

**PROCEEDINGS OF THE NINETEENTH ANNUAL MEETING OF
THE AMERICAN SOCIETY FOR CLINICAL INVESTIGATION HELD
IN ATLANTIC CITY, NEW JERSEY, MAY 2, 1927**

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Dr. John Howland
Born 1873 Died 1926

Since the last meeting of the Society we have suffered the loss of another of our founders: John Howland. He was born in New York City in 1873. In his undergraduate days at Yale he displayed qualities which were later to distinguish him. His social success was due to an attractive capacity for meeting his fellows; and as an athlete he learned to do things well and ranked as one of the best tennis players in the country. He studied medicine and graduated in 1897 from the New York University and Bellevue Hospital Medical School, served his internship in Presbyterian Hospital, and was later on the staff of the New York Foundling Hospital. As an assistant of the late Dr. L. Emmett Holt he was inspired to pursue the study of pediatrics. He was called from his post at the College of Physicians and Surgeons to become Professor of Pediatrics in the newly organized school of Washington University, St. Louis, and shortly after was appointed Chief of the Department of Pediatrics at Johns Hopkins Medical School, which position he held until his death. It is no exaggeration to state that he founded the first real University Department of Pediatrics in this country, and hence his influence will be long felt in the development of this important branch of medicine. He himself regarded this as his most important contribution. But we, as fellow members of a Society in which he took such a leading part, have derived great inspiration and instruction from the successive stages of his career as a clinical investigator. In his younger days he made contributions in morphology, physiology and pharmacology. Finally, with the trend of the times, he foresaw the possibilities of applying chemical methods to the solution of the problems of disease; and his contributions to the subject of rickets stand as milestones in medicine. But with all of these studies he was first

and foremost a clinician and teacher. His great capacity for friendliness and his sympathy made his influence felt far beyond the circle of his immediate daily associates. He combined a variety of abilities as few men do, and because of his stimulating qualities of mind, was the ideal head of a clinical department and an ideal member of this Society.

For all these reasons and because of the affection of its members for him, the American Society for Clinical Investigation wishes to place on record its feeling of great loss caused by his departure from us.

The Effect of Fever on the Basal Metabolism, Insensible Perspiration, and Skin Temperature of a Child. By FRITZ B. TALBOT, Boston, Mass.

A case, J. E., aged nineteen months had regular and repeated elevations of temperature which could be predicted, prepared for, and studied. These febrile attacks persisted for several weeks and finally disappeared. Repeated physical examinations and numerous laboratory tests failed to reveal their cause. After a long illness of several weeks he was discharged well from the hospital.

The basal metabolism, insensible perspiration, and skin temperatures were measured at various times and compared with the height of the fever. The relation of the basal metabolism to the body temperature confirmed the findings of DuBois and his co-workers.

The metabolism increases in the same manner that it does in the adult, and the variation from the average is no greater than that found by DuBois (1). This case indicates that the metabolism of a young child is affected by fever in the same way as in the adult.

The "insensible perspiration" was obtained by weighing an infant for periods of one-half hour on delicate balance scales in the open room and observing the loss in body weight. It is seen to increase with increasing body temperature in the same manner as does the basal metabolism. The insensible perspiration shows a definite relationship to the basal metabolism. Such a relationship has also been found in three cretins before and after administration of thyroid extract and in a series of normal infants (unpublished data) now being studied.

The skin temperature was measured by a thermo-couple and a portable string galvanometer as devised by Benedict (2). The temperature of various prescribed points was taken underneath the clothing. The temperature of the trunk is higher than that of the extremities, but both tend to increase in a corresponding manner with the body temperature.

The skin temperature under the clothing shows that there is also a regular relationship between the external skin temperature and the rectal temperature during fever. This relationship apparently also holds during the fever of lobar pneumonia. A series of skin temperatures now being collected indicate that

this measurement is a very valuable adjunct in the study of heat elimination from the body.

Bibliography. (1) DuBois, E. F., *Basal Metabolism in Health and Disease*, 2nd Edition, Philadelphia, 1927, p. 390. (2) Benedict, F. G., *Asher-Spiro's Ergeb. D. Physiol. Suppl. Bd.* (Festschrift F. L. Asher, 1925).

The Effect of Iodin in Cases of So-called Toxic Adenoma. By JOHN B. YOUMANS and (by invitation) RUDOLPH H. KAMPMEIER, Ann Arbor, Mich.

The favorable effects of iodine in exophthalmic goiter suggested to the authors that should similar effects be obtained in cases of "toxic adenoma" they would constitute evidence for the fundamental identity of these two conditions. The general belief in the concept of two entirely distinct forms of thyrotoxicosis is emphasized by the common acceptance of the view that iodine is harmful and contraindicated in cases of toxic adenoma.

Three years ago we began the use of iodine in unselected cases of "toxic adenoma." The cases were hospitalized and following a period of observation under medical regime iodine was administered (usually Lugol's solution, minims V, three times daily), and careful observations made including basal metabolism determinations. A series of similar cases not treated with iodine and of exophthalmic goiter treated with iodine was studied.

Satisfactory data were obtained in 30 cases of "toxic adenoma" treated with iodine, and somewhat less complete data in 48 more. The results obtained indicate that the response to iodine of cases of "toxic adenoma" previously untreated with iodine is essentially the same as that of exophthalmic goiter. No instance of harmful effect was observed. Characteristic escape from iodine effect following discontinued or prolonged administration of iodine was observed.

The Relation between Seizures in Epilepsy and the Acid-Base Balance in the Blood.

By WM. G. LENNOX, Boston, Mass.

A study has been made of 4 epileptic patients, each having constantly many seizures a day. In conditions of alkalosis induced by administration of alkali or over-ventilation, seizures were much more frequent. In conditions of acidosis induced by fasting, ketogenic diet, administration of acid-forming salts or by rebreathing, seizures were much less frequent. Because curves signifying acid-base changes in the blood and frequency of seizures did not maintain a constantly parallel course, associated changes in nerve cells, such as the tension of oxygen, the equilibrium of electrolytes, or the permeability of cell membranes may play a more fundamental part. Because in conditions of acidosis tendon reflexes were diminished, we believe that acidosis acts by causing a decrease in the irritability of nervous tissues. Although these observations do not offer immediate hope of therapeutic results in the treatment of adult epileptics, they do bring us nearer to an understanding of the mechanism involved in seizures.

The Regulation of Circulation; Studies on the Mechanism Whereby Anoxemia Causes an Increased Cardiac Output. By G. CANBY ROBINSON, and (by invitation) ALFRED BLALOCK, TINSLEY R. HARRISON, and COBB PILCHER, Nashville, Tenn.

Severe anoxemia of short duration has been demonstrated to cause an increased minute cardiac output in morphinized dogs and "trained" unnarcotized dogs. The present work is concerned with an attempt to study the mechanism in the body responsible for this apparently compensatory reaction.

Observations have been made as to the "anoxemic threshold," i.e., the mildest degree of anoxemia which leads to an increased cardiac output. In experiments of short duration, this value seems to lie in different normal animals between 65 and 85 per cent of arterial saturation. Studies were made of the various factors which might influence the circulatory response to anoxemia.

(a) *The adrenal glands* are not necessary for this reaction as anoxemia causes increased cardiac output in adrenalectomized dogs.

(b) *The central nervous system.* After removal of the stellate ganglia and thoracic sympathetic trunks the response to anoxemia is unchanged. After double vagotomy, anoxemia usually causes an increased cardiac output but the degree of increase is apparently less than in animals with intact vagi. Results up to the present time have led to the tentative hypothesis that deficient oxygenation of the coronary blood stimulates the cardiac output by a direct myocardial action but that the sensitiveness of the myocardium to this stimulus is partially controlled by the medulla through the vagi. Changes in the peripheral circulation have not been adequately studied as yet, and must be evaluated before this problem can be regarded as settled.

Pulse Wave Velocity under Varying Conditions in Normal and Abnormal Human Cardiovascular Systems. By ROY H. TURNER (by invitation) and GEORGE R. HERRMANN, New Orleans, La.

The study of the velocity of the pulse wave under suddenly varied conditions of pressure has been made easily possible by a helium lamp recording apparatus recently devised by Dr. Turner.

Patients whose pulse wave velocity was studied by this method have been grouped into five classes as follows:

1. Normal individuals, among whom the highest P. W. V. was 6 meters per second.
2. Cases of hypertension without arterial changes, who showed increases as follows: one, 40 per cent; three, 80 per cent; two, 100 per cent.
3. Cases of hypertension with large tortuous, slightly thickened arteries, two of which showed a normal P. W. V., one a 33 per cent, two a 100 per cent and one a 125 per cent increase.
4. Cases of hypertension with large, tortuous, definitely thickened vessels

showed one a 25 per cent and three a 100 per cent increase with one increase of 200 per cent in a case with marked calcareous deposits in the arteries.

5. Patients with large, dilated and thickened vessels with normal blood pressure showed one a 25 per cent and three a 40 per cent increase with one 175 per cent increase in a patient with the most advanced corrugating sclerosis.

The data now available indicate that there are other factors aside from elasticity and blood pressure that influence pulse wave velocity. The change in calibre of the artery, especially enlargement, may be a most important compensatory factor resulting in alterations in P. W. V. Reducing the pressure actually increased the P. W. V. in two instances. The method gives a definite index of the functional efficiency of the peripheral arteries.

The Effect of Digitalis upon the Pulse Rate and Circulatory Minute Volume of Normal Human Subjects. By C. SIDNEY BURWELL and (by invitation) DEWITT NEIGHBORS and E. M. REGEN, Nashville, Tenn.

One year ago Harrison and Leonard demonstrated a fall in cardiac output of the dog after the administration of "therapeutic" doses of digitalis. This observation differed so profoundly from those on the perfused and isolated heart, and the difference had such significance that it was felt essential to determine whether or not digitalis produced a similar effect in man.

Accordingly digitalis leaf of known potency was administered to a series of normal men, and the cardiac output and "basal" pulse rate observed before and after its administration. All observations were made in the morning, with the subject in the post-absorptive condition and at complete rest. The cardiac output was determined by the method of Field, Bock, Gildea and Lathrop. By the "basal pulse rate" is meant an average of the 8 to 12 half-minute counts made during each determination of cardiac output. The usual procedure was to train the subject in the respiratory maneuvers necessary for the determination on one or two occasions before his cardiac output was actually observed. The control observations were then made on successive days until an apparent normal level was established. If, as was often the case, the first one or two determinations were higher than subsequent ones, these high figures were discarded.

Digitalis leaves were given by mouth. The initial dose was usually 1 gram, and this was followed by smaller doses at intervals of twenty-four hours until a stage of undoubted digitalis effect was reached as judged by the changes in pulse, cardiac output and electrocardiogram and by the occurrence of nausea. Observations of cardiac output and basal pulse rate were made daily during the period of administration and of maximum effect and at slightly longer intervals during the recovery period. Such studies were carried out upon five individuals.

Following the administration of digitalis there was in each case a drop in the basal pulse rate of from 8 to 12 beats per minute. After the cessation of digitalis administration there was a gradual return to the predigitalis level in approximately 3 to 4 weeks. Some drop occurred in each case after the initial dose of the drug.

The effect on cardiac output was in general similar in all five individuals studied. Each one showed a diminution in output immediately following administration of the drug. This "initial" drop averaged 16 per cent of the previous cardiac output. As the administration of the drug was continued and nausea supervened the cardiac output rose until it was only 6 per cent below the original average. The drug was then discontinued. Following this "toxic period" there was a "secondary" drop to 18 per cent below; and after this a gradual return to 4 per cent less than the original normal. The output per beat was diminished as well as the pulse rate.

These studies include a small number of individuals but a considerable number of generally concordant observations.

The following conclusions may be drawn:

1. Digitalis diminishes the basal pulse rate and this diminution persists for three weeks and upwards.

2. The cardiac output per minute is not increased by digitalis. On the contrary it shows a definite diminution, due not only to the fall in pulse rate but also to a lessening of the output per beat.

The Velocity of Pulmonary Blood Flow in Health and Disease. By HERRMANN L.

BLUMGART and (by invitation) SOMA WEISS, Boston, Mass.

The radium active deposit method enables one to study for the first time the velocity of blood flow through the lungs of man. Active deposit of radium is injected into the cubital vein of one arm. When the active deposit reaches the right chambers of the heart the gamma rays produce an ionization current which, when amplified, is automatically registered by an appropriate recording device. Similarly, the time of arrival of the active deposit in the arterial vessels about the elbow is automatically recorded. The time that elapses between the instant of injection and the time of arrival of the active deposit in the right chambers of the heart measures the velocity of venous blood from the arm to the heart. The time that elapses between the arrival of the active deposit of radium in the right heart chambers and the arrival in the arteries about the elbow of the other arm gives, after the application of a standard correction, a measurement of the velocity of blood flow through the lungs.

In fifty normal persons in whom the venous pressure and vital capacity were normal, the pulmonary circulation time ranged from four and a half to seventeen seconds. The average time was eleven seconds. Pulmonary circulation times above seventeen seconds were always associated with pathological conditions of the circulation. In general, the slowing of the venous blood flow and of the pulmonary blood flow corresponded to the degree of circulatory failure, in the most severely decompensated patients the venous circulation time being as long as thirty-four seconds and the pulmonary circulation time sixty-eight seconds. In the presence of emphysema the velocity of blood flow through the lungs may be normal.

In normal persons the administration of digitalis to the point of toxicity produces no demonstrable effect on the velocity of pulmonary blood flow, whereas in cardiac patients in whom there was definite clinical improvement following digitalization, the velocity of blood flow through the lungs was increased.

According to the formula, developed by G. N. Stewart, that $V = Q \frac{60}{T}$ where V equals the minute volume flow through the lungs, Q signifies the quantity of blood in the lungs and T is the mean velocity of pulmonary blood flow, if two of the three factors are known the third can be calculated. In fourteen individuals actual measurements of both the minute volume output and of the pulmonary circulation time were accomplished. Using the pulmonary circulation time as the mean velocity in this formula, the quantity of blood in the lungs was calculated and found to be approximately 18 per cent of the total blood volume. This is in accord with the estimates of physiologists based on observations in animals. It is noteworthy that substitution of the circulation time for the mean velocity secures such a plausible estimate; for if the circulation time were not closely comparable to the mean velocity the calculation would have produced an estimate wholly unreasonable.

The Behavior of Pulmonary Vessels as Determined by Direct Observation in the Intact Chest. By JOSEPH T. WEARN and (by invitation) ARTHUR C. ERNSTENE, J. S. BARR and W. J. GERMAN, Boston, Mass.

A method has been devised which permits study of the pulmonary circulation in the cat by direct observation and under physiological conditions.

Under amylal anesthesia the parietal pleura of the eighth interspace is exposed in the right anterior axillary line over an area measuring 0.75 by 1.5 cm. Through an abdominal incision a similar pleural window is prepared by removing the muscle fibres of the diaphragm immediately opposite the window in the chest wall. The animal is now curarized, and the lungs are held stationary in the normal inspiratory position by means of a gentle blast of air through a small catheter introduced to the bifurcation of the trachea. By means of the diaphragmatic window a beam of light is passed through the tip of the lower lobe of the lung at sufficient intensity to permit direct observation of the pulmonary vessels with a microscope at the outer window, using a magnification of 110 diameters. Carotid pressure tracings have been made in all experiments. It has been possible with this method to observe the number and calibre of the capillaries and of the smaller arteries and veins. In addition, it is possible to detect relative changes in the velocity of blood flow through these vessels.

The number of active capillaries has varied greatly in different preparations. In some instances there have been but one or two capillaries per air sac. In the majority of experiments, however, there have been six to eight capillaries per air sac, while in a few instances the capillaries have been so numerous and have formed such a close-meshed network that accurate counts were impossible.

Furthermore, the number of active capillaries in an individual air sac has been observed to vary from time to time. Capillaries have been seen to disappear and reappear without changes in the systemic blood pressure.

Small intravenous doses of adrenalin have been given in a few experiments and, as the systemic blood pressure rose, a variable number of new capillaries has been seen to appear in the air sacs under observation. Further studies upon the effect of this and other drugs are now under way.

Vasomotor Mechanism in Cerebral Circulation. By STANLEY COBB, and (by invitation) H. S. FORBES and H. G. WOLFF, Boston Mass.

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 calibrations 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 rises or falls in arterial pressure. In addition to these passive changes in caliber, the arteries show changes exactly opposite in direction to the above. These latter changes can be brought about by stimulation of constrictor or dilator nerves, and by other means.

The conclusion seems justified that the cerebral circulation is not regulated wholly from a distance by splanchnic or general systemic vaso-constriction and dilatation (passive) but is also dependent upon an active vasomotor mechanism within the cerebral vessels themselves.

The Circulating Blood Volume in Diabetes Mellitus and Diabetic Acidosis. By GEO. A. HARROP, JR., and (by invitation) H. C. CHANG, Baltimore, Md.

A critical study has been made of the carbon monoxide method for the determination of the circulating blood volume in man, and particularly of the extent to which the gas is mixed in the circulating blood and the loss to the extra vascular hemoglobin. Series of estimations using prolonged experimental periods and taken at different stages during continuous exercise have indicated that the errors involved from these factors under controlled conditions is slight. A more delicate technique has been developed for the quantitative estimation of carbon monoxide in the blood.

The method has been applied to a study of the relationship existing between hyperglycemia, the occurrence of polyuria and polydipsia, acidosis, clinical dehydration, and the circulating blood volume in diabetes mellitus. In patients with marked hyperglycemia, thirst and polyuria, and even with rather marked dehydration, the circulating blood volume is high as compared with the normal when calculated on the basis either of cubic centimeters of blood per kilogram of body weight or per square meter of surface area. In patients with acidosis, even where the plasma bicarbonate capacity is as low as twenty volumes per cent, no

blood volume values have been found below the lowest obtained in normal subjects. Significant diminution, however, of the plasma volume has been found in three such cases in which the hematocrit determinations and erythrocyte counts showed an increased red cell volume. The blood volume in such cases under insulin and dietary treatment later again became high. No determinations have been made in cases of actual coma. Patients under dietary treatment with or without insulin where hyperglycemia has not been present over long periods have normal circulating blood volumes and plasma volumes.

The circulating blood volume, then, in severe and in untreated diabetes, when associated with polyuria, polydipsia and hyperglycemia appears to be increased, notwithstanding the presence of clinical dehydration. Where acidosis supervenes, the blood volume is diminished but we have not even in this condition found abnormally low blood volumes.

Synthalin. By ELLIOTT P. JOSLIN, Boston, Mass.

The extraordinary improvement of the modern diabetic with diet and insulin makes it exceedingly difficult to estimate the value of any new method of treatment. Particularly is this true with patients who have been under observation for only a few years.

During the last three months synthalin has been employed with eight of my cases, but only with one of these cases, case no. 4306, for the greater portion of the time. With this case the insulin has been reduced from 28 to 16 units daily and the carbohydrate, protein and fat in the diet maintained at their previous levels. I have tried to omit six more units, the evening dose, but as yet without success as glycosuria appears. With another patient, case no. 5900, insulin, 13 units, has been totally replaced with synthalin and the patient's blood sugar for an interval of two weeks has fallen nearly to normal. To the former patient 50 mgm. synthalin were given daily for two days and then as a rule omitted for one or two days, and the cycle repeated; to the latter 30 mgm. synthalin were given daily for three days and then omitted for a day and then repeated. None of my other cases are as convincing. A third patient, case no. 5974, became sugar-free with diet and insulin; the insulin was then omitted and he too remained sugar-free with synthalin, but he was a recently treated case and might have behaved so without synthalin. One patient, case no. 3483, with hyperthyroidism did better after operation with synthalin, replacing insulin, than one would have expected without insulin, and this observation is of some significance because I have experience, thanks to F. H. Lahey, with 75 cases of diabetes with hyperthyroidism. One patient, case no. 5608, disliked synthalin; two others, old ladies, cases no. 1494 and 3751, with a few grams of sugar in the urine appeared to be more nearly sugar free and more consistently sugar free when synthalin was used.

Synthalin did not act efficaciously in one true diabetic, case no. 2296, who happens to have a low blood sugar threshold, but I am yet in hopes for better results.

Synthalin caused nausea and even vomiting in our first case. Subsequently when the drug was resumed no nausea appeared, but the dosage, 4×25 mgm. in two days, was spread over a few more hours or even several days.

Synthalin appeared to work better after successive turns of two days at a time with a day's interval without the medication.

Synthalin acts in diabetes. Three milligrams replaced 1 unit of insulin in my first case, if one includes in the effect the two days of medication and the day following as well, and 1 mgm. replaced approximately 1 unit in the second case, but in this case perhaps the patient's tolerance was improving.

None of my diabetic children and none of my patients with acidosis have been given synthalin.

I wish to acknowledge my indebtedness to Professor E. Frank of Breslau and to the Messrs. Kahlbaum Company for the privilege of using synthalin. I believe it is worthy of continued use and that with a better knowledge of it, there will be a group of diabetic cases that can employ it advantageously. More important is the probability that it is the forerunner of other and better preparations which one can give by mouth and which to a certain degree will replace insulin.

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Hyperinsulinism, from Carcinoma of the Islands of Langerhans. By R. M. WILDER and (by invitation) H. N. ALLAN and H. E. ROBERTSON, Rochester, Minn.

This case, I can say without exaggeration, is one of the most significant in medical experience. Its study yields new knowledge, important in clinical medicine, in physiology and in pathology. We were fortunate not only in having the opportunity to conduct a very complete clinical investigation, but also in obtaining the end picture from the pathologists.

We are dealing here with a disease that is new in the sense that heretofore it has not been described, namely, carcinoma of the Islands of Langerhans with hyperinsulinism. We also possess in this case what is, I think, the first well authenticated instance of a carcinoma of any origin possessing the function of the parent cells. The tumor in this case is a cancer by all the commonly accepted criteria of carcinoma and from this cancer a substance has been extracted which, so far as we can tell, has the same physiological action as insulin.

The disease in this case existed for a good many years, at least eight, but the picture of excessive insulin action only became evident in 1924. The patient, a surgeon forty years of age, suffered acute abdominal pains in 1918. An exploratory operation at that time revealed no gross pathology, nevertheless a gastroenterostomy was performed. In 1921 and again in 1924, the continuance of vague

upper abdominal symptoms brought him to the Mayo Clinic, but no definite diagnosis could be made at either of these examinations. Later in 1924, he began to develop acute attacks of weakness while engaged at his morning work and found that he could antidote these attacks by drinking coca-cola or malted milk. Then an attack occurred while he was operating, an attack associated with convulsions and loss of consciousness which so closely resembled the clinical picture of a diabetic patient who has been over-dosed with insulin that the thought occurred to the attending doctors to inject him intravenously with glucose. This, fortunately, was done and recovery of consciousness followed immediately. Thereafter, sugar was taken by mouth at regular intervals; larger and larger doses and shorter intervals being needed until before the time of death he took 65 grams of glucose hourly day and night to prevent hypoglycemia.

In July, 1926, an examination was made by Dr. Ulrich of Minneapolis who recognized the fact that he had to deal with an unusual clinical picture associated with hypoglycemia, but was unable to determine its nature. In November, the patient again consulted the Clinic, arriving at the hospital in a state of collapse which had all the ear-marks of hypoglycemic shock and with a blood sugar so low that it could only be determined with difficulty.

Our studies and experiments are too extensive to permit of more than partial summarizing. At first, we directed attention to the liver, being impressed by the fact that the amount of sugar necessary to prevent hypoglycemia was approximately equal to that which Mann finds to be the requirement for each kilogram of body weight in dehepatized dogs. We found, however, that the liver was normal in every function that we could test, amino acids were properly deaminized and urea formed in normal amounts; there was a normal secretion of bile and no retention of pigments. We found then that the metabolism was abnormally stimulated and respiratory quotients indicated that the materials burning were made up largely of carbohydrate. We obtained evidence also of rapid formation of fat in the fact that the respiratory quotients, after test meals of sugar, rose over unity, to 1.20. This was confirmed by the fact that the patient was gaining weight. We found also that the phosphates in the blood would fall with the fall in the blood sugar after test meals, exactly as occurs after injections of insulin and sugar and our opinion of the etiology veered away from the liver to the pancreas and the idea of hyperinsulinism.

An exploratory operation was performed on the fourth of December by Doctor Mayo who described a hardening and irregularity of the body and tail of the pancreas and two unusual nodules palpable on the surface of the liver. The gall bladder was diseased and this he removed. He also took out a small piece of liver. The liver thus removed in the middle of an operation with ether anesthesia contained nearly 4 per cent of glycogen. This, to judge from experience with dogs, is a high glycogen content and this finding excluded the possibility of the patient's symptoms being due to loss of glycogen function, and, together with the other findings at operation, focused attention still more closely on the pancreas.

It was proposed tentatively that a carcinoma of the pancreas with metastasis to the liver would explain the clinical picture; and, since the Island tissue and presumably also functioning carcinoma in the pancreas would be under the normal nerve control and, therefore, should not over-function, it was further suggested that the metastasis should be functioning and producing insulin widely. On the basis of this tentative diagnosis and with the purpose of inhibiting the functioning of metastatic Island tissue in the liver, Doctor Bowing was asked to use radium over the liver. This he did without, however, noticeably affecting the clinical condition. The patient finally died not from an attack of hypoglycemia or from cachexia, but apparently from exhaustion.

The findings of Doctor Robertson at the necropsy are in entire harmony with the idea of metastatic carcinoma of Islands of Langerhans and evidence of the functioning of this cancer tissue is supplied by Doctor Power who has painstakingly applied Best's technique for insulin extraction both to a portion of the tumor in the liver and to an equal portion of the non-tumorous liver tissue. From the non-tumorous liver taken as a control, 33 mgm. of material was obtained; one-half of this was injected into a rabbit without appreciable effect. From the tumor 57 mgm. of material was obtained and when one-fourth of this was injected into a previously standardized rabbit, the blood sugar fell from 0.121 to the definite hypoglycemia of 0.047.

The Histogenesis of Renal Casts. By HENRY JACKSON, JR., Boston, Mass.

From observations on animals and man it would appear that some, at least, of the renal casts are formed by a degeneration and coalescence of the circular reticulum of the kidney. This circular reticulum, in turn, is undoubtedly formed by a process of budding in the renal cells. The cells of the convoluted tubules swell at their tip, form buds and these buds, becoming globular in shape, are pinched off from the parent cell and come to lie free in the lumen of the tubule.

The process, at least in its initial stages, is to be regarded as a type of reaction to injury, rather than a process peculiar to the kidney, for similar if not identical changes have been found in other organs, especially the uterus and adrenal.

The Mechanism of Phlorhizin Diabetes. By HENRY B. RICHARDSON and (by invitation) EPHRAIM SHORR, New York City, N. Y.

The nature of the action of phlorhizin is at present controversial. Recent investigations have led a number of workers to the conception that the drug causes a break in the chain of carbohydrate oxidation; in other words a true tissue diabetes and not merely an increase in the permeability of the kidney.

We have investigated the oxidation of carbohydrate in excised surviving tissue of the phlorhizinized rat, using the method developed by Warburg for the study of respiratory exchange in vitro. With this technique it is possible to measure two quotients at the same time using the same organ. White rats were phlorhizinized and when chemical and respiratory studies demonstrated that the action

of the drug was maximal, the kidneys or testes were removed for study. Oxidation of carbohydrate was inferred when the respiratory quotient or the oxygen consumption was higher, when glucose was added to the tissues than in its absence. A control series of observations with normal animals has already been reported from this laboratory.

In completely phlorhizinized animals the excised tissue was found to oxidize carbohydrate to the same extent as that of the normal animals. Moreover when phlorhizin was added directly to the excised tissues of normal animals quotients of 0.800 to 0.930 were measured indicating that carbohydrate is oxidized in abundance. Work is now being extended to the tissues of depancreatized animals. Should these fail to oxidize carbohydrate, the inference will be that in the white rat at least, phlorhizin has no effect on the combustion of sugar in excised tissue. This would support the older theory that phlorhizin acts by increasing the permeability of the kidney.

A Comparison of Glycolysis in Muscle and in Cancer Tissue. By DAVID P. BARR and (by invitation) ETHEL RONZONI, St. Louis, Mo.

It has been demonstrated by Warburg that malignant tumors possess a power of glycolysis much greater than that of normal tissue, a property which may possibly furnish the energy for their rapid and continuous growth. Superficially the process appears the same as the glycolysis which provides the energy for muscular contraction inasmuch as carbohydrate is converted in each instance to the same end product, lactic acid. A more thorough examination, however, reveals important differences both in the carbohydrates which are utilizable and in the circumstances which modify the reactions. At the present time, therefore, it is impossible to predict whether a substance which affects the glycolysis of muscle will similarly influence the glycolytic activity of tumor tissue.

In 1923 Foster was able to prepare from the pancreas an alcoholic extract which would inhibit the glycolysis of muscle about 50 per cent. In our experiments Foster's extract was tested for its effect upon the glycolysis of muscle, of muscle extract and of malignant tumors. Foster's original statements have been confirmed. It has been determined moreover that the pancreatic inhibitor will check almost completely the glycolysis which is produced by Meyerhof's recently described muscle extract. While sufficient data has not been accumulated to allow a positive statement it appears that the glycolysis of malignant tumors is also inhibited by the pancreatic substance, although to a degree somewhat less than that observed in muscle and in muscle extract.

On the Nature of the Immature Cells in the Blood in Leukemia. By RAPHAEL ISAACS and (by invitation) GENEVA A. DALAND, Boston, Mass.

Determination of the oxygen absorption by whole blood were made over periods of from one to seven hours in a specially devised microspirometer. Comparative studies of the amount of oxygen used by blood from normal individuals and from

patients with chronic myelogenous leukemia show that the rate is faster when the leucocyte count is high than when the count is low. The rate is not influenced markedly by the number of red blood corpuscles or the amount of hemoglobin, provided that the blood is saturated with oxygen when the observations are begun. In terms of rate per 1000 cells, the adult polymorphonuclear neutrophils use more oxygen per hour than the immature blood cells in chronic myelogenous leukemia, the most immature cells using the least. In this respect the blood cells in leukemia behave in a way similar to that described by Warburg for cancer cells.

The Effect of Liver Feeding on the Blood Sugar. By WILLIAM P. MURPHY and (by invitation) HARRY BLOTNER, Boston, Mass.

We have noticed that persons partaking of a diet rich in liver often develop excessive hunger, and complain of a group of symptoms similar to those described during the hypoglycemia resulting from insulin overdosage.

This observation led us to make blood sugar curves in a series of cases following the ingestion of a known quantity of liver or fraction thereof. The blood-sugar levels obtained following a test meal containing a known quantity of liver, fell and remained at a lower level than curves obtained after a meal containing similar amounts of protein, carbohydrate, fat and calories but from which liver was omitted. In certain cases a marked lowering of the blood sugar level occurred such as is obtained following the injection of insulin. The feeding of the fractions of liver composed of the connective tissue, insoluble fats and the liver proteins precipitated at pH = 5 resulted in a blood sugar curve similar to the ones obtained after feeding whole liver. Certain other liver fractions effective in the treatment of pernicious anemia appear to contain an inappreciable amount of the blood sugar reducing fraction. These observations suggest that liver may contain a blood-sugar reducing substance, active when ingested by mouth, non-toxic, and with an effect on blood-sugar concentration like that obtained with insulin.

Demonstrable Differences between Antibodies in Natural and Artificial Hypersensitiveness. By ROBERT A. COOKE and (by invitation) W. C. SPAIN, New York City, N. Y.

There is considerable doubt regarding the relation of or the identity of the natural form of hypersensitiveness as manifested clinically in man by asthma and hay fever, and that form of hypersensitiveness immunologically induced in animal and man and generally called anaphylaxis.

The problem is one of more than academic interest as a knowledge of the nature of the reaction may lead to a proper conception of the etiology and the prophylaxis of allergy in man.

Comparative studies have been made on the reacting antibodies in the sera of: (1) Naturally sensitized humans with asthma; (2) artificially sensitized (a) humans with serum disease, (b) rabbits.

The sera have been tested for: (1) The capacity to sensitize passively normal human skin areas; (2) the presence of specific precipitating antibodies; (3) the capacity to sensitize guinea pigs passively (the Dale reaction).

These studies have shown that both the artificially sensitized (anaphylactic) serum as well as the naturally sensitized (allergic) serum has the power passively to sensitize the skin of normal humans. However, precipitating antibodies have not been found in naturally sensitive patients with asthma in striking contrast to their almost uniform presence in sensitized animals and their frequent occurrence in man after serum disease.

By the Dale reaction it is shown that the naturally sensitive human serum will not sensitize passively a guinea pig's uterus, whereas the serum of an artificially sensitized man (serum disease) or rabbit has this ability.

Studies on the Pathogenicity of Brucella Abortus: Preliminary Report. By ERNEST C. DICKSON, San Francisco, Calif.

The question of the pathogenicity of *Brucella abortus* for human beings is one which is attracting considerable attention and is of importance because of the prevalence of infectious abortion in dairy herds in many parts of the country.

Evidence of human infection is two-fold in character: (a) Demonstration of living *Br. abortus* in blood cultures and in urine cultures from patients suffering with low grade undulant fever; and (b) demonstration of specific immune bodies, particularly agglutinins, in the blood of patients who have low grade fever or in persons who are afebrile and who show no clinical signs of infection.

If we accept the present methods for differentiating *Br. abortus* from the true *Br. mellitensis*, there can be no doubt as to infection in the first group, but there is doubt in the minds of some investigators as to whether the presence of agglutinins in the blood of afebrile individuals is indication of active immunization from low grade infection or whether it indicates passive immunization produced by absorption of the agglutinins from the milk of infected cattle.

Preliminary experiments on guinea pigs indicate that agglutinins are not found in the blood after feeding milk containing agglutinins but that they are found after feeding milk containing living *Br. abortus*. The agglutinin-containing milk was prepared by heating fresh milk to destroy all bacteria and adding immune goat serum of high agglutinin titre which had been prepared by immunizing a goat with killed antigen.

In every instance in which agglutinins were demonstrated in the blood, necropsy showed anatomical signs of *abortus* infection.

Two Ward Infections of Rheumatic Fever. By ERNST P. BOAS and (by invitation) SIDNEY P. SCHWARTZ, New York City, N. Y.

Two ward infections of rheumatic fever have been observed at Montefiore Hospital. In one instance five children developed rheumatic fever within a period of five weeks, in another instance six children were taken ill within a period of

four weeks. The rheumatic manifestations noted in these epidemics include pericarditis, heart block, arthritis, carditis. One child in each epidemic came to autopsy and showed Aschoff bodies in the myocardium. Only children with previous rheumatic heart disease contracted rheumatic infections, the non-rheumatic children in the same ward did not become ill. It remains a question whether these were epidemics of true rheumatic fever or whether a non-specific infection activated the rheumatic virus latent in the several victims. There is much evidence in the literature supporting the view that rheumatic fever may partake of the nature of an epidemic disease and that contact infection is possible.

In a number of the cases of this series the bout of rheumatic fever was ushered in by a bronchopneumonia, and in these children it was impossible to know when the bronchopneumonia ceased and when the rheumatism began. The two conditions merged insensibly one into the other. We have been impressed with the importance of the lungs as a source of reactivation or as a possible portal of entry of rheumatic infection.

The Antagonism of Cations in Their Action on the Living Cell. By PAUL REZNIKOFF and (by invitation) ROBERT CHAMBERS, New York City, N. Y.

The mechanism of antagonism underlies all questions of immunity, therapeutics and the maintenance of physiological states. To study the nature of antagonism in the living cell the Chamber's micrurgical technique was used. By this method NaCl, KCl, LiCl, CaCl₂, and MgCl₂ and mixtures of these salts, were brought into direct contact with the interior of a living cell by means of injection as well as with the plasma membrane from the outside by immersion. The cell used in the experiments was the *Amoeba dubia* which is relatively independent of osmotic changes.

The results of these experiments indicate that antagonism depends upon the ability of the protecting agent to prevent the toxic agent from reaching or irreversibly affecting the vulnerable part of the cell. The particular mechanism involved varies with the specific salts used and with the special part of the cell studied.

Relationships between the Concentration of Sugar and Other Diffusible Substances in the Blood and the Rates of Their Supply, Circulation, Excretion, etc. By R. T. WOODYATT, Chicago, Ill.

Normal resting dogs given lactose intravenously at constant rates of 5 and 10 grams per 10 kilos per hour for 4 hours in half molecular solution show a rising lactose excretion in the urine in the first and second hours of each period and a virtually constant output thereafter, when the output per hour in the urine equals the intake showing that lactose is virtually unsusceptible of chemical change in the body and unsusceptible of excretion by channels other than the kidneys. Other things being equal, the rate of lactose excretion depends on the rate at which lactose enters the circulating blood. The failure of lactose to appear in the urine quantitatively at the rate of injection in the early hours of injection is due to the

progressive retention of unchanged lactose in the body until the total quantity rises to a certain level. If S is the rate of lactose supply from all sources (in this case the rate of injection); E the rate of lactose excretion; R the rate at which the total quantity of lactose in the body increases; then, in the hours of equilibrium R is 0 and $S = E$; whereas, in the earlier hours, R has a positive value and $S = E + R$. In hours of equilibrium E is directly proportional to the total quantity of lactose in the body Q . This quantity Q is contained in a state of aqueous solution in a certain volume of water in the body which is in the state that permits it to act as a solvent for lactose. Anatomically this volume of water is represented by the blood, the lymph and analogous tissue fluids (blood-plasma-lymph phase). The lactose contained in the body tends to be in equilibrium throughout this phase, being partitioned between the different anatomical parts in proportion to their relative volumes. The concentration of lactose in the body as a whole, or in the watery phase of the body, or in any part of this phase such as the blood, need not be directly proportional to Q , because the volume of the body as a whole, or of the phase in question, or of that part of the phase represented by the blood is subject to change with variations of the total volume of water in the body, in the phase in question, or in any part of this phase. With Q constant, any change in the volume of the watery phase of the body necessitates a change of the blood lactose concentration, whether the volume of the circulating blood itself changes or not. Whereas during life changes in the volume of blood in actual circulation may be relatively small, changes in the volume of the watery phase as a whole can be relatively great. Hence the possibility of constancy of S , and Q with wide variations of the blood lactose concentration or of constancy of the blood lactose percentage with S and Q varying or of S and Q constant and E varying by virtue of a shifting of water from the blood into the extravascular parts of the watery phase of the body or *vice versa* in response to physico-chemical factors.

The rate of excretion of lactose depends primarily on the rate at which lactose enters the kidneys in the blood of the renal arteries. The latter rate is expressible as the blood lactose concentration times the rate of blood volume flow through the renal arteries.

Physico-Chemical Changes in the Blood of a Case of Pernicious Anemia. By A. V. BOCK and (by invitation) D. B. DILL, C. VAN CAULERT and H. FOLLING, Boston, Mass.

The Effects of Anesthetics on the Recovery Process of Skeletal Muscle. By J. C. MEAKINS and (by invitation) C. N. H. LONG, Montreal, Canada.

According to A. V. Hill, Meyerhoff and Embden, during muscular contraction glycogen is broken down to lactic acid via the intermediary substance "lactacidogen," while during recovery four-fifths to five-sixths of this lactic acid is reconverted into glycogen by both the active and passive muscles and also by the

liver. During an investigation on the relative parts played by the muscles and liver in this synthesis it was found:

1. That anesthetics (amytal, ether and chloroform) prevent this resynthesis to such a marked extent that three hours after stimulation under amytal practically none of the glycogen broken down had been restored.

2. Under amytal this resynthesis is delayed as long as the effect of the anesthesia persists, i.e., up to 12 hours, but under the volatile anesthetics it commences as soon as the full effect of them has worn off.

3. Under *local* anaesthesia an 80 to 100 per cent resynthesis of the glycogen broken down had occurred within three hours after stimulation.

4. Insulin by promoting glycogen deposits throughout the body hastens this recovery process, even when anesthesia is present.

5. Infusions of glucose without insulin act in the same manner.

6. The effect of anesthetics alone without any stimulation is to cause a decrease, some 10 to 15 per cent in 3 hours, in the glycogen content of the muscles.

The Source of Readily Available Body Calcium. By WALTER BAUER and FULLER ALBRIGHT (by invitation) and J. C. AUB, Boston, Mass.

Collip's parathyroid extract raises the blood calcium and the calcium excretion. However, no one has ever demonstrated whether this calcium comes equally from all bone structure or from some particular portion of each bone. It has been proven in lead poisoning (1), that upon administration of parathormone the excretion of both lead and calcium is increased at first, but after replacing the calcium loss by a high calcium diet a second administration of parathormone increases the calcium excretion alone. This indicates that a certain supply of calcium is readily available for sudden demands. The anatomic structure and blood supply of the bone trabeculae suggests these structures as the most probable source of this calcium.

Our problem was to see if we could influence the amount of cancellous bone by long continued administration of parathormone and by high and low calcium diets. Long continued administration of parathormone to rabbits resulted in definite signs of decalcification, most marked at the epiphyseal portion, easily demonstrated by x-ray. These bones on cross section, when compared with those from their normal litter mates showed a marked reduction in the number of trabeculae.

Eight cats were chosen for the experiment upon effect of diet. Four were placed on a low calcium diet of liver and meat and four on a high calcium diet of milk. At the end of six months the left foreleg was amputated at the shoulder and the diets reversed. At the end of a like period of time the animals were sacrificed. The bones representing the period when the cats were on a high calcium diet constantly showed many more trabeculae than did the bones representing the low calcium diet period.

In conclusion we can state the following:

1. The cancellous bone serves as the most readily available supply of calcium.

2. One can decalcify bones by the long continued administration of parathormone.

3. The decreasing potency of Collip's parathyroid extract seen in certain cases after prolonged administration may be dependent upon the depletion of this easily available calcium.

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The Influence of Pituitrin and Adrenalin on Insulin. By REGINALD FITZ and (by invitation) HARRY, BLOTNER, Boston, Mass.

We have observed in normal rabbits the effect on the blood sugar concentration of varying doses of insulin, pituitrin and adrenalin. Blood sugar curves obtained following the intravenous injection of insulin were much alike regardless of the amount introduced. There was, uniformly, a fall in blood sugar concentration followed by a more or less rapid rise to normal.

Pituitrin acted in an opposite fashion to insulin. Following its injection there was at first hyperglycemia followed by a fall in the blood sugar concentration with a resulting blood sugar curve almost directly the reverse of that obtained with insulin. In one fatal case the blood drawn immediately after death contained so low a sugar concentration as to suggest insulin poisoning.

Adrenalin acted not so exactly in an opposite fashion to insulin. Following its injection, there was at first hyperglycemia followed by a fall in the blood sugar concentration. The fall in the blood sugar level, however, was not immediate and resembled that obtained after intravenous injection of glucose rather than that obtained after pituitrin, and was not directly the reverse of that obtained with insulin. In one fatal case of adrenalin poisoning, the animal died with a very low blood sugar level and in convulsions. The clinical appearance suggested insulin poisoning.

We attempted to ascertain whether the fall in blood sugar concentration and resultant hypoglycemia obtained after injections of pituitrin and adrenalin were of the same nature, due to insulin set free in antagonism to the hyperglycemia at first produced by these substances or due to some other mechanism. Normal blood was transfused into an animal. It was followed by a pronounced hyperglycemia which gradually disappeared. Blood drawn from an animal which had been injected with 5 units of insulin 15 minutes previously was transfused into a normal rabbit. There was no resultant hyperglycemia, in contrast to that observed in the control animal, but an initial hypoglycemia and gradual rise to the normal level so that the curve obtained was entirely comparable to that seen in animals treated with insulin alone. Blood drawn from an animal which had been made hypoglycemic from pituitrin was transfused into a normal rabbit. There was no resultant hyperglycemia, in contrast to that observed in the control animal, but there was an initial hypoglycemia and gradual rise to the normal level so that the

curve obtained was entirely comparable to that seen in animals treated with insulin alone and to that recorded in the animal transfused with "insulinized" blood. Similar transfusion experiments were carried out by injecting normal animals with blood made hypoglycemic from adrenalin and glucose. In these cases there was an initial hyperglycemia followed by a return to the normal level so that the resultant curves resembled more closely those obtained in the control experiments than those obtained from "insulinized" or "pituirized" blood.

These experiments suggest that the effect of pituitrin upon the blood sugar is directly antagonistic to that of insulin, and that pituitrin hyperglycemia is controlled by a compensatory increase in the circulating insulin. In contrast, the disappearance of an excessive amount of blood sugar obtained from adrenalin injections appears to take place through some other mechanism and without the aid of an appreciable increase in the circulating insulin.

The Clinical Applications of Quantitative Pettenkofer Tests to the Blood. By L. G. ROWNTREE and (by invitation) M. ALDRICH and C. H. GREEN, Rochester, Minn.

Abnormal Specific Dynamic Action of Protein, Glucose and Fat Associated with Undernutrition. By EDWARD H. MASON, Montreal, Canada.

Six cases of undernutrition with definite abnormalities of specific dynamic action for protein, glucose and fat are reported. In five the onset of undernutrition was associated with definite symptoms of ill-health, the loss of weight varying from 5 to 28 kilos. These five cases had low basal metabolic rates.

The findings were controlled by similar experiments in seven normal individuals.

In four of the cases the maximum percentage increase in heat production over the basal level after a fat breakfast containing 74 grams of fat varied from 20.7 to 47.7 per cent. In three cases, after 100 grams of glucose the maximum rise in heat production varied from 22.8 to 52.0 per cent. Five cases, after a meal containing 150 or 200 grams of beef, showed a more rapid percentage rise in heat production than did the controls, but the total caloric increase did not vary greatly from the controls.

Regulation of the food intake in accordance with the altered specific dynamic action has resulted in a gain of weight in four cases. In the other two the period of observation has been too brief to judge.

Coincident with an improvement of nutrition the altered specific dynamic action returned to normal (two cases studied).

Varicella in Monkeys: Nuclear Inclusions Produced by Varicella Virus in the Testicles of Monkeys. By T. M. RIVERS, New York City, N. Y.

Many workers believe that acidophilic nuclear inclusions are the manifestation of the presence of certain viruses, amongst which is varicella. In a previous communication a report was made concerning eosin-staining nuclear inclusions

observed in the cells of monkeys' testicles inoculated with emulsified human varicella papules and vesicles. At the time of the previous paper there were reasons for the belief that the nuclear inclusions were produced by the action of varicella virus. Proof of this, however, was obtained only recently by means of neutralization and reinoculation tests and consists, in brief, of the following facts: Nuclear inclusions were not found in monkeys' testicles inoculated with a mixture of varicella virus and convalescent varicella serum. On the other hand, they were found in testicles inoculated with a mixture of virus and non-immune serum collected from varicella patients early in the disease. Furthermore, the inoculation of one testicle with varicella virus prevented the formation of nuclear inclusions in the other one when it was inoculated at a later date with the same virus.

Insulin Utilization in Acidosis. By H. FIELD, JR. (by invitation) and L. H. NEWBURGH, Ann Arbor, Mich.

An attempt has been made to determine the factors involved in the increased dosage of insulin required to produce a given effect on the sugar metabolism during the state of acidosis.

Observations have been made on completely depancreatized dogs receiving a constant intravenous infusion of glucose and insulin by means of a motor-driven pump. It has been possible to adjust the dosage of insulin and glucose so that the blood sugar, reduced to a normal level by a previous dose of insulin, has been maintained at that level. In animals so treated, the intravenous injection of hydrochloric acid has been followed by a sharp rise in blood sugar. In other experiments the order of procedure was reversed and acid injected at the beginning. In such animals it has been necessary to use a smaller inflow of glucose to maintain a constant blood sugar. The subsequent injection of a neutralizing dose of sodium bicarbonate has been followed by a progressive decrease in blood sugar.

Since, by such treatment the distribution of ions has been changed but none of foreign character added, this is considered to be evidence of a depressing influence on sugar metabolism of increased H-ion concentration.

The Specific Treatment of Pneumococcus Type II Pneumonia. By HORACE S. BALDWIN and WHEELAN DWIGHT SUTLIFF (by invitation) and RUSSELL L. CECIL, New York City, N. Y.

Pneumococcus Type II pneumonia is the most serious type encountered in Bellevue Hospital. In 89 cases that received no specific therapy the death rate was 42.6 per cent. Type II pneumonia is the pneumonia of septicemia. In a series of cases studied with blood cultures 43.3 per cent showed septicemia, and of the septic cases 90.3 per cent died. On the other hand, when the blood culture remained sterile the death rate was only 16 per cent. The object of the present study was to determine whether any of the specific agents now available for the treatment of Type II pneumonia were capable of sterilizing a patient's blood and

producing a balance of immune bodies in the patient's serum. Some of these cases were treated with a potent Type II antipneumococcus serum; others were treated with a concentrated serum prepared by the method of Felton.

Conclusions. With a potent Type II antipneumococcus serum it is possible to sterilize the blood in a certain number of cases of Type II pneumonia. The most striking results are obtained when serum is administered early in the course of the disease.

The Inhibiting Influence of Formaldehyde upon the Dale Reaction. By ARTHUR I. KENDALL (by invitation) and HARRY L. ALEXANDER, St. Louis, Mo.

Kendall (1) recently has shown that formaldehyde will inhibit smooth muscle contraction induced by histamine. It is believed that formaldehyde acts upon the amine group of histamine and that H_2 is removed. The resulting product is a methylene compound similar to that obtained in formol titration.

Essentially nothing is known concerning the stimulus which causes smooth muscle to contract in anaphylaxis. The above principle was applied to the Dale experiment as follows: The two uterine horns of a guinea pig sensitized to egg-white were suspended each in a separate Dale apparatus with baths of 150 cc. of oxygenated Tyrode's solution. To one bath 0.5 cc. egg-white solution was added and the immediate characteristic smooth muscle contraction recorded. To the other bath treated with 1.0 cc. of 3 per cent formaldehyde solution, 0.5 cc. egg-white solution was added. No contraction resulted. This bath was washed out and refilled with fresh Tyrode's solution. The addition of histamine then caused muscle contraction indicating that the contractility of muscle had not been impaired by formaldehyde.

When smooth muscle was allowed to contract in the absence of formaldehyde the reaction could be inhibited immediately by formaldehyde. This phase as well as the nature of the reaction is being studied.

It is possible that this demonstration may indicate the nature of the stimulus of smooth muscle contraction in anaphylaxis.

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Development of Agglutinins and Protective Antibodies in Rabbits Following Inhalation of Pneumococci. By E. G. STILLMAN, New York City, N. Y.

Rabbits are very susceptible to infection by inhalation of Type I pneumococci.

When rabbits are exposed to a pneumococcus spray, the bacteria readily penetrate into the lower respiratory tract. The pneumococci which reach the periphery of the lungs as a result of this procedure usually disappear within a few hours but a generalized and fatal septicemia frequently appears later. Pneumococci may then be recovered from the periphery of the kidney, liver, and spleen. In the animals which die, pleurisy and pericarditis are common but pneumonia does not occur.

Rabbits may recover from pneumococcus septicemia.

Following repeated inhalations of Type I pneumococci, agglutinins remain stationary after the fifth exposure, but the percentage of rabbits showing protective antibodies in their sera steadily rises.

The Heart after Severe Diphtheria. By T. D. JONES (by invitation), Charlottesville, Va., and PAUL D. WHITE, Boston, Mass.

The aspect most important for study in dealing with cardiovascular disease is its etiology, since further progress in the control and prevention of such disease is dependent on greater knowledge of its causes. One of the infections which is known sometimes to involve the heart severely during its course is diphtheria, but there has been insufficient knowledge of the more remote effects of diphtheria on the heart. Hence a study has been made by us by history, physical examination and electrocardiograph, of 100 young people who had severe diphtheria a few years before the examination, without complications from congenital defects or rheumatic valvular lesions. From this study there is no evidence of appreciable chronic effects of diphtheria on the heart.

Hyperthyroidism Associated with Bacterial Endocarditis. By JOSEPH A. CAPPS, Chicago, Ill.

Skin Reactions to Streptococcus Filtrates in Acute Streptococcus Infections in Acute Nephritis. By OSCAR C. HANSEN-PRUSS and D. P. O'BRIEN (by invitation) and WARFIELD T. LONGCOPE, Baltimore, Md.

Skin reactions to filtrates of various strains of streptococci have been studied in normal people and in patients with acute nephritis, and in patients suffering from acute streptococcus infections, such as tonsillitis.

The organisms which were used for the production of the toxins were obtained from the tonsils (either by tonsillar swabs or from the interior of the infected organ after operation) or from the sinuses or adenoid tissue of individuals which showed evidences of an active infection. Freshly isolated organisms were grown on blood agar slants for twenty-four hours and then transferred to 7.4 bouillon where they were allowed to grow for eighteen hours. The broth culture was then filtered through a Berkefeld N candle and the "toxin" injected intracutaneously in amounts of 0.1 cc. in dilutions varying from 1:100 to 1:5000. The reactions were read after eighteen and twenty-four hours. Reactions were interpreted as positive when the area of erythema, occasionally associated with edema, measured at least 1 cm. in diameter. As a control 7.4 bouillon was injected simultaneously in 1:100 dilution. A Dick reaction was performed at the same time.

1. Reactions were made in fifty-five normal adults and twelve normal babies as controls. Twenty per cent of the normal adults showed moderate reactions to at least one of the several different strains of streptococcus filtrates in dilutions of 1:100. These did not bear any relation to the presence or absence of a positive Dick test. In 16.5 per cent of the cases, reactions occurred in dilutions

greater than 1:100 (0.001 cc. of toxin). The babies varied in age from two to seven days; none of them gave a positive skin reaction to the Dick toxin or to the various streptococcus filtrates. The mothers of these babies were tested simultaneously with streptococcus filtrate and Dick toxin and in several instances gave positive reactions to the Dick toxin, streptococcus filtrates, or both.

2. Thirty-two adults suffering from acute tonsillitis or other forms of streptococcus infection were tested during the acute stage of the disease and at intervals after recovery. Cultures from the throat, nose or sinuses were made each time that they were subjected to skin tests. Positive skin reactions with 0.001 cc. of toxin were obtained almost uniformly in the acute stage of the disease; 37.5 per cent reacted to dilutions greater than 1:100; few reacted to more than three or four strains. It was found that this susceptibility to the streptococcus filtrates diminished as the infection subsided, or persisted if the organisms remained in the nose and throat for any length of time. In several instances it was possible to test the individuals with toxins made from the organisms obtained from their own nose and throat, to which they often reacted more vigorously than to heterologous strains.

3. Sixteen adults suffering from acute or subacute nephritis were tested repeatedly during the course of the disease. Positive skin reactions were obtained in 80 per cent of these cases during a period in which the evidences of acute illness were at their height. It was found, however, that these individuals tended to react to most of the strains which were tried. Fifty-six per cent gave reactions in dilutions greater than 1:100. These positive reactions did not bear any relation to the presence or absence of positive Dick tests. Most of these individuals were also tested with filtrates of streptococcus cultures from organisms obtained from their own nose, throat and sinuses. It was found that they were likely to react more strongly to filtrates from their own strains than from heterologous strains, and that they remained susceptible to these filtrates for a longer time than they did to the various other filtrates, especially if the local infection persisted. In a few instances a diminution, or even a complete loss of skin reaction to the streptococcus filtrates was observed when the acute nephritis subsided.

The Effect of Intravenously Injected Phosphate Solutions on the Blood and Urine Phosphorus in Man. By I. SCHULZ (by invitation) and N. M. KERR, Rochester, Minn.

The solution injected was a mixture of dibasic and monobasic sodium phosphates, balanced to give a pH of 7.1 to 7.2. Amounts up to 15 mgm. of phosphorus per kilogram of body weight were administered. No untoward subjective effects were noted. The normal subject was kept on a weighed, controlled diet. Phosphorus and calcium studies were made on blood, urine and feces.

After injection of the phosphate solution, there occurred an immediate rise of inorganic phosphorus in the blood, followed by a rapid fall. The normal phosphorus concentration was approached in four hours. The urine output ran

parallel to the blood concentration. An immediate rise of from 15 to 30 times the average normal output occurred, followed by a rapid drop for 3 hours. The phosphorus in the feces also definitely increased. The urinary excretion of calcium was slightly increased. The calcium of the feces was not affected. The ingestion of calcium chloride previous to injection of phosphate solution did not alter either the amount or the path of excretion of the phosphorus, although the calcium content of serum, urine, and feces was definitely increased.

In cases of renal disease with retention of creatinine and with a low excretion of phenolsulphonaphthalein, there was a retention of phosphorus after the injection of phosphate solution.

Liver Fractions in Pernicious Anemia. By RANDOLPH WEST, New York City, N. Y.

Since Minot's (1) demonstration of the great therapeutic efficacy of a high liver diet in pernicious anemia, we have been endeavoring to determine what substances in liver are responsible for this effect.

Spermine phosphate (2) which is present in much greater concentration in liver, kidney and pancreas than in muscle tissue, was fed in doses of 100 to 150 mgm. daily to four cases without any improvement in three of them over two-week periods. On switching to liver the improvement was dramatic.

Thioneine recently isolated by Benedict (3) from red blood cells was fed to one patient with a negative result.

Fresh minced moist liver was next extracted with 60 per cent alcohol (including tissue water), then ether, and finally boiling 95 per cent alcohol. The three extracts were filtered through paper and evaporated to dryness in vacuo. This residue in 10-gram doses twice daily was highly efficacious in five consecutive cases.

The 60 per cent alcohol fraction alone, after evaporation to dryness and repeated washings with 95 per cent alcohol and ether was then found effective in 8- to 10-gram doses daily in one case.

The material is water soluble, biuret negative, iron free, and contains 5.7 per cent N, 2.4 per cent amino-N, 2 per cent P and 1 per cent S.

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Further Studies on the Relation of Monilia to Pernicious Anemia. By O. GARCIA, CECILE GARCIA, and NANCY BOYCE (by invitation), and G. O. BROWN, St. Louis, Mo.

Ten strains of *Monilia* derived from cases of pernicious anemia, are closely related morphologically to each other and to the *Monilia Psilosis* of Ashford. Strains isolated from cases other than pernicious anemia sometimes show similar

morphological characters and sometimes differ widely from the *Monilia Psilosis* type.

The pernicious anemia strains so far studied all produce acid in media containing dextrose, levulose, maltose, galactose, dextrin and sucrose. The action on lactose, mannite, inulin and xylose varies with different strains. They do not produce acid in arabinose, sorbitol, raffinose and dulcitol. Four pernicious anemia strains which produce acid in dextrose, levulose, maltose, galactose, dextrin and sucrose are identical in fermentation reactions with nine other strains isolated from a wide variety of pathological conditions. One strain shows identical fermentation reactions with *Monilia Psilosis* of Ashford. The others fall into two groups which differ from all other strains studied.

The *Monilia* complement fixation test carried out with antigens made from a number of strains of *Monilia* show definite specific differences between strains. The pernicious anemia strains show some serological relationships but also some serological differences.

The *Monilia* isolated from pernicious anemia cases are therefore not absolutely identical although belonging to a closely related group.

Observations on the Size of the Red Blood Corpuscles Before and After Splenectomy in Hemolytic Jaundice. DUNCAN GRAHAM and (by invitation) R. F. FARQUHARSON and E. J. MALTBY, Toronto, Canada.

In the investigation of cases of hemolytic jaundice, both familial and acquired, considerable variation has been found in the degree of microcytosis present in the blood of different patients. In some it was so slight as to be of no significant importance in the diagnosis of the disease. A more careful study was therefore made of the size of the red blood corpuscles at different times, both before and after splenectomy, together with observations on the color, volume, and icterus indices, and the resistance of the red blood corpuscles to hypotonic salt solution. Measurements were made of the diameter of the red blood corpuscles at intervals before and after splenectomy in five cases of hemolytic jaundice and the frequency distributions of the red blood corpuscles of different sizes were determined.

Summary of results. 1. The mean diameter of the red blood corpuscles in cases of hemolytic jaundice before splenectomy is less than normal.

2. Shortly after splenectomy the mean diameter of the red blood corpuscles remains less than normal and may be even less than before splenectomy.

3. Later, after splenectomy, the mean diameter of the red blood corpuscles becomes greater and the percentage of cells having the mean diameter of normal red blood corpuscles increases.

4. Both before and after splenectomy the mean diameter of the red blood corpuscles may show definite variations at different times, more marked in certain cases than others.

5. The percentage of red blood corpuscles less than seven microns in diameter

decreases within a few weeks after splenectomy but this percentage always remains greater than normal.

6. The individual character of the microcytes present in cases of hemolytic jaundice, before and after splenectomy, remains the same.

The significance of these results is discussed.

Skeletal Changes in Gaucher's Splenomegaly. By SARA WELT, and N. ROSENTHAL (by invitation) and B. S. OPPENHEIMER, New York City, N. Y.

The diagnosis may be aided by finding (1) gross skeletal changes (gibbus, pathologic fracture, etc.), (2) characteristic x-ray changes in the bones, (3) Gaucher cells in material secured by bone-marrow puncture, splenic puncture, or splenectomy. Gross osseous changes were first described by Pick (1922) and have been present in 2 of our 8 cases collected since 1918. Characteristic radiographic changes were found in 3 cases, and bone-marrow involvement also in 3 cases. The family of every case of Gaucher disease should be investigated for gross skeletal changes, and should also be x-rayed to detect evidence of the disease.

Gaucher's original conception that this disease is a neoplasm of the spleen has been abandoned. Since the Gaucher substance has now been demonstrated to contain "kerasin," one of the cerebrosides, and a large proportion of phosphatids, the disease should now be considered a disorder of lipid metabolism in which complex lipoids fail of complete disintegration and are stored in the histiocytic elements of the reticulo-endothelial apparatus. Splenectomy cannot cure the disease, and is indicated only if the weight of the spleen becomes burdensome, or if the hemorrhagic tendency becomes serious. The characteristic low blood platelet count returned to normal after splenectomy.

The Effect of Emotion on the Basal Metabolic Rate. By SOLOMON STROUSE and (by invitation) H. F. BINSWANGER, and HARRY SEGAL, Chicago, Ill.

It would seem that one of the easiest methods of determining the effect of emotion on the basal metabolic rate would be its study in hospital patients just before operation. A series of such patients with various conditions, including toxic goiter, were carefully studied before and after knowledge of the impending operation. The basal metabolic rate, blood pressure, pulse rate and signs of disturbances of the nervous system were noted before the patient knew of the impending operation. The night before the operation, the patient was told about the operation and determinations were again made the next morning just before going into the operating room. Patients included in this study received no drugs. The results indicated practically no effect from this type of emotion in any of the patients studied.

Sulphemoglobinemia. By WALTER R. CAMPBELL and (by invitation) R. F. FARQUHARSON, Toronto, Canada.

Several cases of so-called enterogenous cyanosis with sulphemoglobin in the

red blood cells have been reported in the literature. Three new cases are described. Spectrographs demonstrating the identity of the pigment in these cases with sulphemoglobin are shown. New methods for the identification and estimation of the abnormal blood pigment have been devised. Chemical and bacteriological studies have been undertaken on these patients. The diagnosis, etiology and treatment of this condition are discussed.

Observations on the Etiology of Chronic Myocarditis. By JAMES P. O'HARE, and (by invitation) ABNER W. CALHOUN, and HUGO O. ALTNOW, Boston, Mass.

In May, 1922, Walker and one of us (O'Hare) presented to the Association of American Physicians a series of observations made on the relation between blood pressure and peripheral and retinal arteriosclerosis. In that paper we concluded that the finding of retinal arteriosclerosis almost invariably indicated hypertension, present or past. We now wish to present a series of cases of known chronic myocarditis without valve lesions and with normal blood pressures but with retinal arteriosclerosis. These patients are known to have previously had hypertension. These cases are offered as proof of the theory that chronic myocarditis without valvular or thyroid disease is part of a hypertensive syndrome. We expect to have a group of cases of chronic myocarditis of valvular origin to contrast with this hypertensive group.

Studies of the Heart in Thyroid Disease. I. Changes in the "T" Wave of the Human Electrocardiogram Following Iodin Medication and Thyroidectomy. By WALTER W. HAMBURGER and (by invitation) MORRIS W. LEV, and HELEN C. HOWARD, New York City, N. Y.

This paper is the first of a series of reports concerning the heart in thyroid disease. Clinical studies of the pulse rate, blood pressure, and heart size during rest, digitalis and iodine medication, and after thyroidectomy, are in progress, as well as experimental studies on the production of iodine and thyroid myocarditis similar to the work of Takane and Hashimoto.

The present paper concerns the changes in the "T" wave of the human electrocardiogram following iodine medication and thyroidectomy. These changes, which are not always constant, may be stated in general as follows: In those cases which are responding favorably, there is a marked lowering of the height of the "T" wave, in some cases continuing to inversion (negativity). In those cases, not responding favorably, the "T" wave increases in height. Similar, though less marked changes occur in some cases in the "P" wave. These changes are probably not specific iodine effects, but more likely indicate changes in the effectiveness of the heart muscle, similar to the changes in the "T" wave resulting from digitalization. Evidence is also offered of the possibility of these changes being due to variations in sympathetic (accelerator) tone, in accord with the experiments of Rothberger and Winterberg.

It is hoped that further studies will show that these changes may serve as a guide for iodine tolerance and sufficient dosage, as well as an aid among the differential indications for digitalis or iodine in the treatment of the goitre heart.

Cardiac Pain with Paroxysmal Tachycardia. By ARLIE R. BARNES (by invitation) and FRÉDÉRIK A. WILLIUS, Rochester, Minn.

Nineteen cases of paroxysmal tachycardia are cited to call attention to the fact that pain, which simulates closely that seen in angina pectoris, may be present in the attacks. The electrocardiographic findings are discussed. A comparison of the duration of time since the first seizures occurred and the time elapsing since pain first occurred in the seizures is made. A detailed description of the type, location, and radiation of the pain together with attendant phenomena is given. The factors precipitating the pain and bringing about its relief are contrasted with those acting in angina pectoris. Abstracts of the histories and findings in six patients are included. Prognosis is discussed and the favorable outlook in these patients as contrasted with patients suffering with angina pectoris is pointed out. Attention is called to the fact that favorable results from therapy may be expected only when the treatment is directed toward the control of the paroxysms of tachycardia. Finally, the mechanism probably concerned in the production of pain in these patients is discussed in the light of recent physiological experiments on coronary blood flow and on the circulation in attacks of paroxysmal tachycardia.

Ergotamine in Hyperthyroidism By E. COWLES ANDRUS, Baltimore, Md.

Ergotamine tartrate injected intravenously in dogs after the vagus has been functionally excluded slows the rate of the sinus rhythm, depresses A-V conduction, and delays the transmission of the excitatory process in the auricle.

Clinical use of this drug has been made in cases of hyperthyroidism. Administered in doses of from 3 to 6 mgm. per diem before and after operation ergotamine inhibits the post-operative tachycardia and enhances the rate of recovery from operation.

The Relation of Size of the Heart to Effectiveness of Digitalis Therapy. By A. E.

COHN, H. J. STEWART, and (by invitation) A. R. GILCHRIST, New York City, N. Y.

Harrison and Leonard contend that digitalis decreases cardiac volume output and rate of blood flow. This idea modifies current notions so much that we have tested its validity. We conclude that heart size neglected by them is of prime importance. If digitalis reduces this below a certain volume, output and flow necessarily decrease. In disease, increased cardiac size is similarly reduced. We studied blood flow in normal dogs' hearts during normal rhythm and auricular fibrillation with and without digitalis. In artificial fibrillation cardiac size increased and the rate of flow decreased. When digitalis was given both size and

flow returned towards normal. After cessation of fibrillation but with digitalis there was a further return towards normal and *beyond*, so that blood flow was reduced. This last state corresponds with Harrison and Leonard's result.

The result with digitalis therefore in normal regular hearts differs from that in enlarged fibrillatory ones and, by inference, from that in enlarged regular ones. The size of the heart should have been considered by Harrison and Leonard; their inferences without considering this factor are not justified. Current belief is therefore correct.

Observations on Synovial Fluid. By RALPH PEMBERTON and (by invitation) F. A. CAJORI, Philadelphia, Pa.

The concentration of certain diffusible constituents and the reaction are very similar in blood and synovial fluid. It has also been shown that glucose readily diffuses from the blood into synovial fluid.

In the present experiments synovial fluid and blood have been compared with respect to non-protein nitrogen, urea and amino-acids. Almost identical values have been found.

The proteins of synovial fluid, which are present in lower concentration than in plasma, have been fractionated. The globulin content was found to vary more in different synovial fluids than is the case in plasmas and the albumin-globulin ratio is somewhat higher than is usually encountered in plasma. This was particularly true in the synovial fluid of the one case of anasarca studied. The mucin content gives to synovial fluid its high viscosity.

One sterile synovial fluid with a white cell count of 14,000, pH 6.50, and containing only traces of sugar was studied. It was found that rapid glycolysis occurred in this fluid with the production of lactic acid. The high acidity and absence of sugar, characteristic of "septic" joint fluids, are probably to be ascribed to glycolysis by the leucocytes occurring in the joint cavity. The degree of acidity and the amount of sugar may be a measure of the extent of the inflammatory process.

The Clinical Symptoms of Bilateral Thrombosis of the Suprarenal Veins. By EDWIN F. HIRSCH and JOSEPH A. CAPPS, Chicago, Ill.

A man, 30 years of age, came under observation because of weakness, shortness of breath, nervousness, sleeplessness, fulness of the head and headache, poor appetite, and attacks of cyanosis accompanied by unconsciousness. The attacks of cyanosis increased in severity, and death occurred nineteen days after admission to the hospital and about six weeks after the onset of symptoms. A careful post-mortem examination of the head, neck, and trunk demonstrated a bilateral thrombosis of the suprarenal veins, and no other lesions that could be considered sufficient to cause death. The thrombi, histologically, were mixed, containing both recent portions and older portions in the process of organization. The origin is considered to be probably bacterial. Our interpretation of the

clinical symptoms is that they followed temporary sudden suppression of the function of the suprarenal glands recurring until finally death occurred.

Some Experimental Observations on the Effect of Diathermy on the Circulation.

By C. L. BROWN and H. L. ALT (by invitation), and S. A. LEVINE, Boston, Mass.

Experiments were carried out on rabbits to study the effect of diathermy on the heart size, electrocardiographic changes and the blood pressure. It was first necessary to study the temperature changes inside the body when the diathermy electrodes were applied on the outside of the chest. It has generally been assumed that the temperature is greatest mid-way between the electrodes, and that in that way localized heat could be produced within the body. In our experiments we found that temperature inside the chest is a great deal less than the skin temperature. In fact, in order to obtain great increases in temperature in the vicinity of the heart, it was necessary to raise the temperature of the skin so that burns and sloughs were produced. One reason for this is that any heat produced in the vicinity of the heart would be carried off by the blood stream. There is also reason to believe that the rise in temperature within the body when diathermy is used clinically is very slight. With the method we employed, no appreciable change in the size of the heart by x-ray examinations and no significant electrocardiographic changes resulted, but a temporary slight fall in pressure was obtained as a result of diathermy.

A Critical Study of Diathermy. By CARL A. L. BINGER and (by invitation) RONALD V. CHRISTIE, New York City, N. Y.

The Static System and Its Relation to Cerebellar Function. By J. RAMSAY HUNT, New York City, N. Y.

According to the author the function of motility is subserved by two separate systems which are represented at all physiological levels of the central nervous system.

The Kinetic System is concerned with movement and the Static System with posture. The Kinetic System is responsible for fibrillary twitchings, the tendon reflexes, convulsions, chorea, tremor and other forms of motional disturbance. The Static System is responsible for the "lengthening and shortening" reactions of muscles, myotonia, catatonia and cerebellar symptoms. The cerebellum is the chief ganglion of the Static System and with its cerebral and spinal connections constitutes the Static System. The various components of the cerebellar syndrome—*asynergia*—are all referable to a disorder of posture—*synergy*. *Posture—synergy*, therefore, is the essential function of the cerebellum.

The Treatment of Pernicious Anemia with a Vitamin-Rich High-Caloric Diet.

By KARL K. KOESSLER and SIEGFRIED MAURER (by invitation), Chicago, Ill.

The vitamin theory of pernicious anemia which forms the basis of the dietetic treatment in man and of the experimental production of the blood picture in the animal may be briefly expressed as follows:

1. The blood changes and the changes in the gastro-intestinal tract may be due to underfeeding with vitamin A or to a vitamin A imbalance over a long period of years.
2. The nervous symptoms may be related to a deficiency in vitamin B.
3. The tendency to hemorrhages may be due to a partial or complete lack of vitamin C.

Twenty-five patients with pernicious anemia have taken a diet devised to be rich in vitamins A, B and C, and of high caloric value from three months to nearly two years.

From two to three weeks after the diet has been started a prompt remission sets in. Blood regeneration increases and proceeds in a normal manner. Blood destruction ceases and inside of from ten to fourteen weeks the blood is normal in every respect numerically as well as morphologically. One patient died suddenly two months after treatment had been instituted. No autopsy was obtained. All others are alive and much improved subjectively as well as objectively. No relapse has occurred in any one of the patients since the treatment has been started. None of our patients has received a blood transfusion. Associated with the improvement of the blood is frequently a definite improvement in the subjective and objective symptoms due to spinal cord degeneration. The achylia gastrica has remained unaffected by the treatment.