

**PROCEEDINGS OF THE TWENTY-THIRD ANNUAL MEETING OF
THE AMERICAN SOCIETY FOR CLINICAL INVESTIGATION HELD
IN ATLANTIC CITY, N. J., MAY 4, 1931**

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The Effect of Phosphate Ingestion in Clinical Hyperparathyroidism with a Note as to What This Teaches Us Concerning the Physiology of the Parathyroid Glands. By FULLER ALBRIGHT and (by invitation) JESSIE REED COCKRILL, Boston, Mass.

Hyperparathyroidism is associated with four well recognized alterations in calcium and phosphorus metabolism: (1) hypercalcemia, (2) hypophosphatemia, (3) hypercalcinuria, and (4) hyperphosphaturia. According to the theory of Albright and Ellsworth these are interrelated facts and dependent on a primary action of parathyroid hormone on phosphorus metabolism. They believe the administration of the hormone produces an increased urinary phosphorus excretion with a resulting decreased serum phosphorus level. The calcium deviations from the normal are, they believe, secondary to and dependent on the phosphorus changes. As a test of this theory phosphate by mouth was administered to patients with clinical hyperparathyroidism in the hope that this would raise the lowered serum phosphorus; that the raising of the serum phosphorus would lower the serum calcium; and that the lowering of the serum calcium would decrease the calcium excretion in the urine. This was accomplished in two patients and the data of one of these patients are briefly presented. Inasmuch as the metabolic abnormalities of hyperparathyroidism can be altered in the direction of normal by influencing the phosphorus metabolism, support is added to the theory that the parathyroid hormone produces these alterations in the first place by acting on the phosphorus metabolism.

Direct Measurements of the Oxygen Consumption of Isolated Beating Auricles from Normal and Thyrotoxic Guinea Pigs. By DONALD MCEACHERN (by invitation) and E. COWLES ANDRUS, Baltimore, Md.

Last year a report was made before this society showing that the auricles and the hearts of thyrotoxic animals continued to beat, when isolated, at a much faster rate than similar preparations from normal animals. This seemed to indicate a persistence of the specific thyroid effect on the isolated tissue. It seemed of interest, therefore, to study directly the oxygen consumption of these preparations.

In a modified Warburg respirometer direct estimations were made of the oxygen consumption of isolated auricles from normal and thyrotoxic guinea pigs. In a series of over 80 experiments the oxygen consumption of the

latter preparations was found to be greater than that of the normals. For a series of auricles weighing between 10 and 20 mgm.¹ the increase amounted to 7.3 per cent; for a series weighing between 21 and 30 mgm., 11 per cent; and for a series weighing between 31 and 40 mgm. the increase in oxygen use amounted to 20.7 per cent above that of the normals.

These increases are considered greater than can be accounted for by the simple increase of rate of beat in the preparations from thyrotoxic animals. The increased oxygen use is thought to indicate an enhanced rate of metabolism in the isolated tissues due to the action of thyroxine. Experiments are under way to determine the same point in regard to resting tissues.

The Effects of Pituitary Anti-Diuresis in Epilepsy. By IRVINE McQUARRIE and (by invitation) DANIEL PEELER, Minneapolis, Minn.

The relationship previously shown to exist between the state of hydration of the body and the occurrence of seizures in severely epileptic children has been found to hold also for early or mild cases under special conditions. Heretofore no satisfactory method has been available for the early diagnosis of the disease, especially during the long, free intervals between attacks. The present study has demonstrated, however, that convulsions or petit mal seizures can be induced almost at will in these patients by placing them on a special regimen with low mineral and relatively high water intake while administering the anti-diuretic principle from the hypophysis cerebri at sufficiently frequent intervals to prevent water diuresis. Seizures occurred regularly in a fairly large series of epileptic subjects when amounts of water equaling from two to four per cent of the body weight had been retained. Non-epileptic control subjects did not have seizures of any kind under the same or even more rigorous conditions.

That the convulsive reactions so produced are not due to the direct pressor action of the extract on the cerebral vessels nor to increased intracranial pressure *per se* has been fairly satisfactorily shown. Under the conditions of this special procedure, the extracellular body fluids probably become sufficiently diluted to cause imbibition of a large excess of water by the brain cells. Preliminary data point to a resulting disturbance in the ionic equilibrium between the fluids on the two sides of the cell membrane. When an amount of NaCl, calculated to be just sufficient to prevent this dilution, was added to the diet, seizures either did not occur at all or occurred only after a much greater gain in weight had been produced. The more or less specific response of epileptic patients to this procedure suggests that the inherent functional abnormality of the brain cells, which is vaguely alluded to by various authors as characterizing the chronic convulsive state, may be brought to light by further investigations along this line.

¹ Dry weight.

The Effect of Epileptic Convulsions and the Ketogenic Diet on Water Balance. By FRANK B. BYROM (by invitation) and RUSSELL M. WILDER. Chicago, Ill.

Water balance studies were made in three epileptic patients, using methods based on the work of Benedict and Newburgh.

The individual convulsions of epilepsy usually provoke a loss of water (up to 1000 cc.); yet subsequent convulsions may occur within a few hours of such dehydration, and be absent in the reactionary period of water retention. These fluctuations coincide with the alterations in sodium excretion described by Gamble and Hamilton.

A ketogenic diet induces an initial loss of 1000 to 2000 cc. of body water. A withdrawal of fixed base (sodium) accompanies it.

Attacks may occur despite such dehydration. Coincident with the adequate mobilization of the urea-ammonia mechanism for economizing fixed base, the rate of water loss diminishes and equilibrium is reestablished at a lower level. A temporary negative nitrogen balance also occurs.

These experiments indicate that, when the body water is allowed to adjust itself in response to fluctuations in fixed base, the onset of the convulsion is not simply determined by the level of body fluid.

Osmotic Pressure and Electrolyte Concentration of Blood Serum in Acute Alcoholic Intoxication and in the Acute Psychoses of Chronic Alcoholism. By ROY H. TURNER, New Orleans, La.

Blood serums from seventeen individuals in various stages of acute alcoholic intoxication and seven patients suffering from acute psychoses of chronic alcoholism have been studied. Total osmotic pressure was determined by cryoscopy. The chemical determinations made were: total fixed base, chlorides, CO₂ content, albumin and globulin, inorganic phosphate, glucose, nonprotein nitrogen, and alcohol. Osmotic pressure was calculated from the results of chemical analyses and calculated values were compared with determined values.

In the individuals with acute alcoholic intoxication, osmotic pressures due to electrolytes were within the normal range; no marked disturbances of acid-base equilibrium were found. The total osmotic pressures were found to be increased roughly proportional to the degree of intoxication, being above the physiologic range in all who were definitely intoxicated and reaching levels above 370 osmolar millimoles in comatose individuals. The increased osmotic pressure was due chiefly to alcohol in the serum.

In four patients showing acute psychosis of chronic alcoholism, total electrolyte concentration was less than normal, though total osmotic pressure as determined was normal. In another such patient, though total electrolyte concentration was normal, base bound by organic acids was greatly increased and chloride concentration was greatly diminished. The serums of three other patients with mild brief symptoms showed little that was abnormal.

It is suggested that the increased osmotic pressure of the blood serum in acute alcoholic intoxication may play an important part in the disturbed physiology and in chronic alcoholism may bring about undue loss of body electrolyte, which along with inadequate electrolyte intake may result in diminished electrolyte concentration in body fluids and cells and thereby play an important part in the production of delirium tremens and alcoholic hallucinosis. The relationship of these findings to various clinical features of alcoholism is discussed.

Spinal Fluids in Hypertensive Disease. By JAMES P. O'HARE and (by invitation) SAMUEL A. SHELBURNE and DANIEL BLAIN, Boston, Mass.

In an attempt to find out whether lumbar puncture might be used as a therapeutic agent in hypertensive conditions we submitted fifty patients with high blood pressure to this maneuver. The dynamics of the spinal fluid were investigated together with the blood pressure, the condition of the optic discs, x-rays of the skull and the renal function. The results of the studies may be summarized as follows.

Spinal fluid pressure was found to be increased in twenty out of fifty cases of hypertension, or forty per cent. The increased pressure occurred independently of renal function but was more often associated with renal insufficiency. Increased spinal fluid pressure was in every case associated with edema of the optic discs and higher spinal pressures seemed paralleled by greater choking. In every case but one increased spinal fluid pressure was associated with a diastolic blood pressure of 120 mm. Hg or more, although there were eight cases of diastolic blood pressure above 130 with a normal spinal fluid pressure. The average blood pressures in the cases with increased spinal fluid pressures were about twenty points higher in both the systolic and diastolic phases. X-rays of the skull showed increased pressure markings in only two out of thirty-two cases. These two were in patients who showed increased spinal fluid pressure. Headache was more frequent with increased spinal fluid pressure but occurred without it.

Fowler's Solution in the Treatment of Chronic Myelogenous Leukemia. By CLAUDE E. FORKNER, T. F. McNAIR SCOTT (by invitation) and GEORGE R. MINOT, Boston, Mass.

Medical literature prior to 1903 contains numerous reports concerning the value of arsenic in chronic myelogenous leukemia. Distinctive data regarding the effect of this element are few. They indicate, however, that the administration of Fowler's solution may reduce the number of circulating white blood cells in leukemia and cause clinical improvement.

With the advent of roentgen ray treatment, the administration of Fowler's solution fell into disrepute.

The effects of Fowler's solution have been studied in ten cases of chronic myelogenous leukemia. Nine of these cases have shown the following responses to treatment brought about in from three to five weeks.

(a) The total number of white blood cells was reduced to near normal limits or even to below normal.

(b) The immature cells practically disappeared from the blood.

(c) In every case the progress of the anemia was arrested and in most of the cases the red blood cell and hemoglobin values rose to near the normal.

(d) The blood platelets remained in normal or moderately increased numbers even in the leucopenic phases.

(e) The spleen and liver were reduced in size in all cases. In two cases, each with a large liver and a spleen extending to below the level of the umbilicus, these organs were no longer palpable.

(f) The basal metabolic rate was reduced to normal.

(g) The patients gained weight and were subjectively and objectively improved.

(h) During the fall in the number of leucocytes, the numbers of nucleated red blood corpuscles and the relative numbers of polymorphonuclear basophils and monocytes may be greatly increased.

(i) When Fowler's solution was omitted the signs and symptoms returned in a few weeks, but the improvement could be maintained at least for a few months by continued small doses of the drug.

One case of six years' duration and in the terminal stage of the disease failed to respond to treatment.

These uncompleted observations suggest that Fowler's solution is of definite value in the palliative treatment of chronic myelogenous leukemia and perhaps can be used in conjunction with roentgen ray therapy for the best known sort of palliative treatment.

The Relation of Available Iron to Acid and Alkaline Diets. By HERMAN H. RIECKER, Ann Arbor, Mich.

Previous experiments upon dogs having chronic anemia from hemorrhage had suggested that in this type of anemia the sole underlying factor was iron starvation. This conclusion was refuted by Whipple, who found an added effect upon blood regeneration when whole liver was added to inorganic iron. Kiefer reported similar results in chronic anemias of patients and Mettier and Minot found that hydrochloric acid administration with iron caused an increased response of the reticulocyte count, over that induced by iron alone.

The explanation for these diverse results is derived from the very sensitive solubility of iron salts in acid and is applied to cases having an anemia of iron starvation.

Experimental studies on this point were carried out as follows: In a normal individual the daily output of urinary iron was determined and its relation to diet, to excessive iron intake and to excessive fluid intake.

In a patient recovering from pernicious anemia with achlorhydria (having large reserve iron stores) the urinary output of iron could be increased

more than 100 per cent by administering sodium bicarbonate. In the same patient the excretion decreased when small amounts of ammonium chloride were given. A diet neutral as to salts and a constant water intake were provided.

The experiment was repeated using a normal dog in which the total iron metabolism (food intake; hair, stool and urine output) was determined, confirming the result that a highly acid salt (NH_4Cl) held iron in the body.

Finally, patients with severe secondary anemia from hemorrhage were used, repeating the previous procedure to show that absorbed iron in iron starvation became increasingly available for blood formation.

It is believed that the results of Whipple on dogs and Kiefer on patients using large amounts of whole liver are explained on the basis that liver, being a highly acid food, conserves the available iron in cases of iron starvation for utilization in blood formation.

Since 100 grams of liver have an acid equivalent of 10 cc. of N/10 HCl, and an iron content of 8.3 mgm., its value in iron starvation is quite apparent.

Mineral Metabolism during Treatment of a Case of Polycythemia Vera. By SAMUEL H. BASSETT (by invitation) and WM. S. MCCANN, Rochester, N. Y.

A case of polycythemia vera presenting the classical features of this condition, namely, brick red color of face, hands, and feet, enlargement of the spleen, and polycythemia, was studied during a period of treatment with acetylphenylhydrazine. Blood studies and mineral balances, including nitrogen, phosphorus, calcium, magnesium, and iron, were carried out simultaneously. The administration of 2.9 grams of acetylphenylhydrazine in doses of 0.2 to 0.3 gram per day resulted in marked reduction of total blood volume, cell volume, hemoglobin, and erythrocyte count. An increase in leucocyte count, icterus index and plasma volume occurred during blood destruction.

The destruction of approximately 900 grams of hemoglobin in 20 days with consequent liberation of about 3 grams of iron did not result in loss of body iron. Hemoglobinuria is believed to have accounted for increased iron excretion in the urine during the periods of erythrocyte disintegration.

Marked loss of nitrogen took place during the periods of blood destruction but the loss did not seem of sufficient magnitude to account for all the nitrogen contained in the destroyed erythrocytes.

Significant changes in the metabolism of phosphorus, calcium, and magnesium were not demonstrated.

The Presence of Heterophilic Antibodies in Infectious Mononucleosis. By JOHN R. PAUL and (by invitation) W. W. BUNNELL, New Haven, Conn.

Heterophilic antibodies are antibodies having the capacity to react with certain antigens which are quite different from, and phylogenetically un-

related to the one instrumental in their production. Horse serum, for instance, when injected into human beings, may produce agglutinins for sheep cells, and their presence, as has been recently shown by Davidsohn, seems to parallel clinical features of serum disease.

That heterophilic antibodies, demonstrable in the form of sheep cell agglutinins, develop in cases of infectious mononucleosis in even higher concentration than in serum disease, is described in this report.

In our study of four cases, their presence was a constant feature of the acute phase of the disease while an excess of mononuclear cells was present in the blood. Among other common blood dyscrasias, including lymphatic leukemia, heterophilic antibodies were not demonstrated. They were noted, however, in a single obscure case, thought to be aplastic anemia.

The reaction described in this disease must be essentially non-specific, although it would seem to be of practical diagnostic value. Our interest centers mainly upon its occurrence in an infectious disease of obscure nature. Theories of the possible mechanisms involved are briefly discussed.

The Significance of the Type Specific Skin Test in the Serum Treatment of Pneumonia. (Type I.) By THOMAS FRANCIS, JR. (by invitation), and WILLIAM S. TILLET, Baltimore, Md.

A study was made of the cutaneous reactions to the specific capsular polysaccharide of Type I pneumococcus in Type I pneumonia patients. A positive reaction, which takes the form of an immediate wheal and erythema, is first elicited at, or about the time of, crisis and is always associated with the presence of circulating type-specific antibodies. In patients treated with Type I antipneumococcus serum it was observed that the mere presence of circulating antibodies was not the only essential factor in the production of a positive test.

Of 35 cases studied, 31 received serum. Four untreated control cases gave positive reactions at the time of recovery. In 5 fatal cases no positive reactions were obtained. Of the 26 serum treated patients who recovered, 25 gave positive reactions when recovery began, but not before. The one recovered case with negative skin tests developed empyema.

A positive reaction denotes recovery and serum therapy may be safely discontinued. A negative reaction is an indication for further administration of serum. If, in the face of prolonged treatment, the reaction remains negative, a purulent complication should be suspected. If none is found, serum administration should be continued although the prognosis is unfavorable.

Experimental Lobar Pneumonia in the Dog. By E. E. TERRELL (by invitation), O. H. ROBERTSON and (by invitation) L. T. COGGESHALL, Chicago, Ill.

Using a method previously described by us for the production of pneumococcus lobar pneumonia in the dog, consisting essentially of the intra-

bronchial implantation of pneumococci suspended in a starch broth mixture, a study has been made of the evolution of the experimental disease from its inception to the complete disappearance of the lung lesions. The disease can be induced constantly with very small quantities of pneumococci; it resembles human lobar pneumonia in that the process produces complete consolidation of a lobe, then spreads from lobe to lobe, is characteristically localized in the lungs and usually terminates abruptly. It differs from the typical disease in human beings by running a shorter course—usually three to five days, although it sometimes lasts six or seven days. One attack does not confer immunity against subsequent infection—although the succeeding attacks are milder in character, indicating the acquisition of immunity. No evidence of allergy to the pneumococcus was obtained either by skin reaction or intrapulmonary injection of the pneumococcus autolysate. The lungs show at different stages engorgement and red hepatization and if the disease lasts six to seven days, a modified gray hepatization occurs. Studies of the pathology of the lesion reveal a histology in its main features analogous to the picture of lobar pneumonia in the human being.

Natural Immunity of Man to the Pneumococcus. By W. D. SUTLIFF, MAXWELL FINLAND (by invitation) and HENRY JACKSON, JR., Boston, Mass.

A search has been made by means of various immunological methods for measurable differences in susceptibility to pneumococci of Type I, Type II, and Type III among persons of different age groups.

Relatively few persons possess blood pneumococidal power for Type I pneumococcus; nearly all possess blood pneumococidal power for Type II pneumococcus; and an intermediate number possess blood pneumococidal power for Type III pneumococcus. The blood of infants obtained at birth from the umbilical cord possesses pneumococidal action fairly frequently. Samples of blood at the time of delivery from the mothers of these infants gave the same results. In the group of infants aged from 1 month to 15 months, pneumococidal action is comparatively rare for all three types. In the age groups 2 to 11 years and 20 to 40 years, pneumococidal action is met with increasing frequency. In old age, fewer persons possess pneumococidal power.

Protection tests and agglutination tests gave comparatively few positive results and thus do not afford reliable comparisons.

The skin reaction to the specific soluble substance could not be interpreted in the infants due to the usual appearance of a marked erythema lasting 30 minutes or more. No characteristic wheals were seen. In the other age groups the number of positive reactors to the specific soluble substance was fairly constant. Type II soluble substance gave rise to reactions more frequently than Type I or Type III soluble substances.

The percentage of reactors to the pneumococcus protein and autolysate is uniformly lower in infants than in the other age groups. This is also true for the protein derived from the *Streptococcus hemolyticus*.

An incidental finding in connection with the skin tests is that of the appearance of antibodies following the skin tests.

The fluctuation in the incidence of pneumococidal power with age resembles inversely the mortality curves of pneumonia with age. The frequency of whole blood pneumococidal power among the admissions to the Boston City Hospital is the reverse of the incidence of the three types in the pneumonia cases in the Boston City Hospital.

The reactions to intradermal injection of pneumococcus proteins and autolysates, which are less frequent in infants than in any other age group, indicate that individuals during childhood become sensitive to proteins contained in the pneumococcus as they do to other bacterial proteins.

A Study of the Rôle of the Phagocytic Mononuclear Cell in Experimental Syphilis. By HUGH J. MORGAN and (by invitation) SEALE HARRIS, JR., R. S. CUNNINGHAM and EDNA H. TOMPKINS, Nashville, Tenn.

Morgan¹ has shown that a basic feature of the microscopic pathology of experimental syphilis is an increase in size, number and physiologic activity of phagocytic mononuclear cells of the tissues. The rôle played by these cells in the pathogenesis of syphilis is being studied.

There is evidence (especially in the work of Simpson²) that intravenous injections of trypan blue stimulate the production of phagocytic tissue mononuclear cells. On this assumption a series of experiments has been undertaken to investigate syphilis in animals receiving trypan blue.

In one experiment rabbits with well developed syphilitic lesions were given trypan blue intravenously. It was found that the lesions in these animals resolved more rapidly than in a control group receiving no dye. The dye did not sterilize the lesions of treponema. This was demonstrated by subsequent transference of the infection to normal rabbits.

In a second experiment trypan blue was given rabbits at the time of inoculation with *Treponema pallidum*. In these animals the lesions appeared later than in the control group which received no dye.

Further studies are being conducted in order to determine whether or not the modification of the disease observed in the above experiments is due specifically to the effect of the trypan blue on the mononuclear cells or to some other factor.

Studies in Rheumatoid Arthritis. By M. H. DAWSON and (by invitation) R. H. BOOTS, New York, N. Y.

(a) *Bacteriological investigations.* Bacteriological investigations have been carried out on the blood, synovial fluid and subcutaneous nodules from a large series of cases of rheumatoid arthritis. In particular, attempts were

¹ Morgan, M. J.: Trans. Assoc. Am. Phys., 1930, xlv, 67.

² Simpson, M.: J. Med. Res., 1921, lxiii, 77.

made to confirm the results recently reported by Cecil, Nicholls and Stainsby. The results of all bacteriological studies have been negative.

(b) *Subcutaneous nodules.* The studies on subcutaneous nodules, reported last year, have been extended. These observations indicate that the subcutaneous nodules occurring in rheumatoid arthritis constitute a classical lesion of the disease. Studies on the histogenesis of the lesions show an intimate relationship between the subcutaneous nodules in this disease and those found in rheumatic fever.

(c) *Sedimentation rate of the erythrocytes.* The determination of the sedimentation rate of the erythrocytes has been found to be of distinct clinical value. The results of approximately 1000 observations may be briefly stated as follows:

(1) The sedimentation rate serves as a useful guide in the differential diagnosis of rheumatoid and osteo-arthritis.

(2) In rheumatoid arthritis the sedimentation rate parallels to an extraordinary degree the activity of the process.

(b) *Agglutination reactions with hemolytic streptococci.* It has been found that the sera of patients with rheumatoid arthritis possess the property of agglutinating hemolytic streptococci to an extraordinarily high titer. The observations indicate that the agglutination phenomenon is confined to *hemolytic* streptococci. The sera of a large series of control cases have failed to show evidence of agglutinins for the strains of hemolytic streptococci examined. The hypothesis is advanced that the disease, rheumatoid arthritis, results from infection with *Streptococcus hemolyticus*.

The Formation of Glycogen in Mammalian Muscle from d-Lactic Acid and Glucose. By J. C. MEAKINS and (by invitation) C. N. H. LONG, Montreal.

The work of Meyerhof and others has shown in the exercised, isolated frog's muscle that as the preformed lactic acid disappears, an equivalent of four-fifths of it reappears as glycogen. Furthermore, Meyerhof has found that perfusion of frog muscle with sodium lactate leads to the formation of muscle glycogen, although others have been unable to confirm these results (Eggleton and Evans).

In the mammal the conversion of lactic acid into muscle glycogen, either after exercise or during perfusion, has not been satisfactorily demonstrated.

In these experiments an attempt has been made to compare the glycogenic power of d-lactic acid with that of glucose and insulin. The decapitated eviscerated cat was used and the solutions slowly and continuously injected into a jugular vein by a Woodyatt pump. The d-lactic acid was used in the form of half-neutralised 5 per cent or 10 per cent solutions.

The results obtained to date are as follows:

(1) d-lactic acid forms muscle glycogen in the cat in the absence of insulin but is about 50 per cent less effective in this respect than are equivalent amounts of glucose and insulin.

(2) A large proportion of the lactic acid disappearing is not found as muscle glycogen and in some experiments the oxygen consumption does not account for all the missing portion. This last conclusion is a temporary one only as we have not yet constructed an accurate balance sheet under these conditions.

We are indebted to Prof. W. H. Peterson, of the University of Wisconsin, for supplying us with pure d-lactic acid.

Calcium Metabolism in "Calcinosis Universalis" or Calcification of the Subcutaneous Tissues. By WALTER BAUER and (by invitation) ALEXANDER MARBLE and GRANVILLE A. BENNETT, Boston, Mass.

The occurrence of calcareous nodules in the subcutaneous tissues is a rare condition, affecting particularly children. Its etiology has remained obscure. It was hoped that a more detailed study of a boy of ten years of age, who had been known to have the disease for seven years, might lead to a better understanding of this obscure condition. Therefore, studies of calcium, phosphorus and nitrogen metabolism in conjunction with chemical and histological examinations of the biopsied material were made.

Chemical examination of the calcareous material showed it to be composed of calcium carbonate and calcium phosphate in proportion essentially the same as that of normal bone or pathological calcifications found elsewhere. There were no findings to suggest any gross abnormality of the uric acid, cholesterol or fat metabolism.

Histological study of the biopsied material revealed none of the abnormalities usually associated with pathological calcification, namely: chronic inflammation, hemorrhage, infarction, tissue injury or tissue necrosis. Examinations of the earliest lesions revealed a deposition of finely divided calcium particles around the periphery of the fat cells, which otherwise appeared to be normal. This process progressed until calcium had been deposited within fat cells and eventually replaced whole fat lobules.

Metabolic studies showed that the serum calcium and phosphorus values were normal. However, there existed an extraordinary ability to retain calcium and phosphorus. This tendency was more marked in the case of calcium than of phosphorus. Regardless of the calcium intake or the medication employed the fecal calcium excretion never exceeded 49 mgm. per three-day period. The urinary calcium was also abnormally low. The low urinary calcium in the presence of a normal serum calcium served as further evidence of this unusual ability of the tissues to retain calcium. Results obtained during certain study periods indicate that when calcium is first retained it is not necessarily accompanied by phosphorus.

As a result of these studies we concluded that the calcium and phosphorus metabolism is abnormal in these rare cases of calcification of the subcutaneous tissues. The increased retention of these salts was evidently due to an unusual affinity of certain tissues for these elements. We are unable to state

what intracellular changes, unrecognizable microscopically, precede the deposition in these regions.

An inadequate calcium diet in conjunction with ammonium chloride medication would seem to be the only rational therapy to be employed.

A Study of the Electrolyte Metabolism in Diabetic Acidosis Induced in Human Subjects. By ROBERT F. LOEB, DANA W. ATCHLEY and (by invitation) DICKINSON W. RICHARDS, JR., and ETHEL M. BENEDICT, New York, N. Y.

We have studied the changes in water and electrolyte balance resulting from the abrupt withdrawal of insulin in three diabetic patients and also the steps taking place in recovery when insulin therapy is again instituted.

The fluid intake was maintained at a constant level throughout the experiment. The patients received and ate identical meals each day. Every fifth day when a fresh supply of food was bought, a complete duplicate day's diet was analyzed for water, K, Ca, total fixed base, P, Cl and N. The diets and insulin dosage were adjusted so that the patients remained sugar-free, in nitrogen balance and at approximately the same weight during the control period of 10 to 16 days. Twenty-four hour urine specimens were analyzed for NH_3 , total fixed base, K, Ca (Na and Mg being determined by difference), Cl, P, inorganic SO_4 , total N, creatinine, glucose, ketone bodies, titratable acid and in one case for organic acids. The pH was also measured. Stools were analyzed in 5-day periods for K, Ca, total fixed base, Cl, P, and total N.

At the end of the control period, insulin was withdrawn abruptly and withheld until definite results had been obtained or until therapy was urgently indicated. The recovery period was studied and then an after period in which the patients were again stabilized.

At various times in the course of the experiments blood samples were taken and electrolyte analyses were made.

The first patient was a comparatively mild diabetic receiving 55 units of insulin a day in the fore-period. Upon the withdrawal of insulin he remained sugar-free for 3 days and only on the 7th day without insulin did he finally excrete as much as 20 grams of glucose in twenty-four hours. In the second case, upon the withdrawal of insulin (80 units a day) there developed a glycosuria of 63 grams in the first twenty-four hours and 120-140 grams a day for the rest of the period. During this interval without insulin practically no ketosis developed. There appeared, however, immediate and striking changes in the water, electrolyte and nitrogen balances. In the third case, the insulin deprivation was associated with immediate and marked glycosuria and the development of progressive ketosis severe enough to require active therapy when the blood CO_2 reached 30 volumes per cent on the fourth day. In this patient even more marked but

qualitatively similar disturbances of water and electrolyte balances were encountered.

Results: (1) The withdrawal of insulin without the development of appreciable glycosuria or ketosis had no apparent effect upon water and electrolyte balance. (2) The withdrawal of insulin when followed by marked glycosuria, either with or without ketosis, resulted in definite and immediate disturbances in electrolyte and water balances as follows: (a) An enormous loss of water, Na, K and Cl, beginning in the first twenty-four hours and associated with loss in body weight and nitrogen. These changes were maintained at an abnormally high level throughout the period of insulin deprivation. (b) Twenty-four to forty-eight hours after the peak of Na, K and Cl loss, the excretion of NH_3 began to be augmented. (c) In the case which developed acidosis the ammonia increase roughly paralleled the increase in ketone acids. (3) Upon restoring insulin therapy and thus marking the beginning of recovery, a series of dramatic changes took place. Among these changes were: (a) The immediate and striking retention of K, Na, Cl and water, associated with an increase in body weight but without the establishment of a positive nitrogen balance. (b) The NH_3 excretion in both cases, i.e., with and without ketosis, remained at an augmented level during the first 4 days of the recovery period. This abnormally great NH_3 excretion bore no quantitative relationship to the disappearance of ketones, the restoration of total base or the replacement of Cl. The excess ammonia excretion did, however, cease in both cases on the day when the K which had been lost with intracellular water, was completely restored.

Finally, we should like to point out that the major fluctuations in weight in our experiments parallel the loss and storage of electrolytes rather than of nitrogen. While these changes are definitely associated with glycogen loss and restoration and while a causal relationship has been generally assumed, no satisfactory explanation for such a mechanism has been advanced.

Surface Temperature and Radiation. By W. S. McCLELLAN and E. F. DU BOIS, New York, N. Y.

The study of patients with malaria in the Sage respiration calorimeter suggested that the radiation of heat is not necessarily proportional to the surface temperature of the body. A series of observations has recently been made determining the heat lost by radiation and conduction and also the temperature changes of seventeen different spots on the skin. Surface temperature measurements are made by means of a small button of Wood's metal in which an insulated wire having a resistance of 100 ohms is embedded. With proper precautions the readings on the Kohlrausch bridge become constant in about ten seconds.†

Experimental subjects have been studied naked and clothed in the respiration calorimeter and the heat production has been varied by muscular activity.

In some experiments more heat was radiated from or through the skin when it was cold than when it was warm. This suggests that the radiating surface of the body is not necessarily the skin surface but may be located at some level underneath the skin and that the radiation of heat is not proportional to the surface temperature of the body.

A Safe Method of Producing Hyperthermia in the Treatment of Disease. A Preliminary Report. By F. W. BISHOP, C. B. HORTON (by invitation) and S. L. WARREN, Rochester, N. Y.

"Radio waves" are passed by means of large electrodes through the trunk of the patient with resulting rapid and safe rise in his general body temperature to 41.5° C. within approximately 2 hours. The electrodes are then removed. The patient is maintained at this temperature in a warm air chamber from 4 to 6 hours. The patient is then given a cold glucose and saline enema, removed to a dry bed, and allowed to cool off, a process taking about 1½ to 2 hours. The patients are slightly weak but can be discharged the following day. 42° C. for more than a few minutes is a dangerous temperature.

Fifty treatments have been given to 25 patients in the current year with one death. Studies of blood chemistry, electrocardiograms, blood pressure, temperature, and other data on patients and animals show no changes below 42° C. which might have a deleterious effect.

Seven of 14 deteriorating parietic patients have been paroled or discharged. All have been clinically improved. The gain in weight has been from 15 to 30 pounds. Striking serological changes have been produced in the spinal fluid without arsenical treatment. Transient herpetic lesions of the face develop in 60 per cent of the cases.

The Presence of Digitalis in Edema Fluid and its Possible Clinical Significance. By GEORGE H. MILLER (by invitation) and FRED M. SMITH, Iowa City, Ia.

Edema fluids from patients who have been under prolonged treatment for cardiac failure have been assayed for digitalis by the Hatcher cat method. Fluids aspirated from the pleural and peritoneal cavities were employed except in two instances. In the latter, the fluid was obtained from the extremities by means of Southey's tubes.

Repeated assays were carried out on each sample to minimize the influence of individual variations in the test animal. Sixty-five assays were done on samples from fifteen patients. In each instance, the fluid showed a digitalis action. The fluid from the patient with the highest assay showed an average of 0.9 cat unit per 100 cc. The samples from the patient with the lowest assay averaged 0.46 cat unit per 100 cē.

Fluids were employed from patients who had not been treated with digitalis as controls. These did not give a digitalis action. On the other

hand, when a known amount of digitalis was added to the control fluids, the full amount was indicated in the assays.

Patients with cardiac failure and edema who respond to treatment frequently excrete two to three liters of the excess fluid through the kidneys in twenty-four hours. It has been repeatedly shown that digitalis is not readily excreted by the kidneys.

Under the above circumstances, it is therefore possible for the digitalis of edema fluid to become effective and induce poisoning. Certain clinical observations support this possibility.

Diuretic Action of Digitalis. By E. LEROY KELLUM (by invitation) and NORMAN M. KEITH, Rochester, Minn.

Since Withering's original communication on digitalis, there are relatively few instances of carefully controlled and standardized studies of digitalis on both the healthy human subject and the cases of congestive cardiac failure. In spite of the vast amount of work on this drug and because of our experience of the not infrequent failure to produce satisfactory diuresis by digitalis therapy in cases of congestive heart failure with edema, the present work was attempted to determine the efficacy of digitalis as a diuretic.

The diuretic effect of digitalis was studied on three healthy human subjects and on a series of cases with congestive heart failure and considerable edema. To insure standard experimental conditions, all of the subjects were given a measured fluid intake and a weighed and constant diet of known low salt and low water content, but adequate in protein and total caloric value. After a preliminary control and rest period with no medication, a standardized digitalis preparation was given to each subject in adequate amount. Careful daily estimations were made of the body weight, the pulse rate, blood pressure, twenty-four hour urinary output and the clinical symptoms. Determinations of chlorides, fixed base and nitrogen were made on the daily urinary output.

Despite the fact that all the subjects, both the healthy and the cases of congestive failure with edema, showed characteristic electrocardiographic and clinical evidence of digitalis effect, the diuretic effect of this drug was only slight in some of the subjects and was entirely absent in the remaining subjects. In none of the subjects was a diuretic effect of digitalis as marked as we have experienced where certain other diuretic substances have been employed. It is suggested that in the treatment of congestive heart failure with edema, digitalis be employed for its beneficial cardiac effect and other diuretics also be employed for their superior diuretic action.

A Comparative Study of the Diuretic Action of Euphyllin and Salyrgan.

HENRY L. SCHMITZ (by invitation) and LOUIS LEITER, Chicago, Ill.

Rehberg's method of using creatinine to calculate the amount of filtration occurring in the glomeruli and the amount of reabsorption taking place in

the tubules has been adopted to compare the diuretic action of euphyllin and salyrgan in the dog.

In the experiments to date, euphyllin has consistently increased the calculated amount of glomerular filtration whereas reabsorption has seldom been decreased significantly. The urine output following injection of euphyllin has only once exceeded 2 cc. per minute. Diuresis has not occurred when the control urine volume exceeded 1.5 cc. per minute even though the calculated rate of filtration was not greater than in those experiments in which diuresis resulted.

In the experiments with salyrgan on the other hand, there has regularly been a decrease in the calculated percentage of fluid reabsorbed while a significant increase in the amount of filtration has occurred only once. The diuresis produced by salyrgan has always been greater than 2 cc. per minute and has also occurred when the control urine volume exceeded 1.5 cc. per minute.

These experiments suggest that salyrgan acts in the kidney by decreasing tubular reabsorption, while euphyllin acts largely by increasing glomerular filtration. Work is being continued along these lines.

Unusual Variations of the Roentgen Shadow of the Elongated Thoracic Aorta. By HUGO RÖSLER, Vienna (by invitation), and PAUL D. WHITE, Boston, Mass.

Unusual undescribed variations from the familiar roentgen picture of the tortuous elongated thoracic aorta deserve attention because of their importance in differential diagnosis. We have encountered three instances. First was a man 60 years old with arteriosclerosis and slight hypertension. The heart size was within normal limits. The descending aorta crossed the midline to the right on its way downward, displaced the trachea forward, and extended far into the right lung field before turning back behind the heart. This finding is to be differentiated from the picture produced by aneurysm of the ascending aorta.

Second, a man of 50 years, with arteriosclerosis and hypertension, showed a moderately enlarged heart, calcification in the aortic arch, and a sharp kink of the aorta just beyond the arch, subdividing the vessel in its course and to be differentiated from coarctation of the aorta.

Third, a man of 61 years, with arteriosclerosis, tabes dorsalis, and slight hypertension, showed slight enlargement of the heart, moderate dilatation and calcification of the aortic arch, and a marked kink, without change in caliber, in the lower third of the descending thoracic aorta.

In all three cases the oblique views proved to be of the greatest value.

The Use of Ephedrine in Complete Heart Block with Adams-Stokes Syndrome. By J. EDWIN WOOD, JR., University, Va.

In many respects epinephrine and ephedrine show a similar action. With

this in mind and the added stimulus of three favorable case reports the following clinical studies have been made.

The first of these summarizes the clinical record of a male patient 51 years of age who developed a severe Adams-Stokes syndrome shortly after coming under observation. In spite of increasing doses of barium chloride, five to six severe attacks and 50 to 75 transient seizures daily almost completely incapacitated the patient. Immediate relief followed the administration of ephedrine by mouth, with the entire absence of long diastolic pauses in subsequent electrocardiograms. Under continued oral administration of ephedrine the patient has experienced relief for more than a year. The constant use of ephedrine has not produced nervousness, unpleasant symptoms, or unfavorable signs.

In this case a 72 mgm. dose of ephedrine by mouth produced a gradual increase in the ventricular rate from 20 to 30. This increased rate was still present at the end of six hours. The long diastolic pauses present (several times the ventricular rate dropped as low as six per minute before ephedrine was given) at the beginning of the experiment completely disappeared under the drug. After nearly a year ephedrine was administered to this same case of complete heart block after full atropinization. A mild but definite ephedrine response occurred.

This patient experienced a violent and alarming reaction in the form of a ventricular tachycardia, rate 112, following the injection of one mgm. of epinephrine subcutaneously.

Two other cases of complete heart block showed a definite increase in ventricular rate following the ephedrine administration. In one instance of paroxysmal complete heart block no evidence could be obtained to indicate that ephedrine improved conduction.

Observations on three cases of complete heart block indicate that ephedrine increases the ventricular rate independently of the auricular rate or blood pressure changes.

The Response of the Circulation to Insulin Hypoglycemia. By A. CARLTON ERNSTENE, MARK D. ALTSCHULE (by invitation) and HERRMAN L. BLUMGART, Boston, Mass.

Several patients with diabetes mellitus and early myocardial failure were observed recently in whom, following the administration of insulin, the symptoms of congestive heart failure increased in severity. Similar clinical experiences have been recorded by other observers, the situation being occasionally complicated by the development of coronary thrombosis or attacks of angina pectoris. It seemed of interest, consequently, to study the changes in the circulation following the administration of insulin.

The pulse rate, arterial blood pressure and minute volume output of the heart were measured in sixteen normal non-diabetic individuals of various ages both before and again during insulin hypoglycemia. In most of the

subjects the pulse rate and pulse pressure were increased during hypoglycemia, the systolic blood pressure being elevated and the diastolic pressure lowered. In every subject the circulatory minute volume, measured according to the acetylene method of Grollman, was increased, although in a few subjects the increase was not beyond the limits of error. The increase in minute volume output following insulin averaged 31.4 per cent and varied in different individuals from 3.1 to 85.7 per cent. The percentage rise in the minute volume output of the heart was not proportional to the extent to which the blood sugar level was lowered.

These observations indicate that insulin hypoglycemia is attended by an increased minute volume output of the heart and an increased amount of cardiac work. In normal individuals this increased work is accomplished without difficulty. In elderly subjects with sclerosis of the coronary arteries and diminished myocardial reserve, the increased burden imposed on the heart may result at times in the development of conspicuous signs and symptoms of myocardial failure. The results of the present investigation, therefore, furnish a rational explanation for the signs of circulatory insufficiency which have been observed during insulin hypoglycemia. In patients with arteriosclerosis or with signs and symptoms of circulatory insufficiency, insulin should be administered with appropriate precautions such as the giving of smaller amounts at more frequent intervals.

Studies of Edema. By F. H. LASHMET (by invitation) and L. H. NEWBURGH, Ann Arbor, Mich.

For the treatment of edema of nephritic origin various types of procedure have been proposed. Superficially, each type is diametrically opposed to the other. Evidence will be presented to illustrate the following points:

(1) Restriction of fluid intake has no influence in preventing or eliminating edema.

(2) Acids and acid producing salts will cause diuresis.

(3) A neutral type of diet, instead of the high alkaline nephritic diet commonly used, increases the effectiveness of acid therapy.

Other observers have reported the same results by the use of huge doses of alkali. Since both acid and alkali therapy produce diuresis, it seems that the reaction of the medication has less to do with diuresis than the osmotic effects which these drugs produce. Experiments are under way to test this hypothesis.

The Influence of Water Balance on Manifestations in Pulmonary Tuberculosis. By BURGESS GORDON and (by invitation) EN SHUI TAI and R. J. TITHERINGTON, Philadelphia, Pa.

The daily variations in urinary output and the occurrence of perspiration and expectoration were recorded in twenty-four tuberculous patients. These data were correlated with notes on dry cough, pleurisy, hemoptysis, weak-

ness and elevation of temperature. Records of the extremes in humidity and temperature of each day were kept.

It was found on certain days that marked differences in the output of urine occurred. There was an apparent relationship between increased fluid loss through the skin and the exaggeration of symptoms. A rather typical course was as follows: With a difference of more than 10° to 20° F. in the minimum and maximum temperature or a difference of more than 15 to 25 per cent in humidity there was increased perspiration (frequently one or two night sweats). Urination was decreased, usually expectoration also, and 12 to 24 hours later an elevation of body temperature (beyond the usual level for the patient) occurred. This was followed by an exaggeration of the clinical symptoms.

It is suggested that dehydration may explain, in part, the periodicity of certain manifestations in tuberculosis. Whereas increased fluid intake with free urination is helpful in removing toxic products, the loss of fluid through sweating is perhaps harmful. This may explain the fact that tuberculous patients with good nutrition and apparently greater fluid reserve suffer less frequently from exacerbations than individuals underweight and with low storage of fluid. It would appear that equitable climate in undernourished patients with progressive disease is desirable or a plan of management which provides an increased fluid intake, restricted exertion and sedatives on days with rising temperature and humidity.

The Utilization of Glucose Derivatives by Cancer Cells. By WILLIAM T. SALTER, OVID O. MEYER (by invitation) and JOSEPH C. AUB, Boston, Mass.

In studying differences between the biochemical behavior of malignant tissue (mouse sarcoma number 180) and that of normal tissues, the utilization of various derivatives of glucose (in which successive chemical groups were systematically substituted) was measured under anaerobic conditions by Warburg's method. Barring differential permeability of those substances through cell membranes (and similar complications), such compounds may be considered as substrates, the chemical change in which gives quantitative evidence of the activity of intracellular enzymes.

The splitting of hexoses ("glycolysis") is peculiarly restricted to d-glucose itself, the chief exception being mannose (as Warburg pointed out). Of various simple derivatives of glucose, most failed to show acid formation. That the configuration of the oxygen ring is of prime importance is indicated by the fact that Pringsheim's glucose (hexylene-oxide ring) showed no glycolysis. Glucofuranose compounds (butylene-oxide ring), however, were encountered, which did yield acid under anaerobic conditions, though not so readily as normal dextrose.

Although no anaerobic acid formation was encountered with pentoses, it was definite in the case of several 4-carbon and 3-carbon aliphatic carbo-

hydrates. Acid production from these substances by rapidly growing tumor, however, may be less active than by normal tissue.

Acid production was also observed in the case of polysaccharides, particularly with disaccharides containing glucose.

Studies on Obesity: the Specific Dynamic Action of Food. By FRANK A. EVANS and (by invitation) J. M. STRANG, Pittsburgh, Pa.

The total extra heat produced in response to a fixed meal was the same in the obese and in those of normal weight. The meal was made up of 40 grams of protein, 52 grams of carbohydrate and 26 grams of fat, which gave 610 calories. The observed extra heat production averaged 57 calories or 9 per cent of the total food calories.

The Peripheral Circulation in Heart Disease. By SOMA WEISS and (by invitation) LAURENCE B. ELLIS, Boston, Mass.

In order to gain further knowledge of the state of the peripheral circulation in various stages of circulatory failure due to heart disease, studies were made of the oxygen utilization in the forearm and leg, both in the horizontal and upright positions, and before, and at intervals after, a standard walking exercise. These findings were correlated with the lactic acid contents of arterial blood and blood from the femoral and antecubital veins obtained at the same time, as well as with the basal metabolic rate, vital capacity, cardiac rate, arterial and venous blood pressures, and the clinical manifestations of each of the patients studied. The results obtained furnish significant information regarding the blood supply to the great bulk of the body musculature, particularly of the legs, and may be considered an index of the state of the entire peripheral circulation. A total of 17 normal subjects and 50 patients with cardiovascular disease was studied.

At rest, in the horizontal position, there is a tendency for the oxygen utilization in the arms and legs to increase as the heart failure progresses, although in several instances of pronounced circulatory failure normal oxygen utilization was observed. The lactic acid contents in the arm and leg blood were above the normal limits only in the presence of marked congestive failure and then not always.

In the upright position, both in normal persons and in patients with severe congestive failure, the oxygen utilization, particularly in the legs, increases more than would be expected from the theoretical rise in the metabolism. The lactic acid contents of arm and leg blood showed no, or very slight, elevation in this position.

Upon exercise, the oxygen utilization is greater in patients with cardiac failure than in controls or compensated cardiacs. In pronounced circulatory failure as high as 16.5 volumes per cent oxygen utilization was obtained, and the oxygen content of the femoral venous blood reached as low as 1.0 volume per cent. In both normals and cardiacs the return of oxygen utilization to

the resting level occurred promptly, within ten minutes. Following exercise, the average rise in the lactic acid in the femoral blood draining active muscle, in normals, was to 30 mgm. per cent, much higher than in the arm; but the two approached each other in about ten minutes, and the lactic acid fell to a resting level in about one hour. In patients with circulatory failure, there was a tendency for the lactic acid to rise somewhat higher and fall more slowly. This difference between normal persons and patients with circulatory failure was probably due to slower blood flow, relative tissue anoxemia, and possibly was influenced by the liver damage accompanying heart failure.

In this study no evidence was obtained that in congestive circulatory failure there is an increased cardiac output or a more rapid blood flow than normal through edematous tissues. On the other hand, a decreased cardiac output is not regularly found in the presence of circulatory failure and the degree of the circulatory failure cannot be estimated by any change in the volume flow of blood. No evidence of a primary disturbance in the lactic acid metabolism or resynthesis was obtained.

The Differentiation of Peripheral Arterial Spasm and Occlusion in Ambulatory Patients. By W. J. MERLE SCOTT and JOHN J. MORTON, Rochester, N. Y.

To differentiate the effects of spasm from those of occlusion is an essential step in the study of arterial diseases in the extremities. This can not be done by the usual methods of clinical investigation. The reaction to foreign protein and the effects of spinal or general anesthesia have previously been used to accomplish this differentiation. A satisfactory test to measure these elements is outlined. It consists in following the surface temperature in the distal parts of the extremities before and after the blocking of the nerve trunk to the area. The vasodilatation obtained in this way compared with that following spinal or general anesthesia is nearly as complete. This test is so simple that it is applicable without inconvenience to ambulatory patients. Examples of its application and value in Raynaud's disease, thromboangiitis obliterans and arteriosclerotic endarteritis are given.

Cardiac Dyspnea: The Relative Importance of the Chemical and of the Reflex Control of Respiration in the Mechanism of its Production. By T. R. HARRISON and (by invitation) GLENN E. CULLEN, J. A. CALHOUN, W. E. WILKINS and COBB PILCHER, Nashville, Tenn.

The mechanism of orthopnea and that of dyspnea produced by slight exertion have been studied in a group of patients with various types of cardiac disease. In an orthopneic subject the shift from the recumbent to the sitting posture was not usually accompanied by significant changes in the carbon dioxide content, carbon dioxide tension, pH, or oxygen content of the arterial blood or of the blood from the internal jugular vein. The difference between the oxygen content of blood from these two vessels was the same as

that found in normal subjects and was unaltered by change of posture. Therefore, orthopnea is probably not due to decreased cerebral blood flow. Increased vital capacity, decreased ventilation and decreased respiratory rate were usually observed in the sitting as compared to the recumbent posture.

Observations made on dogs showed that, when the vagus nerves were intact, artificial diminution in vital capacity produced by pneumothorax, by introducing Ringer's solution into the lungs or by distending the vessels of one of the lungs with blood, caused increased respiratory rate and increased ventilation. No significant changes in the pH or the gases of the arterial blood or of the venous blood from the brain were observed until the decrease in vital capacity was of marked degree, whereas relatively slight decrease in vital capacity was accompanied by increase in respiratory rate and ventilation. After bilateral vagotomy reduction of vital capacity did not change the breathing until decreased oxygen content or increased acidity of the blood occurred.

It therefore appears probable that orthopnea and cardiac dyspnea at rest (aside from Cheyne-Stokes respiration and "cardiac asthma") are due to alterations in the Hering-Brauer vagal reflex from the lungs.

Dyspnea produced by mild exertion was also found to be unassociated with significant changes in the pH, carbon dioxide content or tension, or oxygen content of the venous blood from the arm, the blood from the internal jugular vein, or the arterial blood. It is evident that this type of dyspnea is also of "reflex" nature, but further studies are necessary in order to determine its nature more precisely.

Similar findings have been obtained on normal subjects and again, with mild exercise, chemical alterations in the blood were absent. It seems probable that the nervous regulatory mechanism is more delicate than the chemical, and that the former is largely responsible for the changes in ventilation which occur with the usual activities of life, aside from severe exertion.

The Clinical Value of the Erythrocyte Sedimentation Test. By C. P. HOWARD and (by invitation) E. S. MILLS, Montreal, Canada.

The corrected sedimentation velocity of the erythrocytes has been determined on 250 patients. Many of these patients were suffering from an acute or chronic inflammatory disease. Where possible the test was repeated at regular intervals during the course of the disease.

This test was compared with the leucocyte count, the pulse rate, and the temperature at the time of the test in order to determine if possible the relative sensitivity of these factors in recording the degree of activity of the inflammatory process.

As a general rule it was found that the corrected sedimentation velocity is a better indication of activity in such inflammatory diseases as tuberculosis, endocarditis, and the various forms of arthritis than is one or all of

the other factors with which the test was compared. The test is therefore a valuable aid in both diagnosis and prognosis in these diseases.

An Analysis of Thyroid Clinic Data by a Code and Punch Card System.

By J. LERMAN (by invitation) and J. H. MEANS, Boston, Mass.

Methods for accumulating and analyzing clinical data in vogue at the present time are cumbersome and inadequate. The application to clinical, statistical problems of mechanical accounting systems such as are used in business was first proposed by Raymond Pearl. Believing these methods worth further study, we have applied them to the material of a Thyroid Clinic. The hope is that should we be able to demonstrate their value in a special clinic, it might pave the way to application of the methods to all hospital entries.

A special coded record for thyroid cases is presented. The method of transfer of its information to statistical punch cards and the classification of these by a sorting machine are described. The results of the past year have been analyzed. Examples are given to illustrate significant findings and correlations for conditions such as exophthalmic goiter, colloid goiter, nodular goiter, and myxedema.

A great many questions which are constantly being asked can now be answered with specific facts and figures rather than by impressions.

Age and the Susceptibility of Rabbits to Scarlet Fever Toxin. By JAMES D. TRASK, New Haven, Conn.

The report of Parish and Okell on the greater susceptibility of mature as compared to young rabbits to lethal doses of scarlet fever toxin was confirmed and extended. It was found that old rabbits were more susceptible than young ones to skin test as well as to lethal doses of scarlet fever toxin, that with both methods the toxin was neutralizable with scarlet fever antitoxin and that the activity of the toxin was destroyed by heating to 100° C. for two hours. It was shown that scarlet fever antitoxin was not present in detectable amounts in the blood of normal rabbits either young or old.

The above findings furnish data for a consideration of the natural acquisition of susceptibility to a bacterial toxin.

Respiratory Responses to Anoxemia. By A. V. BOCK and (by invitation) D. B. DILL and H. T. EDWARDS, Boston, Mass.

This study shows a wide variation in the reaction of ten normal men while breathing oxygen-poor mixtures. The total ventilation, alveolar CO₂ pressure, arterial saturation with oxygen, pH, and the partial pressures of oxygen and carbon dioxide in the blood were determined. The mixture breathed contained 9 per cent of oxygen.

Subsequent experiments on the same subjects with mixtures containing varying amounts of CO₂ and O₂ (now in process) are leading to interesting implications.

The experiments from a theoretical point of view bear out the hypothesis that there is no single hormone or mechanism responsible for the control of breathing.

Studies in Intestinal Anaphylaxis. By ALBERT J. SULLIVAN (by invitation) and FRANCIS G. BLAKE, New Haven, Conn.

In an effort to obtain some knowledge concerning the so-called intestinal anaphylaxis of man, a study of the enteral sensitization and intoxication of guinea pigs with normal human serum has been undertaken. Mature pigs of 350 to 500 grams were sensitized by the oral administration of 2 cc. of human serum daily for ten days. No reactions were noted during this period. After an 18-day rest period the animals were subjected to the intravenous injection of 1 cc. of the same serum. Fifty per cent died within 5 minutes, 25 per cent developed severe shock but recovered. In the remaining 25 per cent no reaction occurred.

In repeating the experiment with young pigs of from 110 to 250 grams it was found that severe reactions, consisting of vomiting, choking, convulsions and death, frequently developed during or a few minutes after the oral administration of the serum. Control animals given water reacted likewise. It was therefore decided that because of this danger of aspiration, any further studies on small pigs must be conducted by the administration of the antigen through a stomach tube. Such studies indicate (1) that occasional mild and moderate reactions which may be anaphylactic in nature can be obtained by the stomachal administration of antigen to previously sensitized animals and (2) that animals sensitized intravenously are not easily desensitized by the stomachal administration of the antigen.

Studies in Sleep. By H. G. WOLFF and (by invitation) W. HORSLEY GANTT, New York, N. Y.

The conditioned reflex was used as indicator, along with other reactions, in an attempt to determine the nature of sleep and what circumstances precede, occur during, and finally dissipate it. Dogs were used as experimental animals and they were observed in an environment in which essentially all external stimuli could be controlled by the experimenter.

It has been shown that when a conditioned stimulus which has always been followed by food is no longer followed by its unconditioned stimulus (food) the conditioned salivary reflex will disappear or be extinguished. In our animals extinguishing well established conditioned reflexes was followed by marked alterations in the behavior of the animals. The salivary reflex diminished and ultimately became zero, the general motor activity of the animal decreased, the breathing was slowed and deepened, the eyelids drooped or closed, the animal rested or leaned against the apparatus, and eventually gave every ordinary evidence of being asleep. Such experimen-

tally induced sleep could be dispelled immediately and completely by once more accompanying the conditioned stimulus by its unconditioned stimulus.

It was also observed that the act of establishing a difficult discrimination between allied stimuli was often followed by the same evidence of decreased motility, eyelid and breathing changes and eventually sleep.

These observations indicate that the disturbance created in the central nervous system under the described experimental circumstances becomes widespread in its influence. They confirm those earlier reported by Pavlov and are most readily interpreted in terms of his concept. It is found that sleep follows periods of internal inhibition, i.e., negative excitation. In certain instances it is initiated by such a process involving first the cerebral cortex but subsequently including subcortical structures and their functions.

Reduction in the Total Number of Eosinophils in the Circulating Blood by Various Experimental Procedures. By A. IZARD JOSEY (by invitation) and JOHN S. LAWRENCE, Rochester, N. Y.

Guinea pigs deprived of food for six to seven days almost invariably have shown diminished numbers of eosinophils in the circulating blood. A much more sudden and marked drop in the number of the eosinophils has occurred following the intraperitoneal injection of sodium bicarbonate, ammonium chloride, and *B. coli*. The maximum drop with these latter procedures has been within six to twelve hours. It has been associated with a corresponding diminution in the number of lymphocytes in the peripheral blood. A similar response on the part of eosinophils has been shown to occur following the intravenous injection of sodium bicarbonate in the guinea pig, in the dog, and in one adult patient with trichinosis. Studies of sections from various organs of the guinea pig have indicated that the reduction in the number of eosinophils was not limited to the blood but involved the tissues (with the exception of the bone marrow). Finally it has been shown that the eosinophils can, within certain limitations, perform some of the functions of the neutrophile in inflammation.

The Hemogram (Leucocyte Picture) in Convalescence from Acute Infectious Diseases. By PAUL REZNIKOFF, New York, N. Y.

It is relatively easy to determine that a patient is acutely ill from an infectious disease but more difficult to decide when he is well. One of the best aids in gauging the convalescence of a patient is the hemogram or leucocytic picture of the blood.

Daily leucocyte and differential counts were made on 68 patients suffering from various acute infections. In the cases of 50 other patients counts were made at critical points in their illness.

In conditions such as pneumonia, tonsillitis, and acute rheumatic fever, recovery is presaged by a transitory monocyte increase. This occurs, as a rule, while many immature polymorphonuclear cells are still present. With

a return of the monocytes to normal and the presence of a normal number of immature polymorphonuclear cells, the lymphocytes rise and remain elevated for a long time (35 to 50 per cent). An eosinophilic increase occurs with the lymphocytic phase. In acute rheumatic fever and tonsillitis and a few pneumonic patients an eosinophilic increase is seen early as well as late in convalescence.

In fatal cases the monocytes rarely increase and the lymphocytes are always depressed. A marked delay in lymphocytic and eosinophilic increase is characteristic of complications, such as pleurisy in the course of pneumonia.

Rheumatic Fever in Adult Porto Rican Immigrants. By E. P. BOAS, New York, N. Y.

Rheumatic fever and rheumatic heart disease are very rare in Porto Rico. Rheumatic infection is not uncommon among Porto Ricans who have immigrated to New York City. When infection occurs it is apt to be severe, and in adults tends to approach the childhood type of the disease. This occurred in 9 of 13 cases of active rheumatic fever in Porto Ricans studied at Mt. Sinai Hospital. A similar behavior of the disease has been noted in negroes who have recently come from the Southern States. The average age of the Porto Ricans at the time of their immigration was 19.8 years, and the average age on the occasion of their first rheumatic infection 22.6 years. Severity of infection among the Porto Ricans was manifested by a stormy onset with chills and abdominal symptoms, by the frequent development of pericarditis, by a prolonged course, and by higher mortality. The cause of the great severity of rheumatic fever in Porto Ricans living in New York remains obscure. It may be that they lack immunity, due to the absence of subclinical infection in Porto Rico before their arrival in the United States. Again, climatic factors may be determining. These data point to the importance of a more systematic and intensive study of the semeiology and the prevalence of rheumatic fever in different parts of the world.

Blood and Organ Changes in Rabbits Following the Intravenous Injection of Non-pathogenic Bacteria. By ROBERT N. NYE and (by invitation) VIDA F. RANDOLPH, Boston, Mass.

Heavy suspensions of *B. subtilis* were injected intravenously in rabbits. Within a few minutes the circulating leucocytes, particularly the polymorphonuclear cells, were markedly decreased. This change also occurred in "immune" and splenectomized rabbits, but the return to within normal limits was more rapid with the former. The majority of bacteria were removed from the blood stream within a few minutes in all animals.

In the normal uninjected rabbit there were about as many polymorphonuclear leucocytes in the liver as there were in all the circulating blood and there were about twice as many in the lungs. Following injection there

was a marked increase of these cells in the lungs and liver with a decrease of such cells in the bone marrow. The increase in the liver persisted for longer than that in the lung. The organ changes in splenectomized animals were similar. In "immune" animals the increases in the lungs and liver were more pronounced, but there was no decrease in the bone marrow. Large numbers of the bacilli were found in the lungs and liver, most marked in the former relatively soon after injection and in the latter several hours after injection.

On the basis of these observations certain facts relating to resistance in the rabbit can be obtained.

Experimental Study of the Probable Chemical Basis Producing Systemic Reactions in Certain Cases of Cold Allergy. By GEORGE E. BROWN and (by invitation) BAYARD T. HORTON, Rochester, Minn.

Local and systemic histamine-like reactions in cases of cold allergy have been observed in a series of nine cases. The local effects on the hands or feet consist of pallor, followed by redness, swelling and increased heat. After a latent period of three to four minutes a characteristic systemic reaction appears. This consists of a fall in the blood pressure, a sharp rise in the pulse rate, flushing of the face, and a tendency to syncope with recovery in fifteen to thirty minutes. The local reaction persists for from eight to eighteen hours. The reaction suggests that which is observed after the injection of small doses of histamine. Further studies on the gastric secretion and electrocardiographic changes during the attack give further confirmatory evidence of the probable chemical basis of this unusual clinical syndrome. The release of histamine or histamine-like substances from the skin as the result of cold seems probable.

Oxygen Treatment in Chronic Pulmonary Disease. By ALVAN L. BARACH and (by invitation) DICKINSON W. RICHARDS, JR., New York, N. Y.

Seven cases of chronic pulmonary disease have been treated over long periods (2 to 7 months) with high oxygen.

Group I. Two cases had active pulmonary tuberculosis, without cyanosis or signs of pulmonary insufficiency. No effect was noted on the patients' general condition or on the course of the disease.

Group II. (a) Two cases had active chronic pulmonary tuberculosis with extensive lung involvement, moderate cyanosis and dyspnea. They were treated in an oxygen chamber and (in one case) later by nasal catheter for 2 months. There was definite though only moderate improvement in general condition and symptoms. The course of the disease was not apparently altered.

(b) Three cases had chronic pulmonary fibrosis, non-tuberculous, with profound cyanosis and dyspnea. They were treated with high oxygen (cham-

ber or catheter) for 6 to 7 months. Marked improvement resulted. Two patients were restored to limited ambulatory activity.

Studies of arterial blood were made on one patient of Group II (a) and two of Group II (b). In one case the CO_2 increased by 34.5 volumes per cent, in a second by 18.6 volumes per cent, while in the third, after 7 months in 50 per cent oxygen, the arterial whole blood CO_2 content was 130 volumes per cent.

We have considered this rise in CO_2 to be in effect an adaptive change: with high alveolar CO_2 the excretion of this gas by the lungs can be accomplished in spite of severely limited pulmonary ventilation.

The Permeability of Blood Capillaries to Protein. By CECIL K. DRINKER and (by invitation) MADELEINE FIELD, Boston, Mass.

Since the work of Starling in 1894 it has been held that impermeability of capillaries to the blood proteins, except for the capillaries of the liver, spleen and intestine, is a general and fundamental property. Protein impermeability has been deemed essential in order to govern the movements of water out of and into the capillaries. It is considered proved by the fact that the glomerular, choroidal and ciliary capillaries do not permit the passage of protein, and by the direct observations of Landis.

Experiments carried out during the past two years have convinced us that permeability of capillaries to the blood proteins is a more general property than impermeability. Lymph collected from many different sources in the same animal contains from 0.4 to 4.5 per cent of protein. This protein can be shown to consist of serum albumin, serum globulin and fibrinogen. It must come from the blood, since there is no evidence that the tissues in general, or the lymphatic endothelium, can form it. The impermeability of renal, choroidal and ciliary capillaries to protein is not evidence applicable to capillaries in general, since in all three of these cases the capillary membrane is reenforced by a second layer of cells. Our experiments indicate that lymph and tissue fluid are identical in composition, and that the protein content of the tissue fluid is of prime importance in maintaining the water balance of the body.

The Mean Electrical Axis in Bundle Branch Block and its Significance. By A. GARRARD MACLEOD, PAUL S. BARKER (by invitation) and FRANK N. WILSON, Ann Arbor, Mich.

If the electrocardiogram is enlarged by projection the area of the various deflections may be measured with a suitable planimeter.

From the areas of the initial deflections in the three leads the mean electrical axis during the *QRS*-interval may be determined by means of the principles of Einthoven's equilateral triangle.

The mean electrical axis determined in this manner gives the average direction in which the excitation wave spreads over the ventricular muscle.

The mean electrical axis in bundle branch block points from the contralateral toward the homolateral ventricle. Consequently, the position of this axis is in accord with the view that the current interpretation of the electrocardiograms ascribed to human branch block must be revised.

In fact, a general law may be formulated that in a mass of excitable tissue the mean electrical axis will always point from the point or center of stimulation toward a determinable point in the tissue which in symmetrical masses coincides with the center of mass.

Growth in Private School Children. By H. GRAY and (by invitation) J. G. AYRES, San Francisco, Calif.

For the study of growth, nutrition, and diseases of the ductless glands accurate standards of build are necessary. Such standards exist only for a few characteristics for public school children in this country, and hardly at all for private school children. Since the latter differ in build from the former, new data are especially desirable. The constitution of these children, whose parents are characterized by professional or economic success, and who therefore by heredity and nurture may be expected to be future leaders, is therefore here studied on the basis of fifteen physical measurements on about three thousand boys and about fifteen hundred girls from the ages of one to nineteen years. The topics treated are averages at each age and the variations around the average; also differences between these children and those reported by others, differences in racial stocks, types of build, and the like. The results are designed to be of service to physicians concerned with questions of normal and abnormal development in this special category.

Further Evidence as to Metabolic Disturbances in Bright's Disease. By G. P. GRABFIELD, Boston, Mass.

It has been shown that the urinary sulphur and nitrogen excretion and the nitrogen-sulphur ratio in Bright's disease is of a different type in patients with and without renal edema. The changes are of such a character as to make it probable that there is a fundamental disturbance in the intermediary sulphur metabolism in this condition.

It seemed desirable to extend these observations by observing the effects of salicylates and iodides on the nitrogen and sulphur excretion in Bright's disease. This has been done. All the subjects were on weighed diets and the figures are derived from three-day periods of observation. The drugs were administered for three days after meals; the iodides in doses of 0.3 gram, the salicylates in doses of 1 gram. It has been shown that both these drugs caused an increase of about 10 per cent in the nitrogen excretion in the urine of normal individuals but that the increase in nitrogen excretion after iodide is not accompanied by an increase in sulphur excretion, whereas in the case of salicylates the two are parallel.

In studying patients with Bright's disease which have been reported elsewhere, we have found that such patients without renal edema showed after sodium iodide an increase in the nitrogen-sulphur ratio, similar to, though to a lesser extent than, that seen in the normal. The patients with renal edema showed the opposite reaction. It seems not unlikely that the patients exhibiting the nephrosis syndrome had some difficulty in the mobilization of deposit nitrogen by means of iodides.

When we consider the effect of sodium salicylate, we note that patients with nephritis show a similar reaction to that observed with iodide; namely, that the increase in the nitrogen excretion exceeds the increase in sulphur excretion. This is not due to a difficulty in the excretion of sulphur through the kidney, because it has been shown that these patients remain for long periods in negative sulphur balance and it is known that sulphur is more easily excreted by the kidney than nitrogen. Patients exhibiting the nephrosis syndrome showed a normal reaction to salicylates, so that in the case of this drug, as well as that of iodides, we have evidences of deviations from the usual reaction. These reactions are presented as further evidence of anomalies in the nitrogen and sulphur metabolism occurring in Bright's disease.

The Prognostic Value of Blood Fat Curves after Adrenalin in Liver Disease. By CHESTER M. JONES and (by invitation) JOSEPHINE C. WOOD, Boston, Mass.

Determinations of the blood fatty acids following the injection of adrenalin have been made on thirty-five patients with various types of liver disease and in addition on a group of normal individuals and in certain disease entities in which there is a known disturbance of fat metabolism. Normally there is a sharp rise in the fatty acid during the first half hour after adrenalin, followed by a more gradual fall to the previous level. Where the liver is diffusely damaged by an infiltrative process or by serious infection, we have noted either a lack of rise in the blood fat after adrenalin or an actual fall. Those cases that were clinically the sickest showed the greatest variation from the normal curve. In patients with extreme jaundice but with a good prognosis the shape of the curve was normal. The actual level of blood fat varied between extremely high and abnormally low figures. Patients with high blood fat and no liver disease failed to show the type of curves described above. We believe that as a test of liver function the above method has distinct prognostic value.

Studies on Hunger, Insulin, and Gastric Activity. By WALTER L. PALMER and (by invitation) THEODORE E. HEINZ, New York, N. Y.

In 1916 Carlson published his classical treatise on hunger in which he discussed the earlier theories and the relationship between hunger and appetite.

and showed that the primary and essential factor in the hunger complex is the gastric sensation arising from contractions of the empty stomach. In 1929 Quigley, Johnson and Solomon reported that the subcutaneous injection of insulin produces an increase in gastric motility and tone and a prolongation of the hunger period. They concluded that insulin sensations, especially hunger, parallel rather closely the degree of gastric activity.

The present work represents a study of the relationship between hunger, insulin reactions, blood sugar levels, and gastric activity in 28 experiments on 17 subjects. The findings of previous workers were only partially confirmed. "Hunger pangs" were present in only four subjects. They were definitely coincident with gastric contractions, but were not increased in frequency or severity by insulin. The sensation of hunger, however, usually accompanied the insulin reaction and was fairly well correlated with the blood sugar level. Gastric activity was not clearly correlated with hunger, the blood sugar level, or the severity of the insulin reaction. The results suggest that the extra-gastric factors may be more significant in the genesis of hunger than is recognized at present.

Studies of Acid-Base and Water Balance in Edema. By A. B. HASTINGS and S. H. LIU (by invitation) and F. R. DIEUAIDE, Chicago, Ill., and Peiping, China.

Measurements of the acid-base and water balance have been made on two patients with nutritional edema and one with nephrosis over a period of approximately two months. These patients had total plasma protein values between 4.0 and 6.0 per cent and plasma albumin values between 2.0 and 2.8 per cent. All showed slight pitting edema. During the period of observation, the acid-base balance was displaced for intervals of four or eight days to the alkaline side by the administration of sodium bicarbonate and to the acid side by ammonium chloride or hydrochloric acid. The extent of the acid-base displacement to the alkaline side was from serum pH 7.40 to 7.55 and from serum bicarbonate 26 to 40 millimols per liter; the displacement to the acid side was from serum pH 7.40 to 7.20 and from serum bicarbonate 26 to 14 millimols per liter. The effects of these acid-base shifts may be summarized as follows:

(1) During the periods of alkali administration, there occurred for the first two to five days an accumulation of water. Toward the end of the periods, a loss of water occurred in spite of the continued alkali administration. Upon the discontinuation of the alkali therapy the loss of water was prompt with a return to the original water balance level within four days. The amount of water accumulated during bicarbonate administration varied between 220 and 900 cc. The pitting edema usually became more noticeable while water was being retained. The plasma proteins while sometimes tending to decrease slightly during alkali ingestion did not vary extensively nor consistently.

(2) During the periods of acid administration essentially the opposite chain of events was observed. There was an immediate loss of water for two to four days followed by a gain which was especially marked after the acid was discontinued. With ammonium chloride the water loss amounted to 400 to 650 cc. During the periods of water loss, a decrease of the pitting edema was usually recorded. Again the variations in plasma proteins were slight and rather irregular.

Endemic Seasonal Edema Accompanied by Changes in the Serum Proteins.

By JOHN B. YOUMANS and (by invitation) AUSTIN BELL, Nashville, Tenn.

For the past three years cases of obscure edema of the legs and sometimes of the face and hands have been observed during the spring and early summer. Many gave a history of previous attacks. None of the usual causes, renal disease, heart failure, et cetera, were found to account for the swelling. Although the patients were well nourished and had no diseases which might have caused malnutrition, it was thought that the diet though not of a starvation type might be low in protein and the edema due to a protein deficiency. Analysis of the blood serum usually revealed a normal or increased total protein but with the serum albumin at, or below, the lower normal value. The globulin was increased in all cases, giving a lowered, or sometimes reversed, A/G ratio. Close correlation between the presence and degree of edema and the serum protein levels was lacking, but in general the albumin or globulin increased as the edema lessened. With increases in the albumin, the globulin fell. Calculated oncotic pressures were, in general, low during the period of edema.

The Influence of the Thyroid on the Concentration of Protein in Cerebrospinal Fluid.

By W. O. THOMPSON and (by invitation) PHEBE K. THOMPSON and MARY ELIZABETH DAILEY, Boston, Mass.

In myxedema the concentration of protein in the cerebrospinal fluid is high and in toxic goiter it is low. In both, the concentration returns to the normal level when the basal metabolism is restored to normal by appropriate treatment. In cases of myxedema the protein concentration is constant under the same conditions but can be varied at will by varying the level of the basal metabolism. Repeated lumbar punctures have shown that the concentration in the lumbar region in cases of myxedema returns to its initial level only very slowly (at least six days) following the withdrawal of all readily available fluid. The pressure and the quantity of circulating fluid appear to return to their initial levels before the concentration of protein.

Studies on the Mechanism of So-called 'Opening Snap' (Claquement D'Ouverture de la Mitrale) of Mitral Stenosis. By ALEXANDER MARGOLIES (by invitation) and CHARLES C. WOLFERTH, Philadelphia, Pa.

The generally accepted hypothesis that the characteristic diastolic snap or click of mitral stenosis is due to opening of the stenosed mitral valve has been subjected to analysis. Sixty cases of mitral stenosis as well as many normals and various types of cardiovascular disease were studied and the following data obtained: The sound was elicited only in mitral stenosis, the incidence being 60 per cent. It is a short snap or click, heard best in the third or fourth left interspace. It begins 0.07 to 0.13 second after the second sound and, if the latter becomes reduplicated, may maintain its time relation to either component. The interval shortens as the cardiac rate increases. In auricular fibrillation it varies according to the length of the preceding ventricular diastole. The snap precedes the diastolic murmur by 0.03 to 0.05 second and the peak of the protodiastolic wave of the apex cardiogram by approximately 0.02 to 0.04 second. Comparison with roentgen kymograms of the left border demonstrates that the sound occurs at approximately the instant passive rotation has been completed.

The findings indicate that the characteristics of the "opening snap" are different from those of any other sound heard over the heart and are in accord with the view that it is due to the vibrations produced in a stenosed valve when its opening movement in response to the pressure of blood from above is suddenly limited.

The Cerebral Circulation. XIV. Changes in the Human Retinal Circulation and Cerebrospinal Fluid Pressure during Carbon Dioxide-Oxygen Inhalation. By STANLEY COBB and FRANK FREMONT-SMITH, Boston, Mass.

Wolff and Lennox (Arch. Neurol. and Psych., 1930, xxiii, 1097) showed in animal experiments that breathing a mixture of carbon dioxide (90 per cent) and oxygen (10 per cent) caused a dilation of the cerebral vessels and an increase in the rate of blood flow through the brain so that the venous blood became more arterial. Coincidentally, the cerebrospinal fluid pressure was increased. We have made analogous observations on man although our observations on the cerebral circulation are confined to the retinal vessels. Rebreathing a mixture of carbon dioxide (10 per cent) and oxygen (90 per cent) caused the retinal veins to become bright red and almost indistinguishable from the arteries, the maximum effect being reached in about six minutes. The intracranial pressure was definitely increased during such breathing. It is probable that the cerebral vessels, particularly the arterioles, are thus dilated in man as well as in animals and that the increased intracranial pressure is due to the cerebral vascular dilatation. It is interesting

that voluntary hyperpnea caused a decrease in spinal fluid pressure in contrast to the increased pressure produced by such carbon dioxide-oxygen mixtures.

These experiments are of interest in that they offer an explanation for the dramatic effects of carbon dioxide and oxygen rebreathing in arousing patients from stupor (Loevenhart and his co-workers, J. Am. Med. Assoc., 1929, xcii, 880), i.e., by increasing the oxygen supply to the brain, and at the same time they suggest the possibility that some of these stupors may be due to chronic cerebral anoxemia.

The Relative Importance of Bile Salt Toxicity and Bacterial Invasion in Bile Peritonitis. By G. O. BROUN and (by invitation) A. P. BRIGGS and ELIZABETH MCGARRY, St. Louis, Mo.

The clinical manifestations which follow introduction of whole bile or solutions of bile salts into the peritoneal cavity were described in a communication presented at the meeting of this society two years ago. Recent publications have stressed the importance of the gas-forming bacilli as etiological factors in bile peritonitis. Rewbridge has given evidence which indicates that in dogs bile peritonitis is accompanied by invasion of the peritoneal cavity by *B. welchii*.

The present report is an effort to evaluate the relative importance of infection and bile salt toxicity.

We have found that in mice and guinea pigs death is regularly caused by intraperitoneal injections of sodium taurocholate in dosage of 800 mgm. per kilo body weight and frequently in dosage of 500 mgm. per kilo. Death occurs in from one to forty-eight hours. In these animals we have not found bacterial invasion of the peritoneum to be an important factor. Aerobic and anaerobic cultures taken immediately after death have invariably been sterile.

In dogs similar dosages likewise cause death. Here bacterial invasion of the peritoneum occurs much more frequently. We likewise find *B. welchii* to be the organism usually present. In some instances *B. welchii* has not been found and other organisms have been present. We have been able to demonstrate toxic effects from the bile salts such as depression of blood pressure, dehydration, formation of peritoneal exudate prior to invasion of the peritoneal cavity by the organism. The bacterial infection would appear to be an effect secondary to the irritation of the peritoneum by the bile salts.

On the Nature of the Action of Iron in "Secondary" Anemia. By RAPHAEL ISAACS, CYRUS C. STURGIS and (by invitation) JOHANNES LODEESEN-GREVINCK, Ann Arbor, Mich.

A study of three stages in the development of red blood cells (reticulocyte, granule red blood cell and mature cell) in the blood of patients with anemia of hemorrhage, chlorosis and cancer, suggests that, following the administra-

tion of iron in various forms, there is a very transient outpouring of the more mature types, followed by an increase in the more immature forms. In the hemodiagram the "shift" is to the "left" in both the blood and bone marrow in contrast to the condition in pernicious anemia where "shift" is to the "left" in the blood, but to the "right" in the bone marrow. The maximum reticulocyte count is higher, the lower the initial red blood cell count.