaved identically, and no increase in iron reserve could be demonstrated in these experiments, although, as we have previously shown, the administration of food rich in iron will increase the iron reserve in similar rats about thirty-three per cent. The practical bearings of these experiments are referred to.

*The Energy Exchange in Obesity.* By JAMES M. STRANG (by invitation) and FRANK A. EVANS, Pittsburgh, Pa.

Observations are reported on the energy exchange in the basal state of five obese patients who were reduced by diet alone over an average period of 3¾ months. The data are expressed in terms of the percentages of excess weight, surface,

and calories-per-hour as compared to the probable values for persons of corresponding ages and heights, but of ideal weights. This method of expression, we believe, depicts more accurately the pathological physiology of the obese.

The initial data show an average weight of 222 pounds, 72 per cent above normal, and average surface 2.0 square meters, 26 per cent above normal. The calories-per-hour average 71, giving an average basal metabolic rate of −2.0 per cent as usually calculated, but actually 23 per cent above the calories produced at normal weight. Conversely, it may be stated that the increase in basal calories corresponds to the increase in surface (26 per cent) but not to that of weight (72 per cent). There is no evidence of a metabolic economy in obesity but rather an excessive energy exchange.

After reduction, the average losses were 41 pounds and 0.17 square meters corresponding to a diminution of 47 per cent of the excess weight and 45 per cent of the excess surface. The calories-per-hour average 61, a drop of 10 calories or 77 per cent of the excess energy. Hence there is a definite decrease in energy exchange coincident with weight reduction. The rate of change of calories is, however, over 1½ times as great as the rates of change of either weight or surface. This evidence indicates again that body surface is not the sole regulator of metabolism.

*Observations on the Circulation of Guinea Pigs during Bronchospasm.* By F. M. SMITH and J. S. HARTER (by invitation) and H. L. ALEXANDER, St. Louis, Mo.

In order to determine the extent of filling of the heart during bronchospasm, the effective right auricular pressure was calculated.

*Method:* Large guinea pigs (650 to 1000 grams) were sensitized by intraperitoneal injections of egg white. Under amytal anesthesia, cannulae were placed in the left carotid artery, in the right auricle (through the external jugular vein) and in the right pleural cavity. Simultaneous pressures were recorded by tracings as were respiratory volumes. Bronchospasm was then induced by intravenous injection of egg white and the circulatory response in relation to intrapleural pressure and depth of respiration noted.

*Results:* Unless bronchospasm comes on very suddenly there is a decreased filling of the right heart until asphyxia supervenes. This is determined by plotting the algebraic difference between the mean right auricular pressure and the mean intrapleural pressure. This gives the effective right auricular pressure which indicates degree of filling. Sudden bronchospasm induces normal or increased filling.

*Serum Electrolytes in Infections and Nephritis.* By J. H. AUSTIN, and (by invitation) F. WILLIAM SUNDERMAN and J. G. CAMACK.

The serum electrolytes in infections and nephritis were studied in the same manner as previously reported in lobar pneumonia. In lobar pneumonia, tuberculosis, chronic glomerular nephritis, and mercurial poisoning there was found a

decrease in both base and chloride of the blood serum with the decrease in the chloride tending to be relatively greater. In acute nephritis, eclampsia, and rheumatic fever there was a decrease in chloride without significant change in base. The series as a whole suggested the readiness with which chloride is reduced in the serum to make way for other anions.

*The Rôle of Total Base in Normal and Abnormal Gastric Secretion.* By CHESTER M. JONES, Boston, Mass.

The determination of total base has been made in gastric contents with a view to determining its normal level in the stomach. Confirmation has been made of the fact that basic ions are secreted by the stomach in most instances with the difference between total chlorides and free hydrochloric acid equaling the amount of total base. This does not hold true in any case of achlorhydria. When the base usually is in excess of total chlorides, evidence has been obtained indicating that it is unnecessary to explain the appearance of base in the stomach contents as due to regurgitation of duodenal content. The effects of alkali and acid, alkalosis and acidosis on the character of gastric secretion have been studied.

*The Symptom of Sighing in Cardiovascular Diagnosis.* By PAUL D. WHITE, Boston, Mass.

The symptom of sighing is a common phenomenon occurring occasionally or rarely in normal people when tired, depressed, or bored, but I have found it to be a much more common and constant symptom of nervous fatigue and of "effort syndrome." As such it has proved helpful in the analysis of patients who complain of cardiovascular symptoms like dyspnea, palpitation, and precordial pain. Such other symptoms may be due to heart disease or "effort syndrome" while I have never found sighing to be the result primarily of heart disease. When both heart disease and fatigue or "effort syndrome" are present in the same patient the presence or absence of well-marked sighing is very helpful in determining the relative responsibility of these two conditions in the production of the patient's ill health. One hundred cases of heart disease with and without congestive failure and relatively uncomplicated by "effort syndrome," one hundred cases of "effort syndrome" uncomplicated by heart disease, fifty cases of heart disease and "effort syndrome" and several hundred normal controls have been studied. Respiratory tracings obtained from thirty-five cases, representative of all these groups just mentioned, have confirmed this clinical observation. The simplicity and apparent unimportance of this symptom of sighing have led to its neglect hitherto.

*A Note on "Deposit Nitrogen" in Disease.* By G. P. GRABFIELD, Boston, Mass.

In previous studies it has been shown, that following the administration of sodium iodide there is an increase in the nitrogen excretion in the urine, and that this nitrogen is presumably of the same nature as that spoken of by various titles, such as deposit nitrogen, circulating protein, etc. Previous studies have also

shown that the administration of salicylates is followed by an increased nitrogen excretion in the urine, but that this increase in nitrogen excretion is of a different type of nitrogen than that following iodides. It was, therefore, decided to attempt a study of the reaction of patients suffering from various diseases to these drugs. The patients were all on a constant protein diet with a constant water intake, taking due account of the water in the food. In later experiments, the sulphur and phosphorus intake were also kept constant.

In one case of "complete" myxedema there was no reaction after the ingestion of iodine. This was to be expected from the previous experiments on dogs, in which a removal of the thyroid caused a disappearance of the urinary reaction to iodides. There was a similar lack of response in a case of Addison's disease, but the results in this case are more doubtful, as the patient died a short time after the experiment.

Of course, the chief interest in this connection is the study of nephritis. So far, we have been able to study only two types; one, the hemorrhagic subacute type, in which there was a prolonged delay in the excretion of nitrogen after iodides, but in which the increased excretion of nitrogen after salicylates occurred promptly. On the contrary, in a case which partakes somewhat of the character of nephrosis, there is a tendency to a reversal of this mechanism.

The significance of these observations is not clear at present, but the indication seems to be that there is some fundamental disturbance in the nitrogen metabolism, not dependent upon the insufficiency of the kidney as a filter.

*Blood Volume Preceding and Following Splenectomy.* By H. Z. GIFFIN, GEORGE E. BROWN, with technical assistance of GRACE M. ROTH.

This study was undertaken because of the fact that no data have been published on the spleen and splenectomy with relation to blood volume in man. Observations were made on six cases of primary splenomegaly without anemia, eleven cases of hemolytic icterus, and eighteen cases of splenic anemia. The Congo-red method was used to determine the blood and plasma volume.

In fifty normal individuals, Brown, Rowntree and Roth, the mean values were as follows: total blood volume 89 cc. per kilogram, plasma volume 50 cc. per kilogram, cell volume 39 cc. per kilogram, and circulating hemoglobin 15 grams per kilogram.

Primary splenomegaly without anemia showed a mean blood volume of 102 cc. per kilogram, plasma volume 60 cc. per kilogram, and a cell volume of 42 cc. per kilogram,—a simply hypervolemia, suggesting the possibility that in primary splenomegaly without anemia the enlarged circulatory bed due to the splenomegaly and enlarged blood vessels necessitates a larger blood volume for circulatory needs.

Hemolytic icterus before splenectomy showed a blood volume of 93 cc. per kilogram, plasma volume of 74 cc. per kilogram, and a cell volume of 19 cc. per kilogram,—an oligocythemic normovolemia. After splenectomy in hemolytic

icterus there was a very marked increase in the blood volume and in the cell volume. The actural increase in hemoglobin was much more marked than was indicated by the ordinary clinical method of estimation.

Splenic anemia preceding splenectomy showed a blood volume of 97 cc. per kilogram and a plasma volume of 68 cc. per kilogram,—an oligocythemic hypervolemia. After splenectomy most of the cases showed an absolute increase in the blood volume due to an increase in cells, the plasma remaining constant.

*The Relation Between Cardia Size and Cardiac Output per Minute Following the Administration of Digitalis in Dogs.* By A. E. COHN and H. J. STEWART, New York City, N. Y.

We have continued the study of the effect of digitalis on the behavior of the heart, taking up the problem where Harrison and Leonard left it.

We have found that (1) giving digitalis decreases the size of the heart (effect on tone); (2) for this reason the volume output (oxygen method according to Fick) decreases; (3) one week later the initial output is reetablished; (4) the rate being the same, the extent of contraction increased sometimes 100 per cent (measured by our X-ray method); (5) there is no necessary relation between size, and extent of contraction; (6) digitalis is not a sedative because it increases both contraction and tone; (7) all the evidence indicates that digitalis exerts the same effect qualitatively on normal and enlarged hearts though quantitative differences may occur depending upon the length of the muscle fibres. The effect on enlarged diseased hearts in human beings is not known. In this case though, provided digitalis shortens stretched fibres, an *increase* in volume output may occur because the length of the fibres being shortened to an optimum greater excursions may take place.

*Studies of the Blood by in vivo dialysis. II. The electrolytes.* By CARL H. GREENE and (by invitation) MARSCHELLE H. POWER.

The condition of the electrolytes in the blood has been studied by means of the vivi-diffusion technique of Abel and Rowntree. Normal dogs were operated on under a local anesthetic or amytal narcosis. Heparin was used as an anticoagulant.

Dialysis was carried out in duplicate against hypertonic and hypotonic salt solutions. The dialysis was examined at short intervals and the experiment continued until complete equilibrium was reached. Analyses were then made of the dialysate and blood serum. It is believed that this *in vivo* dialysis against the circulating blood gives a more accurate control of variable factors such as $CO_2$ tension, pH etc. than the usual method of compensation dialysis *in vitro*.

Final comparison was made between the composition of the serum calculated both in terms of the serum and the serum water, and the *in vivo* dialysate, the spinal fluid and the ultrafiltrate of the serum. In general the sodium and potassium were slight but definitely lower in the dialysate, etc. than in the plasma.

It is generally recognized that a portion of the calcium in the serum is combined with protein. Correspondingly the calcium concentration in the *in vivo* dialysate is from 60 to 70 per cent of that in the serum. The spinal fluid and ultrafiltrate contain slightly less calcium than the *in vivo* dialysate. The chloride concentration in the dialysate is higher than that in the serum but less than in the spinal fluid. These reulsts indicate the need for a careful consideration of the state of the electrolytes in the serum, with particular reference to the protein volume and the Donnan equilibrium, as a basis for the study of the equilibrium between the serum and edema fluid.

*The Importance of Hematological Evidence in the Diagnosis of Pernicious Anemia.* By C. P. HOWARD, and (by invitation) E. S. MILLS, Montreal, Canada.

The authors have studied a series of 28 cases diagnosed as pernicious anemia at the Montreal General Hospital. Only cases which were thoroughly investigated and subsequently followed, were accepted. The object of the study was to test the reliability of hematological evidence.

Twenty-three cases had a blood picture characteristic of the disease, while the remaining five were atypical in this respect, though classical in other ways. When the latter group was subsequently followed the diagnosis in each instance was called into question. Not one of these responded to liver treatment.

A high color index, a large type of red cell, and a leucopenia with relative lymphocytosis, are constantly present in pernicious anemia. In our experience cases which fail to show this blood picture are subsequently shown to be incorrectly diagnosed.

There is a type of anemia occurring in young women which often begins during pregnancy and is refractory to ordinary treatment, which clinically resembles very closely true pernicious anemia, but has a distinct blood picture.

*Blood Groups among Maya Indians of Yucatan.* By W. L. Moss and (by invitation) JAMES A. KENNEDY, Boston, Mass., and Rochester, New York.

During the last decade considerable interest has been manifest in determining the percentage distribution among the four blood groups of the population in the various countries of the world.

Geneticists have been active in collecting this data and have attempted to apply it to the investigations of racial origins and relationships.

The bloods herein reported were collected during the summer of 1927 by Dr. G. E. Williams, a member of the Carnegie Expedition to Yucatan.

Blood for serum was collected in Wright's tubes and after coagulation, the serum was taken up in capillary tubes, the ends of which were sealed in the flame. Blood for corpuscles was taken in a preserving fluid recommended by Rous and Turner (J. Exper. Med., 1916, xxiii, 219), consisting of a mixture of two parts of isotonic sodium citrate solution and five parts isotonic dextrose solution. This mixture was put up in U-shaped tubes and after the introduction of one or two drops of blood the ends were sealed in the flame.

The serum and corpuscles thus collected were forwarded from Yucatan to Boston by mail and the blood groups determined by testing the serum against known corpuscles of Groups I, II, III and IV, and by testing the corpuscles after suspending in normal sodium chloride solution, against known sera of Groups I, II, III and IV. The tests were carried out in hanging drop preparations and read microscopically after incubating one hour at 37°C. It was not possible to carry out the complete check on the blood group in every case as given above. Some of the samples of corpuscles had undergone hemolysis before reaching us and occasionally the serum was lacking. The following is a brief summary of the results obtained, the discussion of which will be left to the full report of this paper.

| | *Number* | *Percentage* |
|---|---|---|
| Group I | 10 | 1.2 |
| Group II | 123 | 14.9 |
| Group III | 40 | 4.8 |
| Group IV | 565 | 68.4 |
| Doubtful | 38 | 4.6 |
| Mixed* | 12 | 1.4 |
| Undetermined | 37 | 4.5 |
| | 825 | 99.8 |

* Serum of one group and corpuscles of another.