

**PROCEEDINGS OF THE TWENTY-NINTH ANNUAL MEETING OF
THE AMERICAN SOCIETY FOR CLINICAL INVESTIGATION HELD
IN ATLANTIC CITY, N. J., MAY 3, 1937**

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READ BEFORE THE SCIENTIFIC SESSION

The Etiological Relationship of the Eosinophile to the Gordon Test for Hodgkin's Disease. By JOSEPH C. TURNER (by invitation) and HENRY JACKSON, JR., Boston, Mass.

In 1932 Gordon reported that broth suspensions of lymphadenomatous (Hodgkin's) tissues upon inoculation into the brains of rabbits or guinea pigs produce a characteristic paralysis (Gordon test). Subsequent investigation has established that approximately 75 per cent of cases of Hodgkin's disease exhibit this phenomenon. Friedemann (1933) discovered that a paralysis in the same animals, indistinguishable from that of Gordon, is produced with extracts of normal human bone marrow, spleen, or leukocytes.

The nature and significance of the paralysis-producing agents of Gordon and of Friedemann remain obscure. Their identity has not been proved.

We have performed the Gordon test in ten cases of Hodgkin's disease. The test was positive in six and in these six only could eosinophiles be found. Moreover, the potency of the material used varied directly with the number of eosinophiles present.

In order to test the significance of this observation, suspensions were made of the bloods of normal and diseased individuals, some of whom had a high degree of eosinophilia. Animal inoculations showed that a paralysis-producing factor was present in titers which paralleled precisely the number of eosinophiles in suspension. Suspensions containing few, or no, eosinophiles gave negative results.

It appears that the Gordon test is positive in Hodgkin's disease only because of the presence of eosinophiles. It is tentatively proposed that the paralysis-producing agent present in the tissues of certain cases of Hodgkin's disease and that present in normal leukocytes are both derived specifically from the eosinophile and are therefore identical.

Studies of a Stable Antigen of Vaccine Virus. By ROBERT F. PARKER (introduced by J. T. Wearn), Cleveland, Ohio.

The isolation of a serologically active heat stable substance from tissues infected with vaccine virus has already been reported, and the chemical characteristics of the substance have been described. On inoculation into rabbits, it elicits the formation of antibodies, demonstrated by precipitation and complement fixation tests. The serum agglutinates heated and unheated elementary bodies of vaccinia but apparently neutralizes only very small amounts of vaccine virus. Rabbits subjected to repeated inoculation with the substance and having a high

titer of serum antibodies, are not resistant to infection with vaccinia.

Estimation of Thyrotropic Hormone in Human Urine and Blood in Health and Disease by the Micrometric Analysis of the Response of the Guinea Pig Thyroid. By PAUL STARR and (by invitation) RULON W. RAWSON, Chicago, Ill.

A method of approximating the amount of thyrotropic hormone present in a solution by the micrometric analysis of the response of the guinea pig thyroid has been described. A frequency curve of the heights of the acinar cells measured with an ocular micrometer was plotted and subjected to statistical analysis. Increasing doses of a known thyrotropic preparation (Parke, Davis and Company) gave a series of curves shifting increasingly to the right.

The urine itself, or the acetone precipitate from small amounts, or the isoelectric precipitate from large amounts, injected into the animal, produces characteristic shift of such a curve. In the case of a normal person with a normal metabolic rate and no evidence of thyroid inactivity, there is slight shift to the right. Patients with moderately low metabolic rates, "relative hypothyroidism," have more of this material in the urine. This suggests that the procedure may be used to detect the need for thyroid hormone when general metabolic measurements are inconclusive. Following total thyroidectomy the urine contains excessive amounts.

In hyperthyroidism there is less thyrotropic hormone present than in the normal urine. This is true whether or not exophthalmos is present. This raises the possibility of the use of the procedure as a diagnostic aid in hyperthyroidism. Patients with various types of pituitary tumors and goiters have different amounts of the material in the urine.

The possibility that lack of response to the hyperthyroid urine is due to excess iodine present has been covered by the addition of amounts of iodine of like order to specimens giving marked stimulation. The possibility that the response is not specifically due to thyrotropic hormone has been met by heating the specimen, since the pituitary thyrotropic hormone is heat labile. Furthermore, the hyperthyroid urine containing similar amounts of foreign material fails to give a response.

Blood serum from these groups of patients may be classified in the same way.

Conclusion. The method affords a convenient and specific means of assaying the appearance of thyrotropic hormone in clinical material.

Influence of the Thyroid Gland on Intestinal Absorption of Dextrose, Galactose, and Xylose. By T. L. ALTHAUSEN, with the technical assistance of M. STOCKHOLM, San Francisco, Calif.

Normal rats, rats treated with thyroxin, and thyroidectomized rats were given measured amounts of sugar by stomach tube. The amount of sugar absorbed in one hour was calculated from the unabsorbed residue in the digestive tract. In hyperthyroidism, intestinal absorption of dextrose and of galactose was markedly increased. In hypothyroidism, intestinal absorption of dextrose was reduced considerably.

Depletion of carbohydrates, raised basal metabolism, increased velocity of the blood flow, intestinal hyperperistalsis, and rate of gastric discharge appear to play no part in the observed changes of intestinal absorption. Therefore, a specific action of thyroid hormone on the intestinal mucosa is suggested as a possible explanation.

Increased phosphorylation appears to be the chief mechanism by which thyroxin increases absorption of dextrose because phlorizin which inhibits this mechanism greatly decreases the absorption of dextrose in experimental hyperthyroidism. But simple diffusion also seems to play a part since absorption of xylose is likewise increased by thyroxin.

Clinically, altered intestinal absorption may be an important factor in producing abnormally high dextrose tolerance curves often seen in patients with hyperthyroidism and unusually low curves observed in patients with myxedema. The same mechanism may play a major part in the impairment of "tolerance" to galactose observed in hyperthyroidism in man.

Pressor Effects of Renal Extracts of Normal Dogs and of Dogs with Experimental Renal Hypertension. By T. R. HARRISON, ALFRED BLALOCK and (by invitation) M. F. MASON and J. R. WILLIAMS, JR., Nashville, Tenn.

Hypertension has been produced in dogs by the method of Goldblatt (partial occlusion of the renal arteries). Saline extracts of the kidneys of such animals have been injected into rats and the changes in blood pressure compared with those produced by extracts of the kidneys of normal dogs. The former extracts were found to have greater pressor effects.

In a second series of experiments preparations from the two kidneys of a dog rendered hypertensive by the application of a clamp to one renal artery were studied. Here again the extract of the ischemic kidney caused a greater rise in blood pressure than did that of the normal kidney.

Maintenance of the Functional Integrity of the Occluded Large Arteries as Demonstrated by Thorotrast Arteriography. By WALLACE M. YATER, Washington, D. C.

Arteriography is teaching us many things about the mechanism of the circulation of vascular disease which are not demonstrable otherwise. Large arteries may become completely occluded in some part of their course

without serious trophic disturbance of a permanent nature. Arteriograms in such cases often show direct anastomosis by means of smaller arteries between the segments of the artery above and below the area of occlusion. In such cases the roentgenograms show that the artery below the obturated portion is still functioning, the blood having been shunted around the occluded portion. Arteriograms and drawings of the extremities of patients illustrating this mechanism of readjustment of the circulation are shown. Various types of anastomoses are demonstrated.

The Effects on the Cardiovascular System of Fluids Administered Intravenously. By MARK D. ALTSCHULE and DOROTHY R. GILLIGAN (introduced by Herrman L. Blumgart), Boston, Mass.

The effect on the cardiovascular system of the injection of fluids intravenously, such as is employed routinely in postoperative treatment, has been studied in a large group of patients with no evidence of heart disease. The fluids employed were physiological saline solution or 5 per cent glucose in distilled water, or 5 per cent glucose in physiological saline; the volumes injected varied from 500 to 1500 cc. and the rates of injection from 6 to 80 cc. per minute.

Immediately after the injection of fluids intravenously, the minute volume output of the heart and the blood volume were increased, and the velocity of blood flow was accelerated. When the more rapid rates of injection were employed or the larger volumes of fluid administered, significant and even marked increases in venous pressure were observed; a return to the control level of venous pressure was again observed within approximately twenty minutes after the end of injection in these patients with no evidence of heart disease. Slight increases in pulse rate and in systolic blood pressure and pulse pressure were observed in approximately 40 per cent of our studies. Electrocardiographic studies revealed in some instances appreciable increases in the height of the P and variable changes in the T-waves. The magnitude and duration of the above effects were influenced by the composition of the fluid injected.

These studies have demonstrated that the administration of fluids intravenously under conditions frequently employed routinely subject the heart to increased work, which amounts to about 50 per cent above basal levels. The implications of these findings in the management of patients with cardiovascular disease is clear.

The Estimation of the Subcutaneous Tissue Pressure by a Direct Method. By G. E. BURCH and W. A. SODEMAN (introduced by J. H. Musser), New Orleans, La.

Direct determinations of tissue pressure have not been reported in this country. Wide variations reported in the German literature have prompted us to determine directly the tissue pressure by the simple manometric method employed by Yandell Henderson for the determination of muscle tone. A 26-gauge needle was used in place of a 20. In each determination three readings were taken which agreed within ± 1 mm. of water.

In 10 normal adults the mean values at heart level varied from 17.9 to 37.1 mm. of water in the subcutaneous tissue of the dorsum of hand and foot, volar surface of the forearm and the pretibial area. The tissue pressure in the dorsum of the foot was increased in the erect position and further increased by weight bearing. Six normal subjects stood for one hour against a table inclined at 75°. The mean tissue pressure reading in the dorsum of the foot at the beginning of the hour was 53.5 mm. of water, and at the end 65.2. In all cases there was a rise on standing for one hour not to exceed 31 mm. of water. The effect of venous pressure on tissue pressure readings was determined by inflating a blood pressure cuff around the arm in steps of 135 mm. of water (10 mm. Hg) up to 810 mm. of water (60 mm. Hg) at two minute intervals. In no case was the diastolic arterial blood pressure exceeded. Increase in venous pressure over short intervals of time had relatively slight effect upon the tissue pressure readings. In 10 patients with increasing cardiac edema the tissue pressure was greatly increased. In receding cardiac edema the values were lowered, even below normal, to return finally to a normal level.

These findings indicate: (a) Normal tissue pressure is less than the accepted values for capillary and venule pressures; (b) tissue pressure is an important factor in the control of the movement of fluid between blood vessels and tissue spaces; (c) the full effect of venous pressure on tissue pressure is not immediate; up to one hour the effect of venous pressure upon tissue pressure is slight but in congestive heart failure with prolonged high venous pressure the tissue pressure is greatly elevated; (d) the tissue pressure in patients with cardiac edema varies with the state of the edema, and (e) factors other than venous pressure are important in the regulation of tissue pressure.

Studies of the Salt and Water Hormone of the Adrenal Cortex. By GEORGE A. HARROP and (by invitation) GEORGE W. THORN, Baltimore, Md.

Injections of adrenal cortical hormone have been shown to produce a marked effect on the renal excretion of sodium and potassium in normal male dogs, maintained under uniform conditions with a constant fluid and mineral intake. A subcutaneous injection resulted in an immediate marked reduction in renal sodium excretion accompanied by an increased potassium excretion. Subcutaneous injections produced a much more prolonged action than the intravenous injection of a similar quantity of hormone. Subcutaneous injections twice daily effected a marked reduction in sodium excretion during the twenty-four hour period, followed by a "rebound" effect during the second twenty-four hours in which the increased excretion of sodium approximated the initial retention. It has been demonstrated that this response is proportional to the quantity of hormone given, and that the normal dog can thus be used for assay of the "salt and water hormone" effect of adrenal cortical extracts. Individual animals vary in their response to a given quan-

tity of extract, injected twice daily, but the same quantity of extract consistently produces the same change in a given animal.

A method for the extraction of the "salt and water" hormone from urine has been employed, based on extraction of urine with ethylene dichloride and subsequent distillation at a temperature of 40° C. under reduced pressure. An alcoholic extraction of the residue was distilled at the same temperature, the final residue being taken up in normal saline solution and sterilized by passage through a Berkefeld filter. Extracts of urine to which hormone had been added yielded a 40 per cent recovery when tested by the above method of assay. Acid hydrolysis of the urine, to which adrenal cortical extract had been added, almost completely destroyed the activity of the "salt and water" hormone. Intravenous injections of large quantities of adrenal cortical hormone (3000 dogs units) into normal dogs were followed by only 10 per cent recovery from the urine. Two liter portions of urine obtained from normal male, female, pregnant dog and man, and pregnant mare have been extracted and tested for the presence of the salt and water hormone. No appreciable amount could be demonstrated from this volume of urine.

Studies reported elsewhere have indicated that in the intact dog a sodium sparing effect is common to several crystalline sex hormones and closely related compounds. It is apparent that substances other than the adrenal cortical hormone exert a sodium sparing effect in the intact animal. For this reason, the method of assay which has been described is limited to the determination of the relative "salt and water hormone" content, of adrenal cortical extracts.

Chloride Depletion in Conditions Other Than Addison's Disease. By ALEXANDER W. WINKLER and ORRIN F. CRANKSHAW (introduced by John P. Peters), New Haven, Conn.

Extensive studies of salt metabolism in two cases not having Addison's disease showed persistent urinary Cl excretion at abnormally low Na and Cl concentration in the serum. One was a case of pulmonary tuberculosis, the other a case of primary carcinoma of the lung. In a series of other cases of tuberculosis without Addison's disease, including three cases which subsequently came to autopsy, determinations of Na and Cl in the serum were made. Consistently subnormal values were noted. The difficulties in differentiating such cases from true Addison's disease by a characteristic chemical test are noted.

Heat Stroke: A Clinical Study. By M. A. BLANKENHORN and E. B. FERRIS, JR., and (by invitation) G. E. CULLEN and H. W. ROBINSON, Cincinnati, Ohio.

During two successive heat waves in 1936 studies of patients suffering from heat stroke were made in the Cincinnati General Hospital and the Children's Hospital Research Foundation of the University of Cincinnati. Forty-three patients with high temperatures were received, of whom sixteen died and thirteen were autopsied.

Routine clinical studies were made on thirty-nine patients. On seventeen patients studies of the circulation, including venous pressures, were augmented by analysis of carbon dioxide content and oxygen content of arterial and venous blood to demonstrate the state of circulation. Further chemical studies of the blood were carried out, including determinations of protein concentration, hemoglobin concentration, acid base balance and cell volume.

The results of these studies demonstrated adequate circulation, a moderate but definite hemoconcentration, and a moderate acidosis. There was no striking change in the sodium chloride content of the serum in the seventeen patients who were adequately studied, which indicates that these cramps are distinctly different from the condition of "heat cramps." Absence of sweating was a constant finding on admission and most patients noted a diminution or absence of sweat preceding the onset of heat stroke. No cause for the cessation of sweating is suggested by any of these studies. It is, however, apparent that peripheral or congestive failure, deficient chlorides, and dehydration were not primary factors in the retention of heat nor in the symptomatology.

Of the several methods tried the most successful for the rapid cooling of the patients was that of submerging them in tubs of ice water.

An important question raised by these studies is why the patients cease to sweat and thereby fail to regulate their body temperature.

Clinical and Chemical Observations on Forty-eight Men Suffering from Exposure to High Environmental Temperature. By JOHN H. TALBOTT and (by invitation) D. B. DILL, Boston, Mass.

This communication is a summary of the data obtained on workmen who reported off duty following exposure to high temperatures. The men were employed in the steel mills at Youngstown, Ohio, and previous to the onset of symptoms were considered normal and healthy persons. After admission to the hospital one or more samples of blood were drawn from each patient for the following analyses; oxygen capacity, oxygen content, carbon dioxide content, cell volume, lactic acid, red and white cell count, sodium, potassium, calcium, chloride, phosphate, hydrogen ion concentration, total protein, osmotic pressure and nonprotein nitrogen. In urine samples the following were determined; albumin, sugar, acetone bodies, character of sediment, sodium, chloride, creatine, creatinine, and total nitrogen.

The clinical syndromes observed were placed in one of three categories. These are *heat cramps*, *heat prostration* and *heat pyrexia*. A diagnosis of heat cramps was made in 33 patients who complained of skeletal muscle pain. Analysis of the concentration of the constituents of the blood showed, among other changes, a diminished concentration of sodium and chloride, an increased concentration of hemoglobin and serum protein, and a normal osmotic pressure. In the urine there was a diminished concentration of chloride. During the hospital stay the gain in body weight was as great as 4 kgm.

A diagnosis of heat prostration was made in 12 patients who either collapsed at work or who believed that collapse was impending. On admission to the hospital the patients in this group had no characteristic physical findings, and the chemical studies of the blood and urine were essentially normal. There was no gain in body weight during the hospital stay, and it was presumed that the etiological mechanism was not associated with a loss of water and salt from the body.

Three patients were sent to the hospital because of unexplained fever. The pyrexia lasted 1, 3 and 21 days respectively. Except for the elevation of temperature, the clinical observations were negative and the chemical studies were normal. All of the patients lost weight in the hospital.

This study was an attempt to differentiate clinically and chemically the several syndromes associated with the breakdown of physiological processes in healthy persons. It was believed that more satisfactory data would be obtained with this objective than would be possible in groups of aged or infirm suffering from exposure to heat in large cities during the summer. The changes in the concentration of constituents of the body fluids in patients with *heat cramps* were characteristic of a depletion of body water and mineral salts. The pathogenesis of *heat prostration* is thought to be associated with transient circulatory collapse rather than an alteration of the chemical equilibrium of the body. The pathogenesis of *heat pyrexia* is assumed to be related to failure of the heat regulating mechanism.

On the Mechanism of Migraine Headache and the Action of Ergotamine Tartrate. By J. R. GRAHAM (by invitation) and H. G. WOLFF, New York, N. Y.

New light is thrown on the mechanism of migraine headache¹ through the analysis of the action of ergotamine tartrate. Investigation has been carried out as follows. The amplitude of pulsations in branches of the external and internal carotid as well as other arteries has been ascertained by means of optical levers and photography. In 14 patients with migraine headache, ergotamine tartrate (Sandoz) (0.3 to 0.5 mgm. intravenously) produced a decrease of as much as 80 per cent and an average of 50 per cent in the amplitude of the temporal artery pulsations. This effect persisted for an indefinite period (90 minutes or more). In persons suffering headache there was a simultaneous decrease in the intensity of the headache with the progressive decrease in the amplitude of the pulsations: if the amplitude decreased slowly, the intensity of the headache decreased slowly; if the amplitude decreased rapidly, the headache rapidly disappeared. Direct photography of the temporal artery taken before and after ergotamine injection showed actual constriction of the vessel. The middle meningeal artery also constricts.

On the other hand, ergotamine has little effect, if any, on the internal carotid and its branches, as indicated by

¹ For definition see Wolff, H. G., Arch. Neurol. and Psychiat., 1937, 37, 895.

the following data. The amplitude of the intracranial pulsations was measured through a needle in the lumbar subarachnoid space in 5 patients with migraine headaches, and in 28 controls without headache. Ergotamine sometimes produced a transitory decline followed by an actual increase in the amplitude of pulsations, but usually the effects were inconstant, of varying magnitude, and bore no relationship to the state of the headache. Photographs of the retinal arteries (branches of the internal carotid) before and after ergotamine revealed no change, though slight constriction in the veins was observed.

To show further that headache was associated with increased amplitude of cranial artery pulsations and relief associated with decreased amplitude, the following experiments were performed.

(a) Histamine phosphate (0.1 mgm.) was given intravenously to 3 patients just after the migraine headache had been abolished by ergotamine. The amplitude of temporal pulsations then rose to more than 250 per cent of the post-ergotamine level. With this increase in amplitude there was a return of severe headache.

(b) In one instance, histamine (0.05 mgm.) happened to produce hemicrania indistinguishable from the previously abolished migraine headache. Here the increase in amplitude of temporal artery pulsations was unilateral and on the affected side. In all instances, with the decline in the amplitude of the pulsations to the post-ergotamine level, the headache again disappeared.

(c) Similarly, in 11 subjects without headache, ergotamine tartrate given 15 minutes previously did not prevent the incidence of severe headache after histamine injection. The amplitude of intra- and extra-cranial pulsations increased 250 per cent during the period of most severe headache. These experiments show also that the action of ergotamine tartrate is not analgesic.

(d) In 6 subjects, pressure applied to the carotid or temporal arteries during the course of migraine headache decreased the amplitude of pulsations, and relieved the headache while pressure was applied.

(e) The administration of adrenaline (subcutaneous 0.012 cc. 1/1000 per kilo) during migraine headaches reduced the amplitude of temporal pulsations 30 per cent. This was accompanied by short-lived relief of the headache. With the return of pulsations to their original level within 8 minutes, the headache also returned to its initial severity. It was then abolished by ergotamine which caused a long lasting reduction of 75 per cent in the amplitude of temporal pulsations.

Despite the above described vasoconstriction after ergotamine tartrate, the peripheral circulation in the skin of the ear, cheek and hand (by radiometric determinations) showed inconsequential change, presumably due to the accompanying rise in blood pressure.

During maximum vasoconstriction of the temporal artery and at the onset and during the height of the headache relieving effect, reflex dilatation of the pupils on painful stimulation of the neck, as well as pilomotor reflexes were unimpaired. Moreover, the pressor responses to adrenaline were unchanged. These data indicate that after the given amount of ergotamine tartrate, smooth

muscle is capable of responding to sympathetic impulses and adrenaline.

It has also been shown, by placing a cannula in the temporal artery of a migraine patient, that increased intravascular pressure with distension of the artery was accompanied by pain. These data, and those described above, coupling the vasoconstrictor action of ergotamine tartrate with the relief from pain, lend support to the thesis that migraine headache is an expression of dysfunction of the cranial vascular bed, probably dilatation of certain branches of the external carotid artery.

Antipneumococcus Rabbit Serum as a Therapeutic Agent in Lobar Pneumonia. By F. L. HORSFALL, JR., K. GOODNER, C. M. MACLEOD and A. H. HARRIS, 2d (introduced by Oswald T. Avery), New York, N. Y.

Antipneumococcus rabbit serum has been found to possess numerous characteristics which make it theoretically a more advantageous therapeutic agent in lobar pneumonia than is immune horse serum. Of these the more significant are: (1) higher protective titer per milligram of specifically precipitable protein, (2) smaller size of antibody as determined by ultrafiltration and ultracentrifugation, (3) absence of prozone phenomenon when more than optimum amounts are used in protection test, (4) failure of lipids to inhibit protective action, (5) ease and certainty of immunization, and (6) high potency of unconcentrated serum.

Because of these indications, unconcentrated type specific antipneumococcus rabbit serum has been used in the treatment of 22 patients with pneumococcus pneumonia, 10 with Type I, 4 with Type II, 3 with Type VII, and 5 with Type VIII. Bacteremia was present in 12 of the 22, consolidation of two or more lobes in 7, bilateral consolidation in 3 and pleural exudate containing large numbers of pneumococci in 3.

The results of the clinical use of antipneumococcus rabbit serum have been characterized by: 1, a strikingly low mortality rate; 2, early occurrence of crisis; 3, absence of anaphylactoid reactions; 4, sterilization of infected pleural exudates; and 5, mildness of serum sickness. These results together with the ease and rapidity with which the serum can be administered, as well as the ability of rabbits to produce antisera against each of the various types of pneumococci suggest that antipneumococcus rabbit serum is a therapeutic agent of considerable merit.

Allergy and Desensitization in Tuberculosis. By H. S. WILLIS and (by invitation) C. E. WOODRUFF, Detroit, Mich.

When guinea pigs are infected with tubercle bacilli and become allergic, their allergic phenomena are associated with a demonstrable degree of immunity. It has recently been claimed that, when such animals are desensitized by the introduction of repeated doses of tuberculin, all allergic phenomena disappear but immunity remains. In these experiments groups of normal, allergic and desensitized guinea pigs were inoculated with virulent tu-

bercle bacilli and were sacrificed at varying intervals thereafter. From the spleens of these animals tubercle bacilli have been removed and their numbers determined. The work indicates definitely that tubercle bacilli spread over the body of the desensitized animal with distinctly more facility than they do over the allergic body and that the desensitized animal is actually not the same immune animal that it was during the days of its allergy.

Histological study of the spleen indicates development of widespread fibrosis as a result of the desensitization process.

Studies on Anaphylaxis in the Isolated Heart. By HERBERT B. WILCOX, JR. (by invitation), and E. COWLES ANDRUS, Baltimore, Md.

If the hearts of guinea pigs are isolated and perfused with Ringer-Locke solution, the introduction of horse serum into the normal heart via the perfusate produces no significant effect. In the heart removed from an animal previously sensitized to horse serum the introduction of antigen (0.005 cc.) provokes obvious, though evanescent, alterations in function: (a) Changes in cardiac rate; (b) Alterations in auriculoventricular conduction; (c) The development of ectopic rhythms; (d) Variations in the form of the electrocardiographic complexes; (e) Pronounced diminution in the rate of coronary flow.

The degree of reduction of the rate of coronary flow which always accompanies the other phenomena of cardiac anaphylaxis, and the fact that often it is the first change to appear, suggests that it may be of primary importance.

The effects of small amounts of histamine on such perfused hearts include: (a) Changes in cardiac rate; (b) The development of ectopic rhythms; (c) Variations in the form of the electrocardiographic complexes; (d) Pronounced diminution in the rate of coronary flow.

The presence of atropine in the perfusate in a concentration of 1:100,000 inhibits all the manifestations of cardiac anaphylaxis; but only the coronary-flow-diminishing power of histamine. The possibility of a functional inter-dependence existing between cardiac anaphylaxis, the coronary vascular bed, and perhaps the production of an histamine-like substance is suggested.

The Influence of Diet on the Course of Nephrotic Nephritis in Rats. By LEE E. FARR and JOSEPH E. SMADEL (introduced by Homer F. Swift), New York, N. Y.

The renal injury, induced in rats by anti-kidney serum, provides a tool for testing the rôle of diet in nephritis, a question that has been long under discussion in the treatment of Bright's Disease.

Forty-eight young rats were fed a purified diet for a period of one month, while renal function studies, plasma protein and hemoglobin determinations and urinalyses were made. Then severe nephritis was induced uniformly in all the animals by intravenous injections of nephrotoxic serum given on three successive days. The animals were divided into three comparable groups and

fed different isocaloric diets. Each diet contained 27 per cent fat, 4 per cent salt mixture, and vitamins. They differed as follows: Diet 1, 64 per cent carbohydrate and 5 per cent protein; Diet 2, 51 per cent carbohydrate and 18 per cent protein; Diet 3, 29 per cent carbohydrate and 40 per cent protein. Diet 2 was used during the control period. Observations made during the control period were continued at three-week intervals for eleven months following injection.

The course of the nephritis in all three groups was parallel for one month following injection. During the second month evidences of nephritis markedly diminished or disappeared in all but two animals on Diet 1. These two died in the fifth month without renal failure. All other animals in this group survived, and at the end of the experiment all but three had normal urine. Every animal fed Diet 3 showed progressive nephritis, and thirteen died of apparent renal failure during the experiment; the remaining three were in the terminal phases of the disease when sacrificed. Of the animals fed Diet 2, one recovered in the second month, nine died of apparent renal failure during the experiment, and the remaining six had abnormal urine findings throughout. It is concluded that: 1. Chronic progressive nephritis follows a *single* insult to the kidney, under certain conditions. 2. The course of nephrotoxic nephritis in rats can be markedly influenced by diet.

Hemoglobin Nephropathy; A Pathological Study in Man and the Dog. By ELMER L. DEGOWIN and EMERY D. WARNER (introduced by Horace M. Korns), Iowa City, Iowa.

The tissues of 8 humans dying of transfusion anuria and one dying from quinine hemoglobinuria were studied. It is evident from a study of these and a comparison of other cases reported in the literature that two distinct types of nephropathy occur. In one, there is little evidence of tubular obstruction but there are varying degrees of necrosis, particularly in the epithelium of the proximal convoluted tubules. In the other type, epithelial degeneration is minimal while the distal portions of Henle's loops are plugged with hemoglobin precipitate and crystals while the proximal lumina are dilated. The glomeruli are not damaged in either case.

Dogs were transfused with hemoglobin solutions. When the urine was alkaline the kidneys were not affected. When the urine was acid, however, they developed uremia and died. The recurring portions of Henle's loops were plugged with hemoglobin pigment and crystals while the proximal lumina were dilated. The tubular epithelium showed little necrosis. In one dog subjected to the same procedure, however, there was tubular necrosis but no pigment obstruction.

We conclude that most of the dogs and some of the humans developed renal insufficiency because of the precipitation of hemoglobin in an acid medium producing obstruction of the tubules. This explanation does not account for some of the human cases although the clinical course is similar in all.

The Urinary Excretion of Androgenic and Estrogenic Substances in Normal Men and Women and in Hypogonadism, Gynecomastia and Virilism. By T. F. GALLAGHER, A. T. KENYON, D. H. PETERSON, R. I. DORFMAN and F. C. KOCH (introduced by O. H. Robertson), Chicago, Ill.

Benzene extracts of hydrolyzed urine were assayed for androgenic properties upon the capon's comb and for estrogenic properties upon adult spayed rats. The values given below are based on the two hour hydrolysis.

Four normal young men, studied for six weeks, excreted an average of 40 international androgen units per day (range 13 to 79), and an average of the equivalent of 10 gamma of theelin per day (range 2 to 29), with no conclusive evidence of cyclic variation.

Four normal young women, studied for four weeks, excreted an average of 28 international androgen units per day (range 13 to 51), and an average of the equivalent of 25 gamma of theelin per day (range 4 to 60). The cyclic increase in the estrogen output during the intermenstruum was unaccompanied by alteration in the androgen output.

Eight male hypogonads excreted about a third of the normal androgenic and estrogenic material. Four men with gynecomastia showed no conclusive changes in the amount of excreted hormones. Twenty women with virilism showed normal values as a rule, slightly high values for the androgenic material on occasion, and in one instance (adrenal cortical carcinoma) the high value of 480 international androgen units. The urine with the high values showed spectrographic properties unlike androsterone and like certain adrenal cortical derivatives.

Evidence for the Existence of Two Factors Necessary for the Successful Treatment of Pellagra or Experimental Canine Black Tongue. By JULIAN M. RUFFIN, ELBERT L. PERSONS and H. I. HARVEY (by invitation), and DAVID T. SMITH, Durham, N. C.

Patients with acute pellagra were hospitalized and fed a diet adequate in all respects except the pellagra preventive factor of Goldberger. The tests were limited to those patients who showed increasing symptoms while subsisting on the basic diet and those whose symptoms were reactivated by exposure to graded doses of sunlight. The criteria of a successful remission were (1) prompt disappearance of all symptoms, (2) marked increase in appetite, and (3) failure of maximum doses of sunlight to reactivate the disease.

Rapid and complete recovery was noted in 20 of 22 patients receiving an aqueous extract of 675 grams of liver daily. "Solution liver extract—Valentine (N. N. R.)."

Twenty-three patients were treated by parenteral injections of various liver extracts potent for pernicious anemia. Total doses derived from 400 to 6,750 grams of liver gave prompt improvement in the mouth and tongue symptoms, but there was no improvement in appetite, no constant effect on the diarrhea and in most instances relapse occurred after exposure to sunlight.

One patient was given orally the extract for parenteral use derived from 700 grams of liver daily for 6 days without improvement.

The liver residue discarded in the process of manufacturing the parenteral extract was ineffective in 5 patients who received total doses derived from 7,680 to 9,600 grams of liver. A dose derived from 28,800 grams was effective in one case of pellagra but this same massive dose was also effective in 3 cases of pernicious anemia and one of sprue.

The combination of the partially effective dose of the parenteral extract (derived from 700 grams) and the ineffective dose of residue (derived from 9,600 grams) produced an immediate and dramatic remission in 4 cases of pellagra.

Black tongue was produced in dogs by feeding a modification of Goldberger's black-tongue producing diet number 123. The treatment was limited to a ten day period. The criteria for a good result were (1) cure of the mouth lesion, (2) restoration of the appetite, and (3) a prompt gain in weight which must be maintained for 10 days after the treatment is stopped.

An aqueous extract of whole liver, "solution liver extract—Valentine (N. N. R.)," was effective in 3 dogs receiving a total dose derived from 3,670 grams of liver.

In 5 dogs parenteral injection of pernicious anemia liver extract derived from 300 grams of liver improved the mouth temporarily but had no other effect.

Five dogs received 3,000 grams of the parenteral liver with marked improvement in the mouth but unsatisfactory weight gain and a relapse of black tongue after 22 days.

Eleven dogs received the residue derived from 1,000 grams of liver without improvement. One dog made a slow improvement after receiving the residue derived from 2,000 grams and 3 dogs made a satisfactory recovery when the dose was raised to 3,000 grams. Even better results were obtained in 14 dogs when the 3,000 gram dose was supplemented with 300 of the parenteral.

When the ineffective dose of parenteral extract (derived from 300 grams) was given with the ineffective dose of the residue (derived from 1,000 grams) to four dogs, dramatic improvement resulted which differed from our best results only in the shorter length of time which intervened before the next attack of black tongue.

From these observations it would seem that there are two factors in liver which are necessary for the successful treatment of pellagra in man and experimental black tongue in dogs.

The Relation of Vitamin B to Serum Proteins and to Edema. By HENRY FIELD, JR., Ann Arbor, Mich.

Nutritional edema has been commonly considered to be the result of deficiency in protein intake. In 1935 Elsom reported studies on two patients with decreased serum protein and edema while on a diet adequate in protein but deficient in vitamin B.

We have observed cases with edema and lowered serum proteins despite diets apparently adequate in both protein and vitamin who had no apparent cardiac or renal cause therefor. Relief has followed supplements of vitamin B complex. These include cases of cirrhosis of the liver, one of whom has been maintained edema free and with nearly normal serum proteins for one year despite increasing impairment of liver function by other evidence. In another, who has recently developed evidence of hepatic insufficiency after two years of treatment, edema and lowered plasma proteins have recurred three times when the vitamin supplement has been neglected and have been relieved each time by its resumption.

One case of amyloidosis developed edema four weeks after urine specimens were known to be normal and at a time when he had mild proteinuria. Edema disappeared and serum proteins increased despite greatly increased proteinuria. Another patient had had a partial gastrectomy for duodenal ulcer and a jejunostomy for intestinal obstruction. In three of these patients edema has disappeared before the serum proteins reached the "critical level." One case of nutritional edema with normal serum proteins has been promptly relieved by vitamin B supplements.

It is suggested that vitamin B complex is a factor in the maintenance of serum proteins and that an increased intake may be beneficial when they are lowered in organic disease. It is also suggested that it is a factor in production of edema aside from its relation to serum proteins.

Positive Pressure Respiration and its Application to the Treatment of Acute Pulmonary Edema and Respiratory Obstruction. By ALVAN L. BARACH and (by invitation) JOHN MARTIN and MORRIS ECKMAN, New York, N. Y.

Evidence is presented which supports the concept that obstructive dyspnea produces pulmonary congestion, edema and emphysema because of the pathologically increased negative pressure within the chest during inspiration. The application of moderate positive pressures to inhalation therapy reduces the negative intrapleural pressure, relieves the dyspnea and tends to prevent pathological changes in the lungs.

In various types of experimental and clinical acute pulmonary edema the most important causal factor appears to be the negative pressure in the lungs during the inspiratory phase of respiration, since a suction action is exerted on pulmonary capillaries which may already have a tendency to ooze serum either because of engorgement or increased capillary permeability. Inhalation of air, oxygen or helium mixtures is followed by a clearance of pulmonary edema, the mechanism of which appears to be the lowering of the pathologically increased negative pressure within the chest.

The effects of positive pressure respiration on circulatory function in normals, patients with cardiac insufficiency and patients with asthma were presented.

The Deposition of Radium Salts in Bones, and Their Relation to Calcium Metabolism. By J. ALFRED CALHOUN and JOSEPH C. AUB, Boston, Mass.

Radioactive lead, a disintegration product of the gas Radon, was used to demonstrate the effects of acute poisoning. A small amount of this substance, given intravenously to three dogs, caused death in from ten to twelve days. Because of the presence of a radioactive salt, the bones were self-photographic, and it was shown that most of the radioactive lead had been deposited in the trabeculae. Analyses, done by very delicate physicochemical methods (sensitive to 0.0001 mgm.), showed that the trabeculae contained an average of eleven times as much radioactive lead as the cortical bones.

Bones and teeth from two patients demonstrate the chronic effects of radioactive materials. A self-photograph of a tooth from a living patient, who has been a radium dial painter for fourteen years, shows radium deposited deeply in the tooth. Thus, the area of inorganic salt deposit in teeth has been established. Self-photographs of bones secured at autopsy from a patient who received "Radium water" and who died of a neoplasm of the bones of the knee, demonstrate the position of heavy metals in bones long after exposure has ceased. Analyses of these bones show practically an even distribution of radium between the trabeculae and cortex.

Therefore, it is clear that therapy should be more effective early, for at that time heavy metals are localized in regions where they can be more readily mobilized.

The Use of the Cathode-ray Oscillograph in the Study of the Monocardiogram. By FRANK N. WILSON, FRANKLIN D. JOHNSTON and PAUL S. BARKER, Ann Arbor, Mich.

The concept of a single figure which represents the direction of the electrical axis and the magnitude of the cardiac potential at every instant during the cardiac cycle is not new. Mann has referred to this figure as the monocardiogram. Such curves can be constructed from measurements made on any two of the three standard leads recorded simultaneously, but the process is too laborious for use in the analysis of a large number of electrocardiograms. When conventional Lead I and the potential variations of the left leg (V_F) are amplified to the required degree and impressed upon the plates of a cathode-ray tube, the former upon the horizontal and the latter upon the vertical plates, the monocardiogram is inscribed on the end of the tube by the luminous spot produced by the electron beam and may be easily photographed.

We have taken a considerable number of monocardiograms in this way, using both normal individuals and patients with various electrocardiographic abnormalities as subjects.

The figures obtained are closed loops of varying size and shape. The spot may traverse the loop in a clockwise or counterclockwise direction. Irregularities in its movement, or a reversal in the direction of its motion, occurs in cases in which conspicuous notching of the

QRS group is present. The orientation of the loop with reference to the zero position of the spot depends on the position of the mean electrical axis.

It is hoped that the monocardio-gram may give information of value in the analysis of the electrocardio-gram by making it possible to distinguish between curves which have a similar appearance but are fundamentally different with respect to the origin of their components. The method makes it possible to convert the three curves of the standard leads into a single curve and this greatly simplifies the analysis of the form of the electrocardio-graphic deflections.

Metabolic Studies on Idiopathic Steatorrhea. By SAMUEL H. BASSETT and E. HENRY KEUTMANN (introduced by Wm. S. McCann), Rochester, N. Y.

Lipid, nitrogen, calcium and phosphorus balances have been determined in three cases of idiopathic steatorrhea in an attempt to evaluate various therapeutic procedures. Prolonged administration of large doses of liver extract intramuscularly was found ineffective in all cases. Replacing starches and sucrose in the diet by addition of equivalent amounts of dextrose and ripe banana, while the quantity and source of fat remained constant, did not cause improvement in the steatorrhea. Absorption of fatty acids was not improved by glycerophosphate or ox bile given orally.

Two patients showed the expected decrease in steatorrhea when the intake of fat was sharply restricted. In one of these, defective absorption of calcium was not improved by practically complete removal of fat from the diet. In a third patient with a relatively mild steatorrhea, the fatty acids of the feces could be reduced fifty per cent by shifting from normal to a low calcium intake. It is believed that the steatorrhea in this last patient was caused in part at least by defective absorption of calcium, failure to absorb fatty acids with the usual completeness being due to formation of insoluble calcium soaps in the small intestine.

READ BY TITLE

Factors Controlling the Behavior of Glucose in the Human Stomach and Small Intestine. By W. OSLER ABBOTT, WALTER G. KARR (by invitation) and T. GRIER MILLER, Philadelphia, Pa.

The factors governing the behavior of glucose in the normal human digestive tract have been studied. Evidence has been secured to show that a glucose solution, even of 50 per cent concentration, begins to leave the stomach within two minutes, but that the concentration of the solution as it enters the duodenum may be reduced to 15 per cent or less. The glucose may in turn enter the jejunum within two minutes but when its concentration usually is only 3 to 5 per cent. The rapid reduction in the sugar content of the ingested solution from 50 per cent to 5 per cent within less than five minutes and during its passage along a scant two feet of alimentary canal is accomplished by dilution and by selective absorption of glucose from the fluid of the duodenal

contents. The capacity of the diluting mechanism has been tested and, excluding the bile and pancreatic juice, the fluid derived from the duodenal mucosa alone has been found sufficient to double the volume of a 25 cc. sample of a 15 per cent solution in four minutes. The response of the duodenum to glucose has been compared to that of the jejunum and ileum, and the changes in the electrolyte concentration and the osmotic pressure of the intestinal contents have been determined.

Photometric Studies of Visual Adaptation in Relation to Mild Vitamin A Deficiency in Adults. By JOHN B. YOUMANS and (by invitation) MARVIN B. CORLETTE, HELEN FRANK and MILDRED G. CORLETTE, Nashville, Tenn.

Using an improved type of visual photometer we have studied the dark adaptations of a group of 54 presumably healthy adults and a group of 50 adult outpatients of our clinic. Eighty-three per cent of the former had initial recovery readings, after blanching, of 0.7 millifoot candles or less, while 50 per cent of the patient group showed poorer readings than this. Practically all subjects in both groups who had relatively poor dark adaptations and who were given large amounts of vitamin A for 4 to 6 weeks showed definite improvement and came within the limit of 0.7 millifoot candles. These findings have led us to propose 0.7 millifoot candles in the initial recovery reading as a tentative limit of normal dark adaptation in adults. Normal subjects with good adaptations were improved only very slightly after similar treatment showing that they were already at their optimum levels of dark adaptation, and vitamin A nutrition.

Clinical Results with the Elsberg Olfactory Test. By ALEXANDRA ADLER and KNOX H. FINLEY (introduced by Tracy J. Putman), Boston, Mass.

Elsberg's investigations have opened a wide field for physiological and clinical studies on olfaction.

For clinical purposes his most important methods are:

1. The "M. I. O." (minimal identifiable odor) expressing the minimum amount of air saturated with odor necessary for recognition.
2. "Olfactory fatigue," which is the interval of rest after an odor fails to be perceived before it can be perceived again.

Elsberg found an increased M. I. O. in cases of brain tumor producing direct pressure on the olfactory tract and an increased olfactory fatigue with tumors within the brain substance.

In 7 verified pituitary tumors with signs and supra-orbital tumors respectively we found the M. I. O. normal in 4 and increased in 3. The olfactory fatigue was normal in all 7. In 16 verified cerebral tumors without direct pressure on the olfactory tract we found the M. I. O. increased in 3 and normal in 13. Olfactory fatigue was increased in one, undeterminable in one because of the high M. I. O. and normal in 14.

In conclusion the Elsberg olfactory test enables us to determine quantitatively the olfactory function. In a few of our cases with direct pressure on the olfactory tract the M. I. O. was increased suggesting that this part of the test may be of diagnostic help in such cases. In respect to intracerebral growths the occurrence of increased olfactory fatigue seems to be too rare (1 out of 16) to be of practical clinical value.

Hematopoietic Principle in the Diseased Human Liver.

By LEON SCHIFF and (by invitation) MURRAY L. RICH and STANLEY D. SIMON, Cincinnati, Ohio.

In an attempt to elucidate the mechanism of macrocytic anemia in liver disease, extracts made of livers obtained from two cases of hepatic cirrhosis with associated macrocytic anemia were administered intramuscularly to patients with pernicious anemia in relapse. Positive hematopoietic responses were obtained. Similarly prepared extracts made from cases of acute yellow atrophy, toxic hepatitis, chronic passive congestion and malignant neoplasm of the liver also yielded positive responses.

The results indicate that the severely diseased liver may store the antianemic principle and that the macrocytic anemia of liver disease cannot necessarily be ascribed to failure of such storage.

The Production of Signs and Symptoms of Toxemia of Pregnancy by the Administration of Sodium Salts to Pregnant Women with Hypoproteinemia. By MAURICE B. STRAUSS, Boston, Mass.

Twenty-four women have been studied in the last trimester of pregnancy. Eight women with known pre-existing arterial hypertension without exacerbation in pregnancy and with essentially normal plasma proteins were given daily 6.3 grams of sodium (either as 16 grams of the chloride or 23 grams of the bicarbonate) for one week. Water was allowed ad libitum. Slight increments of weight unassociated with blood pressure changes or other signs or symptoms occurred.

Ten women with hypoproteinemia and arterial hypertension in the last trimester of pregnancy were given similar amounts of sodium daily. Eight of these women had no pre-existing arterial or renal disease. Weight gains of from 3.3 to 7.7 per cent together with gross edema occurred. The arterial blood pressure, particularly the diastolic, rose significantly. In 5 women increasing albuminuria was noted, and in 3 symptoms of pre-eclampsia became so alarming that the administration of sodium had to be discontinued within 4 days. Six women with hypoproteinemia were observed under identical conditions, but without the administration of sodium salts, as a control of the above observations. No gain in weight, edema, elevation of the blood pressure, or other symptoms occurred. The administration of a high protein diet to these women resulted in weight losses of from 2.9 to 4.1 per cent and the subsidence of symptoms.

The conclusion is drawn that the signs and symptoms of toxemia of pregnancy in the patients studied resulted from water retention induced by sodium salts in the presence of hypoproteinemia.

Studies in Pernicious Anemia. Extirpation of "Intrinsic Factor" Sources. By ARTHUR GEIGER, LOUIS GOODMAN and LOUIE N. CLAIBORN (introduced by Francis G. Blake), New Haven, Conn.

Experiments on swine designed to elucidate further the rôle of gastro-intestinal factors in pernicious anemia have been carried into the third year. The main sources of the "intrinsic factor" have been eliminated by total gastrectomy, isolation of the pylorus, duodenectomy, and gastrectomy plus duodenectomy.

Thirty-six young swine were used. Growth and development were normal in all animals surviving simple gastrectomy. Only a mild hypochromic anemia resulted during the first postoperative year despite repeated pregnancies. One sow, now 30 months agastric, has in the past 6 months developed a striking and steadily progressing macrocytic and hyperchromic red cell morphology. Bone marrow studies are in preparation. Spinal cord lesions have thus far appeared in only one animal. Clinical assay of the livers from agastric animals revealed appreciable loss of reticulocytogenic power in 2 months, marked depletion in 6 months, and complete absence of antianemic potency in 18 months. Gastrectomy plus duodenectomy, and duodenectomy alone resulted in considerable disappearance of liver potency within several months. The differentiation between a hormonal and enzymatic nature of the antianemic principle is being sought by assay of livers of newborn pigs obtained from agastric and from normal sows.

Medical Treatment of Hyperthyroidism with a High Fat Diet. By S. SOSKIN and (by invitation) I. A. MIRSKY, Chicago, Ill.

The present adequacy of surgery in hyperthyroidism has left little opportunity for the observation of medical treatment in severe cases. A patient who absolutely refused operation offered us such an opportunity. The results are recorded in order that others may be able to compare their observations as occasion arises.

The rationale of our treatment was based on several reports that diet may influence the hyperthyroid state or the action of administered thyroxin. More specifically, Loumos and also Scoz have shown that the feeding of certain fats may inhibit the activity of thyroxin in experimental animals. It seemed possible that the hypolipemia in hyperthyroidism might be playing a primary rather than a secondary rôle.

A woman, age 36, was admitted to the Max Pam Unit, Michael Reese Hospital, on June 10, 1935, four months after the advent of an acute hyperthyroidism. She complained of nervousness, palpitations, loss of weight and oligomenorrhea. She showed thyroid enlargement, lid lag, tremor, pulse rate of 116, blood pressure 140/74, basal metabolic rate plus 62.9, blood cholesterol from 147 to 176, and she weighed 110 pounds. On a diet of P. 90 F. 230 CHO. 90, with 3 grams of cholesterol per day added to the butter ration for about 3 weeks, she soon showed remarkable improvement. No iodine was given at any time. She was discharged on October 15, 1935,

on the above diet, and has been observed at weekly intervals to date. At present there are no signs or symptoms of hyperthyroidism. Pulse rate is 70 to 80, blood pressure 120/70, basal metabolic rate minus 6 to plus 13, blood cholesterol over 200 mgm. per cent and weight 140 pounds.

*Studies of Blood Formation in the Fetus and Newborn. IV.*¹ By M. M. WINTROBE and (by invitation) DEAN A. CLARK, Baltimore, Md., WILLIAM TRAGER, Princeton, N. J., and LEWIS DANZIGER, Baltimore, Md.

Whereas extracts for parenteral injection made from the livers of pig fetuses showed no antianemic potency in cases of pernicious anemia, desiccated liver of the last third of the gestation period, administered orally, caused a slight reticulocyte response in two out of three cases. However, the erythrocyte count did not rise and desiccated adult liver caused a much more striking response. Desiccated placenta showed no potency whatever. In assays for the growth promoting factor needed by mosquito larvae, the desiccated fetal livers were found to be about half as potent as desiccated adult liver. This factor was present in desiccated placenta but the quantity was small as compared with that found in adult liver.

Desiccated fetal stomach, on the other hand, appears to contain significant amounts of the antianemic substance effective in pernicious anemia, although the quantity may be less than in desiccated adult stomach. A concentrate of milk vitamins has been shown to contain "extrinsic factor." Extracts of the livers of stillborn pigs administered parenterally, have shown no potency but the limited observations made to date indicate that antianemic substance is found in increasingly greater concentration in the liver as age advances.

The Site of the Interaction of Extrinsic and Intrinsic Factors in Pernicious Anemia. By WILLIAM B. CASTLE and (by invitation) R. W. HEINLE, Boston, Mass.

Convincing evidence is lacking for any specific action *in vitro* of normal human gastric juice (intrinsic factor) upon beef muscle (extrinsic factor) responsible for the observed increased blood production and clinical improvement in pernicious anemia. Indeed, since neutral mixtures are effective, the essential interaction between these factors may take place only after their absorption from the alimentary tract. The purpose of the present observations was therefore to discover whether any essential interaction between beef muscle and gastric juice occurs within the alimentary tract, and, if so, whether such interaction results in the production of the active principle of the normal mammalian liver. During successive 10-day periods of the daily administration of test mixtures reticulocyte and red blood cell counts were made

upon 8 patients with Addisonian pernicious anemia while on controlled dietary regimes.

The daily administration of mixtures of beef muscle and gastric juice incubated for 6 hours and administered at an acid reaction (pH 1.8 or 2.5) produced negative results. However, positive effects upon blood formation were observed if, after such incubation, the mixture was administered at a reaction of pH 5 to 7. Control observations showed that a mixture of beef muscle and gastric juice incubated with pepsin for 12 hours at pH 1.8 was effective upon administration after neutralization. The failure of the unneutralized mixtures was therefore apparently not due merely to the prolongation during an *in vivo* period of a destructive process begun during the *in vitro* acid incubation. Thus, the strongly acid reaction seemingly provided an environment unsuitable for the essential interaction of the beef muscle and gastric juice. This unfavorable effect must have occurred *in vitro* or within the intestinal tract rather than parenterally.

The activity of mixtures of beef muscle and gastric juice, with or without the serial addition of normal human duodenal contents or hogs' duodenal and small intestinal mucosa after 2-hour incubation at pH 7, was destroyed by temperatures (40° to 100° C.) not destructive of the activity of aqueous solutions of the liver fraction "G" of Cohn, Minot and their associates. Therefore, contrary to the assertion of Klein and Wilkinson,¹ the formation of the thermostable active principle of liver could not be demonstrated *in vitro* under the above conditions.

As shown above, the active principle of liver is apparently not formed from beef muscle *in vitro* by serial contact with gastric, duodenal or intestinal secretions. It is therefore probable that, although an essential interaction between beef muscle and normal human gastric juice occurs within the alimentary tract, it involves only a preliminary step in the formation of the active principle of liver.

Observations on the Action of Aminophyllin on the Intrathecal and Venous Pressures and on the Bronchi as a Possible Mechanism for Its Beneficial Effect on Cheyne-Stokes Breathing, Dyspnea, and Paroxysmal Dyspnea. By JAMES A. GREENE, and (by invitation) W. D. PAUL and A. E. FELLER, Iowa City, Iowa.

The mechanism by which theophyllin-ethylene-diamine ameliorates cardiac dyspnea and converts Cheyne-Stokes breathing to a regular rhythm is not known and has been the object of this investigation. These effects of the drug are attributed to an improvement in cerebral circulation.

The effect of intravenous administration of the drug upon the intrathecal and venous pressures measured both separately and simultaneously has been observed. The intrathecal and venous pressures decrease almost simul-

¹ This investigation has been made with the assistance of grants from The National Research Council and The Committee on Therapeutic Research, Council on Pharmacy and Chemistry, American Medical Association.

¹ Klein, L., and Wilkinson, J. F., *Biochem. J.*, 1934, 28, 1684.

taneously with the improvement of respiratory distress or change of periodic breathing to a regular rhythm. Amyl nitrite and nitroglycerine, on the other hand, increase the intrathecal and venous pressures and do not alter the respirations.

Bronchial obstruction may be relieved, if it is present, as evidenced by the increase in vital capacity and subjective relief when the drug is administered to patients during an acute attack of bronchial asthma of allergic etiology.

Studies on the Anemia of Chronic Glomerulonephritis and Its Relationship to Gastric Acidity. By S. R. TOWNSEND, E. MASSIE and R. H. LYONS (introduced by J. P. O'Hare), Boston, Mass.

Forty-eight cases of chronic glomerulonephritis were studied in relation to the anemia, degree of nitrogen retention and gastric acidity. In addition, histological studies were made of rib marrow and sections of stomach in thirty-one cases of glomerulonephritis.

The result of our observations indicate that the anemia was of the normocytic type, the red cell being normal in size with the hemoglobin content of the cell slightly decreased. The anemia became manifest with the development of renal insufficiency and increased with the degree of nitrogen retention. As the anemia, renal insufficiency and retention of nitrogen became more marked, gastric acidity was found diminished. Absolute achlorhydria was discovered when acidosis became evident and the blood CO₂ content fell below thirty volumes per cent.

Our investigations, along with those of others, lead us to feel that the diminished to absent gastric acidity plays an important rôle in the improper digestion and absorption of ingested food and iron and can account, in part at least, for the persistence of the anemia and its lack of response to therapy.

Studies of the bone marrow do not support the common theory of lack of active blood-forming tissue as the etiological factor in the production of the anemia since the postmortem rib marrow is in a normal or hyperplastic state. Studies of sections of stomach did not reveal any histopathological explanation for a diminution of the gastric acidity, although many cases died in acidosis and uremia.

The Effect of Alcohol on the Water and Electrolyte Balances in Man. By WILLIAM M. NICHOLSON and HAYWOOD M. TAYLOR (introduced by D. T. Smith), Durham, N. C.

The effects of alcohol on the electrolytes and water balances have been studied in normal, healthy, adult male volunteers. The subjects were placed on a constant diet, aliquots of which were analyzed for their sodium, potassium, chloride, nitrogen and water contents. The day was divided into eight hour periods. Urine and stool collections were made for these periods. At the end of three days on the diet the subjects were given alcohol in sufficient quantities to produce intoxication.

The sodium, potassium, chloride, and nitrogen content of the urine was determined, and complete electrolyte

studies were carried out upon the blood. Plasma volumes were estimated by the dye method of Gregersen. Estimations of the alcohol content of the blood were made to see if any correlation could be demonstrated between alcohol content and changes in the electrolytes.

It was found that during the period of intoxication there was a marked retention of the urine potassium, which was reflected in an increase of the plasma potassium concentration. To a lesser degree there was a retention of sodium chloride and water. An increase in plasma volume and in body weight was also noted. No constant change was found in the blood sugar; there was, however, a slight decrease in the carbon dioxide content and an increase in lactic acid.

From these data it is concluded that in acute alcoholism in man there is an increase in the circulating blood volume. Since the increase in the plasma potassium concentration is not great enough to explain the total potassium retained, it would appear that the intracellular fluid is also increased. It is suggested that some of the sequelae of alcoholic intoxication are due to an excess of potassium.

The Effect of Certain Specific Dietary Factors on the Circulation in Patients with Heart Disease. By SAMUEL H. PROGER and (by invitation) HEINZ MAGENDANTZ, Boston, Mass.

In the past we have reported the results of observations on the effects of general dietary restriction on the circulation in patients with heart failure. On such a regime there is a disturbance of balance in sodium, nitrogen and water. This report deals with an attempt to isolate the effects of these three factors. The results in general have been as follows:

(1) There is under certain circumstances a definite relationship between water and oxygen metabolism, the basal metabolic rate falling as the 24-hour level of water exchange is decreased and vice versa. While there is at times evidence that fluid restriction may have beneficial effects on the circulation, large quantities do not appear to alter significantly the dynamics of the circulation.

(2) When other factors are controlled, a reduction of protein intake with the development of a negative nitrogen balance is associated with a lowering of the basal metabolic rate. This is not constant, and changes in nitrogen balance produce relatively little effect on the state of the circulation of patients with cardiac insufficiency.

(3) After heart failure seems well overcome and a steady state established, a total of 16 grams of sodium chloride in the diet with a retention of 4 to 6 grams daily will, in two to four days, produce striking evidence of heart failure as manifested by increased venous pressure, diminished vital capacity, increased heart rate, elevated blood pressure, enlargement of the liver and edema. The effect upon the liver appears disproportionately great.

The sodium retention in these experiments is of about the same magnitude as in the acute infections and may act in the latter state as an important contributing factor

in the precipitation of heart failure in patients with organic disease.

The Development of Pellagra in Certain Persons Eating a Well-Balanced Diet. By TOM D. SPIES, Cincinnati, Ohio, and (by invitation) AUSTIN B. CHINN, Washington, D. C.

Three selected recurrent pellagrins were admitted to the Tennessee Coal, Iron and Railway Hospital of Ensley, Alabama, and given a diet rich in pellagra-preventive foods and calculated to meet basal energy requirements. Despite the fact that each patient was in good health at the time of admission and was observed to have eaten the required amount of the prescribed diet at each meal, he developed symptoms of pellagra within a month. These symptoms disappeared after the diet was increased in amount and supplemented with large amounts of powdered brewers' yeast.

The findings of this study in no way contradict the statement that pellagra is a dietary deficiency disease, but do point out that an occasional person at least, probably because he is unable to utilize properly the essential substances present in food, is not protected by a diet which prevents other people from developing pellagra.

Effect of Pleasant and Unpleasant Mental Content upon the Respiratory Tracing (Spirogram) in Psychoneurotic Patients. By JACOB E. FINESINGER (by invitation) and STANLEY COBB, Boston, Mass.

Respiratory records were made by means of a Benedict-Roth metabolic apparatus on a series of nineteen psychoneurotic patients of various types, and upon a control series of six subjects, all of whom were under basal conditions. The patients were interviewed and were asked to express any ideas that came up in mind when they were told to think about pleasant and about unpleasant ideas. After the initial interview a six minute record of the respiration was made during which time no suggestions were made (the so-called control period). This was followed by a six minute period during which time the patient was told "think of pleasant ideas," or "let pleasant ideas come into your head." This was followed by a six minute period during which the patient was told to think unpleasant ideas. The "unpleasant period" was followed by another six minute period of pleasant ideas. The second period of pleasant ideas was followed by a six minute period during which the patient was told "just relax." The suggestions were given at intervals of from thirty to sixty seconds. After the experiment the patient was interviewed in an attempt to find out precisely what ideas were present during the various periods.

The respiratory rate, depth of inspiration and expiration, total ventilation per minute, oxygen consumption and the type of breathing, all were noted. In fourteen of the psychoneurotic patients, pleasant ideas were associated with a decrease in rate of respiration, a decrease in amplitude, a decrease in the total minute ventilation, and a marked tendency toward rounding of the spi-

gram at the end of the expiration phase. During the period of unpleasant ideas in fourteen of these patients there was an increase in the respiratory rate, an increase in total ventilation, and a marked tendency to the formation of more acute angles on the spiogram at the end of the expiration. During the relaxed period the type of respiratory curve approximated that of the pleasant period. There was no marked change in oxygen consumption during any of the periods.

In five of the patients no changes were observed. In three of these patients, the report during the interview was an inability to "let pleasant ideas come into mind." Four of the control cases showed similar changes in the same general direction as that of the psychoneurotic patients, but not nearly so marked.

Arteritis of the Temporal Vessels. By BAYARD T. HORTON and (by invitation) THOMAS B. MAGATH, Rochester, Minn.

This report presents a new clinical syndrome, the etiology of which is still obscure. Arteritis of the temporal vessels is a nonfatal disease which is characterized by periarteritis and arteritis of the temporal vessels, with painful tender areas over the scalp. It is accompanied by headache, general malaise and lassitude, weakness, fever, night sweats, anorexia, loss of weight, anemia, and mild leukocytosis. Seven patients, aged fifty-five, sixty-eight, sixty-nine, seventy-five, seventy-two, sixty-five, and sixty-eight years respectively were studied. Segments of the temporal arteries of five of the seven patients were resected for microscopic study, cultures, and inoculation into animals. Each patient made a satisfactory recovery. The microscopic appearance of the arteries and bacteriological studies will be reported in detail. Reports of similar cases have not been noted in the literature.

The Effect of the Administration of Bile on the Behavior of Peptic Ulcer. By EDWARD S. EMERY, JR., and (by invitation) MAURICE A. SCHNITKER, Boston, Mass.

The successful production of experimental ulcers in dogs by the Mann-Williamson type of operation was originally explained by a resulting lack of sufficient gastric neutralization. However, numerous facts justify some skepticism about this explanation, and suggest the possibility of a deficiency being the real cause. Recently Ivy has succeeded in preventing the development of ulcers in his animals by a special diet which includes the feeding of pancreas. We chose to study the effect of giving bile to patients with ulcer because many observers have reported a higher incidence of ulcers in animals deprived of bile than of pancreatic juice. A specially prepared desiccated bile was given to 40 patients over periods as long as two years.

The results were such as to exclude bile as a specific treatment for the disease. However, many of the patients obtained definite relief, and of 27 who had seasonal attacks 18 were kept symptomless. Observations

on these patients suggest that bile has a beneficial effect which does not seem readily explicable by a lowering of gastric acidity.

The Use of Ergonovine in Migraine. By WILLIAM G. LENNOX, Boston, Mass.

Ergonovine is the recently isolated alkaloid of ergot. Its effect in aborting headaches of the migraine type has been tested in a large group of patients. Injection of ergonovine is less effective than ergotamine tartrate in stopping individual headaches, but is preferred by some patients because its use is followed by less nausea and vomiting. The action of the two drugs on blood pressure, pulse and blood gases has been studied and compared.

A Study of the Bactericidal Properties of the Synovial Fluid and Blood of Patients with Gonococcal Arthritis. By WESLEY W. SPINK (by invitation) and CHESTER S. KEEFER, Boston, Mass.

For several years we have been studying the various properties of the synovial fluid obtained from patients with gonococcal arthritis. It was pointed out several years ago that bacteriological study of samples of synovial fluid from patients with this type of arthritis failed to demonstrate the presence of gonococci in all cases. To determine whether this might be explained in part by differences in the bactericidal activity of the synovial fluid, the following investigation was carried out. Bactericidal tests were done on the blood and synovial fluid of a group of patients with gonococcal arthritis; 4 had infected fluids and 10 were uninfected. Four other specimens of synovial fluid which were obtained from other types of arthritis were studied and used as controls.

It was found that when the fluids were infected there was a wide difference in the bactericidal power of the synovial fluid and whole blood. When the fluid was sterile the bactericidal content of the blood and synovial fluid was the same.

The complement titer of the synovial fluid was found to be the same or slightly lower than that of the blood, and the bactericidal action was abolished by heating at 56° C. for 2 hours. The bactericidal action of synovial fluid could be enhanced by the addition of antigonococcal immune serum.

The evidence so far indicates that the difference between infected and sterile samples of synovial fluid from patients with gonococcal arthritis is due in part to the presence of antibodies in those which are sterile and their absence in those which are infected. An investigation of other factors is being pursued at present.

Bacterial Type Transformation. By HOBART A. REIMANN, Philadelphia, Pa.

A strain of *M. tetragenus* isolated from the blood of a patient with purulent arthritis and meningitis produced typical white colonies on agar. In a study of the microbic dissociation of the organism over a period of

two years, four major variant forms of the original "White" form were isolated. The variant colonies were characterized by distinctive pigments and were called pink, yellow, pink-yellow and brown. Since each of the variants were immunologically specific, and since the component M, S and R culture phases of each of these variants were subsequently isolated, they were regarded as specific types. Spontaneous transformation from one type into another in broth, on agar or *in vivo* in mice was frequently noted.

Further studies of the characteristics of differential growth of the five types indicated that the S form of the white type, originally isolated from the patient, was peculiarly fitted to survive *in vivo* as regards optimal growth in certain ranges of temperature and pH concentration *in vitro*. This observation suggested that in the process of bacterial variation of certain so-called saprophytes, variant types which are especially endowed with capabilities to exist *in vivo* under certain conditions, may appear spontaneously. Such variant types may be regarded as possessing potential "virulence." Further observations and evidence that a similar phenomenon occurs among other bacteria will throw considerable light on certain obscure problems of the origin of epidemic diseases and on the problem of virulence.

Further Observations on Anti-Neutrophilic Serum. By JOHN S. LAWRENCE and (by invitation) WILLIAM B. CHEW, Rochester, N. Y.

Guinea pigs injected with antineutrophilic serum have been treated, while the action of the antiserum was at its height, with substances which, under normal conditions, produce distinct changes in the white blood cell picture. Adrenalin subcutaneously, sodium bicarbonate solution intraperitoneally and a broth culture of *B. coli* intraperitoneally have been used. Adrenalin given to normal guinea pigs produced at 2 to 3 hours a neutrophilic leukocytosis with little or no change in the lymphocytes. Sodium bicarbonate resulted in a neutrophilic leukocytosis with lymphopenia at 6 hours; and the broth culture of *B. coli* produced at 6 hours lymphopenia without neutrophilic leukocytosis, but at 12 hours neutrophilic leukocytosis with lymphopenia, and at 24 hours neutrophilic leukocytosis with a normal lymphocyte level.

The results obtained with animals in whom the neutrophils were absent from the blood due to antiserum show that exactly the same response to these substances is obtained on the part of the lymphocytes as in normal animals. In other words, the curve for the lymphocytes, under the condition of these experiments, is independent of the response on the part of the neutrophils. Our data, also, indicate a similar response on the part of the other white blood cells.

On the Prolonged Coagulation Time Subsequent to Anaphylactic Shock. By HARRY EAGLE, Baltimore, Md., and (by invitation) C. G. JOHNSTON and I. S. RAVDIN, Philadelphia, Pa.

The retarded coagulation observed in rabbits and dogs immediately after anaphylactic shock is regularly asso-

ciated with the presence of increased amounts of anti-thrombin in the blood. The increased antithrombic activity may be as much as one hundred times the normal level.

The fibrinogen content of the plasma is unaffected; for the reasons cited in the text, there is reason to believe that even the plasmas completely non-coagulable by calcium and tissue extract nevertheless contain sufficient prothrombin to effect coagulation; and although the platelet count is usually decreased after anaphylactic shock, the amount remaining would ordinarily suffice to cause coagulation within approximately normal time limits.

The increased antithrombic activity of the blood after anaphylactic shock is apparently the primary cause of the observed retardation of coagulation.

Scarlet Fever Immunization by Intracutaneous Injection of Scarletinal Streptococcus Toxin. By RICHARD A. KERN, and (by invitation) JEAN CRUMP and RUDOLPH L. RODDY, Philadelphia, Pa.

In brief, the work grew out of some earlier work in our clinic with diphtheria immunization by the intracutaneous route. Subcutaneous immunization against scarlet fever has been attended by severe local and constitutional reactions in many instances. This has been particularly true among allergic individuals, so that the prophylactic treatment may be worse than the disease. The intracutaneous injection of immunizing material in one-tenth of the subcutaneous dose results in a negative Dick test, as a rule, after four or five injections. There is never a severe local reaction and we have never seen a single constitutional reaction with fever. We have given over 500 injections to over 100 patients.

The Effect of Increased Cardiac Output in Mitral Stenosis and Aortic Insufficiency. By EMMET B. BAY (introduced by C. Phillip Miller), Chicago, Ill.

Formulas for the calculation of the work of the appropriate part of the heart in the presence of the valvular lesions noted were tested on a model of the circulation.

In mitral stenosis:

$$\text{Left auricular work} = Vp + \frac{Vv^2}{2g} + n \frac{Vv^2}{2g},$$

where V is output per beat, p is diastolic intraventricular pressure, v is velocity, g is the force of gravity, and n is a constant for a given stenosis. Doubling the cardiac output per minute requires a relatively large increase in the work of the left auricle since it results in a greater velocity, a factor which is squared in the formula. Doubling the heart rate requires more work to overcome the stenosis than doubling the output per beat.

In aortic insufficiency:

$$\text{Left ventricular work} = (V + X)p,$$

where V is net output per beat, X is the amount re-

gurgitated and p is mean systolic intraventricular pressure. X bears a fairly direct relationship to the duration of diastole in a given insufficiency. Doubling the net output per minute requires a relatively small increase in the work of the left ventricle and may require less than with a normal output when the increased output is obtained by doubling the rate.

These calculations may give a clue to the reason for the clinical impression that patients with mitral stenosis recover more readily from myocardial insufficiency than do patients with aortic insufficiency. They do not permit an estimate of the cost of the work required.

Venous Pressures, Cardiac Output and Blood Volume in Arteriovenous Fistula. By C. SIDNEY BURWELL and (by invitation) J. ALLEN KENNEDY, Boston, Mass.

This report deals with the dynamics of the circulation in a young man with an arteriovenous fistula in his forearm. It deals particularly with the venous blood pressures, the total blood volume and the cardiac output: aspects of the circulation concerning which little is known relating to human subjects.

The venous pressure was increased near the fistula and at all points measured between the fistula and the heart. The venous pressure in the other limbs was not elevated.

It was necessary to test the validity in this patient of the method used for the determination of the cardiac output. To this end measurement was made of the "recirculation time," i.e., the period required for blood to travel from the pulmonary capillaries to the fistula in the forearm, pass through the abnormal connection and return by way of the veins and right heart to the lung. The period was divided into the "vein-to-lung time" and the "lung-to-vein time." The former was determined by the ether method of Hitzig, the latter was estimated by the time required for inhaled carbon monoxide to reach the vein adjacent to the fistula. Carbon monoxide hemoglobin was recognized by means of a specific light filter and a photo-electric cell. It was possible to get checks with the three sample acetylene method within the time limits thus established.

The cardiac outputs thus determined were elevated. When the fistula was closed by a blood pressure cuff on the arm, the output was within the usual limits; after operation it gradually approached the same level.

The total blood volume was determined by the method of Gregersen, Gibson and Stead,¹ using the blue azo dye, T-1824, and spectrophotometric analysis. The volume was elevated when the fistula was widely open, and approached the calculated normal after surgical treatment of the arteriovenous connection. The variations in cardiac output occurred at the same time and in the same direction as those in total blood volume.

¹ Gregersen, Magnus I., Gibson, J. J., and Stead, E. A., *Am. J. Physiol.*, 1935, 113, 54.

*Vasoconstriction as a Response to Increased Venous Pressure.*¹ By WILLIAM A. SODEMAN and GEORGE E. BURCH (by invitation), and ROY H. TURNER, New Orleans, La.

Volumetric changes in the finger tip were studied with the use of a sensitive syphygmoplethysmograph. Immediately proximal to a plethysmographic cup an occluding air cuff was loosely wrapped so as not to produce any constriction when deflated. The cuff was connected to a pressure reservoir and manometer so that any desired pressure might be suddenly applied and the resulting volume changes in the finger tip noted. Thirteen normal subjects, 10 patients with diastolic hypertension and one patient with acrocyanosis were studied under controlled atmospheric conditions. They were seated comfortably with the arm resting passively upon a support with the finger tip at heart level, 30 minutes being allowed to reach a steady metabolic state. Reactions were then noted for obstructing pressures varying from 5 mm. Hg to diastolic pressure and maintained for 15 to 120 seconds, an interval exceeding the time of obstruction being allowed for recovery between each observation.

In the normal subjects, for cuff pressures up to a definite critical level, varying in different individuals from 15 to 40 mm. Hg, there was a sudden increase in finger tip volume, reaching a maximum within 5 to 10 seconds after occlusion and followed by a gradual diminution in volume reaching to or below the original level within one minute (Response A). Release of cuff pressure at that time always resulted in a further diminution in volume, usually greater than the reduction occurring before pressure release. But when cuff pressures above this critical level were applied only swelling occurred, that is until pressure was released (Response B).

In the 10 patients with diastolic hypertension the responses were similar, and the levels at which the reaction changed varied from 7.5 to 60 mm. Hg. No differences were noted between the red and pale hypertension of Volhard. In a patient with acrocyanosis with arteriolar constriction and dilatation of the non-arterial vessels, a response only of Type B was observed.

The gain in volume of the finger tip immediately following application of pressure in the obstructing cuff is probably due mainly to distension of small veins, venules and capillaries, and loss of volume which followed under proper conditions is probably due to active constriction of these same vessels. The critical pressure at which the type of response changes is an index of tone of the vessels responsible for the volume change. The mechanism of the response is not known, but it is likely that it is initiated by intravascular tension.

¹ Aided by grants from the Josiah Macy, Jr., Foundation, the David Trautman Schwartz Research Fund and the American Medical Association.

A Rare Form of Pararrhythmia with "Exit" Block Occurring in a Patient with Multiple Ectopic Pacemakers. By L. N. KATZ and (by invitation) J. L. ESCHELBACHER, S. STRAUSS, S. H. ROBERTSON and H. BINSWANGER, Chicago, Ill.

This patient has shown multiple ventricular and auricular premature systoles for years, together with attacks of paroxysmal supraventricular and ventricular tachycardia and periods of bradycardia. A large number of electrocardiograms had been taken. On three occasions electrocardiograms were obtained sufficiently long for analysis, and on analysis it could be shown that each of the various ectopic pacemakers was discharging at time intervals which were multiples of a common divisor distinct for each pacemaker. It is therefore possible that they represented instances of pararrhythmia not only with interference dissociation and "entrance" block, but also with "exit" block. On one occasion a record was obtained with only one active auricular ectopic pacemaker competing with the sinus node for control of the heart. The "exit" block was marked. The sinus node was kept discharged whenever the ectopic rhythm was active, and the sinus node took control only when the "exit" block increased and prevented the ectopic pacemaker from maintaining control. We have not seen such a mechanism reported in the literature. It offers unusually convincing proof of the theory of pararrhythmia with "exit" block first postulated by Rothberger and Kaufmann.

The Effect of Digitalis on the Anesthetized Dog. By L. N. KATZ and (by invitation) S. ROBBARD, M. FRIEND and W. ROTTSMAN, Chicago, Ill.

In a series of acute experiments on anesthetized dogs with arterial blood pressure within normal limits, digitalis given intravenously in therapeutic doses (0.34 cat unit per kgm. as Digifoline, Ciba) elevates the arterial and portal pressures, lowers the venous pressure, and decreases the venous return flow to the heart. Our experiments indicate that these digitalis actions are due in part to peripheral vasoconstriction and in part to a constrictor action on the blood vessels of the liver. The result is a reduction in venous return and therefore in the minute volume output of the heart. These effects persist but are less in degree when the portal blood is shunted directly to the vena cava without passing through the liver.

In anesthetized dogs with arterial blood pressures at shock level, results are the same as above except that the venous return flow to the heart is increased. These effects also persist when the portal blood is diverted from the liver. The major effect of digitalis at low blood pressure appears to be the result of vasoconstriction improving the deficient coronary circulation by elevating the arterial blood pressure. In this way the heart action is benefited and the minute volume output of the heart is increased. The reduction in venous pressure load on the right heart would enhance this action.

While the experiments reported by us have not ruled out an action of digitalis directly on the heart muscle, they show that such a possible action need not be invoked to explain our observations.

The Electrocardiogram in Air and Fat Embolism. By THOMAS M. DURANT (introduced by Charles L. Brown), Philadelphia, Pa.

A series of experiments was carried out, using the dog as the experimental animal, to determine the type and origin of electrocardiographic changes associated with air and fat embolism originating in the systemic venous circulation. The electrocardiographic changes obtained were of an extreme type and were remarkable for their constancy in all experiments regardless of whether air or fat was the embolic substance. These changes consisted in very marked lowering of the S-T segment in Leads II and III, without appreciable change in Lead I, and not associated with alteration of the QRS complex, corresponding with changes often seen in infarction of the myocardium. That these changes were not, however, due to coronary artery embolism was proven by pathological study. They occurred in association with a marked, sudden rise in venous pressure, and, in animals with the thorax open, appeared synchronously with the onset of right ventricular dilatation. It is concluded from the evidence made available by these experiments that the electrocardiographic changes observed were those of acute right heart dilatation secondary to obstruction of the pulmonary circulation by the embolic substance. The similarity to S-T changes observed in cases of human pulmonary embolism is discussed.

Factors Which Affect the Prognosis of Bundle Branch Block. By A. CARLTON ERNSTENE, Cleveland, Ohio.

That bundle branch block usually is associated with serious organic heart disease is a matter of common knowledge. It is not so generally recognized, however, that the prognosis in patients with this type of electrocardiographic abnormality is determined by the cardiovascular symptoms and signs, which are so often present, rather than by the bundle branch block itself. In the absence of congestive failure or of the anginal syndrome, bundle branch block is not incompatible with several years of life.

In a series of 66 consecutive cases of bundle branch block, there were 7 patients in whom the abnormality is known to have been present for two to ten years and in whom significant symptoms referable to the heart have not developed. Six other patients have had bundle branch block for at least one year and have remained free from symptoms. The case records of these patients have been analyzed, and a comparison has been made with the clinical findings in the patients who have died or who are still living but are experiencing cardiovascular symptoms.

Systolic Gallop Rhythm. By FRANKLIN D. JOHNSTON, Ann Arbor, Mich.

Twenty-one patients displaying on auscultation extra sounds in cardiac systole have been studied by the commonly used clinical methods and by means of sound tracings taken simultaneously with the electrocardiogram.

The clinical data obtained confirms the opinions of

previous investigators that, first, systolic clicks usually occur in individuals who show no evidence of organic heart disease and that they therefore have no unfavorable prognostic significance, and second, that their sole clinical importance lies in the possibility that they may be mistaken for the more common diastolic gallop sounds.

Measurements made from a fixed point of the accompanying electrocardiogram show that, with few exceptions, the position of the extra sound from cycle to cycle is much more variable than is the onset of the second heart sound.

Although the exact cause for systolic clicks remains obscure we believe that their clinical characteristics and the results of the measurements indicate that while they are intimately associated with movements of the heart within the chest they are not intracardiac in the sense that they are due to pressure changes within the cavities of the heart or the aorta.

The Sedimentation Rate in Angina Pectoris and Coronary Thrombosis. By JOSEPH E. F. RISEMAN and MORTON G. BROWN (introduced by Samuel L. Gargill), Boston, Mass.

The corrected sedimentation index was studied in thirty-seven cases of coronary thrombosis, fifty-five patients with angina pectoris, and twenty-one apparently normal persons of similar age.

It was evident that individuals between the ages of 45 and 70, without any evidence of disease, may have a corrected sedimentation index slightly higher (up to 0.70) than the accepted normal for young adults.

Over half of the patients with angina pectoris had a moderate elevation of the sedimentation index (0.73 to 1.38). There is reason to believe that attacks of angina pectoris occasionally result in myocardial damage.

Two-thirds of the cases of coronary thrombosis had rates considerably greater than that seen in any patients with angina pectoris; in the remaining third, the values were above 0.1 mm. The fastest rates were observed between the fourth and twelfth days after the onset of symptoms of coronary occlusion. Measurement of the sedimentation rate is of value in differentiating between angina pectoris and coronary occlusion. The sedimentation rate is of little or no aid in predicting the immediate outcome of the acute attack. The mortality of patients discharged from the hospital with fast rates, however, was twice as great during the first year after discharge as that of patients discharged with low or normal rates. Since the sedimentation rate signifies tissue damage, it is advisable to continue bed rest until the rate either returns to normal or shows no further progression towards normal.

A Clinical Study of the Action of Commonly Used Drugs on the Heart and Circulation. By C. J. GAMBLE, ISAAC STARR and (by invitation) A. MARGOLIES, J. S. DONAL, JR., N. JOSEPH and E. EAGLE, Philadelphia, Pa.

The subjects consisted of about 100 patients suffering chiefly from cardiac or circulatory disease, but not from

congestive heart failure. As far as possible we studied the action of drugs given under the conditions in which physicians are accustomed to employ them. The number of patients receiving a single drug varied from 4 to 14.

The drugs investigated included digitalis, epinephrine, ephedrine, caffeine, theophylline, carbaminoylcholine, sodium nitrite, nitroglycerine, pitressin, quinidine, morphine, and strychnine.

The study consisted of a group of estimations made before, during, and sometimes after, the drugs' action. This group consisted of duplicate determinations of cardiac output and metabolic rate, and repeated estimations of pulse rate, blood pressure, respiratory rate and volume. Orthodiagrams and electrocardiograms were secured also.

A statistical analysis of the data affords a basis for describing the action to be expected after the administration of these drugs in clinical conditions. Almost without exception the results support the conceptions of drug action derived from animal experiments.

The Effect of Epinephrin in Circulatory Collapse. By ROBERT W. WILKINS (by invitation) and SOMA WEISS, Boston, Mass.

Nitrite collapse induced in normal subjects was used to test the therapeutic efficacy of epinephrin. Epinephrin produces elevation of the arterial pressure with essentially unchanged venous pressure both in the horizontal and in the upright position. As indicated by the behavior of the vessels of the hand studied by plethysmographic methods, the arteries and arterioles become sharply constricted and the blood flow decreases. The venous tone, however, remains unaltered or only moderately increased. When epinephrin, in doses which produce therapeutic or slightly toxic effects, is given soon after the administration of nitrites but before the appearance of symptoms, all the manifestations of collapse and syncope develop just as soon as, if not sooner than in the controls, in spite of the fact that the fall of arterial pressure associated with nitrite collapse may be partially or completely prevented. In the presence of collapse, epinephrin augments the already existing arterial and arteriolar constriction with decreased blood flow but fails to produce significant constriction of the capillary and venous reservoirs. The venous return of blood to the right side of the heart is not enhanced. These observations indicate that the level of the arterial pressure is not necessarily a criterion of circulatory collapse. It is concluded that in spite of its arteriopressor effect, epinephrin may be harmful in certain types of collapse as it may further enhance tissue anoxia.

Changes in Blood Volume in Congestive Heart Failure. By WILLIAM A. EVANS, JR., and JOHN G. GIBSON, 2d (introduced by Henry A. Christian), Boston, Mass.

Changes in plasma and total blood volume occurring in chronic heart disease during the transition from compensation to decompensation, and during clinical recovery

from congestive heart failure were studied by means of the dye method of determining the blood volume described by Gibson and Evans (*J. Clin. Invest.*, 1937, 16, 301).

The change from the compensated to the decompensated state is characterized by a progressive increase in the volume of plasma and red blood cells. This increase is shared to a less extent by the plasma than by the red cells resulting in a slight concentration of the blood, as evidenced by an increase above normal levels in hematocrits. The degree of elevation of blood volume above the average normal level, as determined in 90 individuals, parallels the degree of elevation of venous pressure and increase in circulation time above average normal values.

During clinical recovery from congestive heart failure there is a diminution in both plasma and red cell volume, the decrease in plasma volume being at first more rapid than that of the red cell volume, resulting in still further concentration of the blood. With continued improvement the proportion of red cells to plasma tends to return to normal levels. The diminution in total volume is commensurate with the degree of clinical improvement.

An increase in blood volume over levels obtaining during failure was not observed in any case studied during recovery from chronic congestive heart failure. Relapses to more severe degrees of circulatory failure are accompanied by maintained elevation of or further increase in blood volume.

The Influence of Theophylline upon the Absorption of Mercurial Diuretics from the Site of Injection. By ARTHUR C. DEGRAFF and (by invitation) ROBERT A. LEHMAN and ROBERT C. BATTERMAN, New York, N. Y.

It has previously been shown that a mercurial diuretic containing theophylline (mercupurin) is capable of producing a greater diuresis than a simple mercurial (salyrgan). Furthermore, tissue destruction noted at the site of injection with a mercurial diuretic was for the most part prevented by the presence of theophylline in sufficient concentration in the injected solution (DeGraff, Nadler, and Batterman).

In the light of these results it was thought to be of interest to determine quantitatively the rates of absorption of mercurials from muscle with and without the addition of theophylline. Experimentally, this was carried out by giving a series of rabbits intramuscular injections of mercupurin and salyrgan. The animals were killed at definite time intervals and the amount of mercury remaining at the site of injection determined by chemical analysis of the muscle used. By this procedure we have come to the following conclusions: (1) that a mercurial diuretic containing theophyllin is completely absorbed one hour after intramuscular injection whereas a mercurial diuretic without theophyllin is only 25 per cent absorbed after the same interval; (2) that a mercurial diuretic without theophyllin is still only 80 per cent absorbed after 48 hours; and (3) that this marked difference in the rates of absorption of the two drugs is entirely due to theophyllin.

Prostigmin in the Diagnosis and Treatment of Myasthenia Gravis. By GEO. D. GAMMON and (by invitation) E. A. SCHEIE, Philadelphia, Pa.

Relief of myasthenia gravis by eserine and prostigmin suggests the mechanism involved is a failure of the motor nerve impulse to activate the muscle fiber; deficiency of neurohumoral transmission may be involved. The possibility of utilizing the response to prostigmin as a diagnostic test of myasthenia is not widely appreciated. Schwab and Viets have shown cases of upper and lower motor neurone paralysis are not relieved by the drug. In this study we found that various muscular diseases likewise failed to respond. The cases include progressive muscular dystrophy, myotonic atrophy, family periodic paralysis, and amyotonia congenita. Thus the only condition so far examined which is relieved by prostigmin is myasthenia gravis; hence the drug can be used to diagnose the disease. In the treatment of myasthenia, symptomatic relief may be obtained; it appears likely the natural course of the disease is uninfluenced.

The Interpretation of Pathological Joint Effusions. By H. C. COGGESHALL, MARIAN ROPES and ELSIE ROSSMEISL (by invitation), and WALTER BAUER, Boston, Mass.

The cytological, physical and chemical characteristics of normal bovine and human synovial fluid have been established. Normal human synovial fluid is more viscous and the concentration of serum proteins and mucin are greater. Both fluids are relatively acellular. The predominant cells are monocytes.

Having defined normal synovial fluid, we are in a better position to interpret the variations that we have encountered in pathological fluids obtained from patients with various types of joint disease.

Edema from any cause results in a lowering of the total cell count, mucin and protein. Most of the protein is albumin.

The total cell count is increased in hypertrophic arthritis. Both total and polymorphonuclear cell counts are increased in traumatic effusions. The total cell and polymorphonuclear cell counts increase progressively with increasing inflammation of the synovial membrane.

There is no absolute relationship between sugar content and cell counts. Some of the lowest sugar values have been observed in rheumatoid arthritis. The total protein and globulin content increases with increasing inflammation of the synovial membrane, the highest values being encountered in long standing effusions of rheumatoid arthritis. Mucin increases are seen only in non-inflammatory joint diseases.

These and similar data from rheumatoid arthritics with regularly recurring knee joint effusions show that the cytological and chemical variations depend on the severity and duration of the inflammation of the synovial membrane as well as on the etiology. If these facts and the clinical history are taken into account, ex-

aminations of the synovial fluid are of diagnostic and prognostic significance.

Calcium and Phosphorus Metabolism Studies in Rheumatoid and Degenerative Arthritis. By MARIAN ROPES (by invitation), CHARLES L. SHORT and ELSIE ROSSMEISL (by invitation), and WALTER BAUER, Boston, Mass.

The marked decalcification observed in rheumatoid arthritis and the osteophyte formation seen in hypertrophic arthritis suggest the possibility of an altered calcium and phosphorus metabolism in these two diseases.

The fasting serum calcium, phosphorus and phosphatase values in such individuals were found to be within normal limits. Therefore, complete calcium, phosphorus and nitrogen metabolism studies were carried out on eight rheumatoid and three hypertrophic arthritics. When studied on a low calcium intake, the observed negative calcium balances in both groups were essentially the same as in the controls. The four patients with rheumatoid arthritis exhibiting the most marked decalcification had the highest negative calcium balances. That marked restriction of activity is an adequate explanation for the observed increased calcium excretion is suggested by the fact that immobilization of a normal individual in a cast will result in an increased calcium excretion of 0.95 gram per three-day period. Four rheumatoid arthritic patients studied on a high calcium diet showed no abnormalities. The actual phosphorus balances were in all cases in close agreement with the theoretical phosphorus balances.

These results indicate that an altered calcium and phosphorus metabolism is not a primary feature of either rheumatoid or hypertrophic arthritis.

The Mechanism of Human Diabetes Insipidus. By HENRY L. SCHMITZ, Chicago, Ill.

The nature of the disturbance in water metabolism in diabetes insipidus has been studied in four patients with this disease. The following observations were made. The withdrawal of water for periods of four to six hours had no significant effect upon the urine output although the patients complained of thirst. When water was then allowed ad libitum the output was influenced but little, and the enormously excessive intake approximately made up the deficit created during the period of abstinence. Analysis of renal function by the creatinine clearance method of Rehberg indicated that the polyuria was due to a deficient reabsorption of water in the renal tubules. Glomerular filtration was within normal limits. The administration of pituitrin decreased the urine volume by increasing tubular reabsorption. As the effect of pituitrin wore off tubular reabsorption decreased and urine volume increased. Increase in the fluid intake lagged behind the return of the polyuria.

These results are interpreted as meaning that the essential defect in diabetes insipidus is renal, specifically a failure in tubular reabsorption of water and that pituitrin corrects this defect.

Effect on Tumor Growth of Treatment with Colchicine and X-rays. By AUSTIN M. BRUES and BEULA B. MARBLE (introduced by Joseph C. Aub), Boston, Mass.

The alkaloid colchicine is a specific poison for cell division, blocking mitosis in the visible metaphase stage. It is also known to have a specific metabolic effect on tissues, consisting in marked reduction in vitamin C content. The present experiments have been performed on rats and mice bearing experimental tumors, and indicate that the administration of repeated large doses of colchicine retards the growth of these tumors very markedly, although regression of tumors rarely occurs. This seems to be due in part to the effect of the drug on cell division, and in part to vascular injury such as occurs after administration of bacterial filtrates. Retardation occurs only with toxic or near-toxic doses, and many of these animals died of colchicine poisoning. A series of animals receiving smaller doses, in amounts that could safely be administered daily, showed no tendency to retardation of growth and no lowering of tissue or tumor ascorbic acid, although some arrest of mitosis was seen. The smaller doses of colchicine, when combined with x-ray treatment (300 r daily for ten days) caused no further regression of tumors than did x-rays alone.

Insensible Water Loss in Disease. By ALEXANDER W. WINKLER (introduced by John P. Peters), New Haven, Conn.

The daily insensible loss of weight over considerable periods of time was determined in a group of some twenty patients presenting various metabolic disturbances. In 6 edematous nephritic subjects the insensible loss did not vary significantly with urine flow, fluid intake, or change in body water and salt content during diuresis. In both edematous and non-edematous subjects the average insensible loss was definitely correlated with the basal metabolism. The daily insensible loss varied more in individual subjects than did the basal metabolism. In certain cases of renal and vascular disease the average insensible loss over prolonged periods was found to be related to the total metabolism by the following approximate equation:

$$\text{Calories burned} = 2.0 \times \text{I. L. (grams)}.$$

Evidence, however, is presented suggesting that the factor may be greater than 2.0 in certain of the edematous and less than 2.0 in the hyperthyroid cases. In one case of recovered acute nephritis with malnutrition, there was a definite discrepancy between the total metabolism calculated from the insensible loss by this equation, and the insensible loss as estimated from indirect calorimetry. It is concluded that while insensible loss is closely dependent on total metabolism in disease as well as in health, under some circumstances the quantitative relationship may be different.

The Metabolism of Phosphorus in Periodic Family Paralysis. By A. T. MILHORAT (introduced by Eugene F. DuBois), New York, N. Y.

The metabolism of calcium, phosphorus, and magne-

sium was studied in a patient with periodic family paralysis. The patient was a 15 year old male who had periodic attacks of paralysis involving most of the voluntary muscles, lasting for about 24 hours. Following the occurrence of a few of these attacks, the urinary and fecal output of calcium, phosphorus, and magnesium was determined for 8 periods of 6 days each during which carefully weighed diets were given. The mineral content of the diet was kept constant from day to day during each period, but varied for the different periods. The calcium balance was normal. The patient was in balance on a diet containing 1.0 gram of calcium daily. On a daily intake of 2.0 grams of calcium, 0.550 gram were retained daily; on a daily intake of 0.100 gram there was a negative balance of 0.260 gram. Likewise, the output of magnesium was normal. The amounts of magnesium eliminated daily were similar to those in the diet on intakes varying from 0.162 gram to 0.306 gram. On the other hand, there was a negative balance of phosphorus during all the periods of investigation. During the periods when 1.6 grams of phosphorus was contained in the daily diet, the average daily negative balance was 0.362 gram. On an intake of 2.0 grams the average daily negative balance was 0.147 gram and when 0.60 gram of phosphorus was given daily the amounts eliminated exceeded the intake by 0.358 gram. By the use of similar methods and diets the mineral balance of 2 patients with progressive muscular dystrophy and 2 patients with myotonia atrophica was determined. In these 4 patients without periodic family paralysis the metabolism of calcium, phosphorus, and magnesium was normal.

The data suggest that in periodic family paralysis there is a disturbance in the metabolism of phosphorus without any involvement of the metabolism of calcium or magnesium. These observations were made after the occurrence of a few attacks of paralysis. Whether a similar loss of phosphorus precedes an attack of paralysis or whether phosphorus is retained at that time has not yet been determined.

Further Experiments on Experimental Hyposthenuria.

By PAUL DUMKE (by invitation) and J. M. HAYMAN, JR., Cleveland, Ohio.

This is a continuation of experiments reported last spring by Shumway and Hayman. At that time, it was shown that dogs subjected to subtotal nephrectomy excreted an increased volume of dilute urine, but could be made to put out a concentrated urine under certain experimental conditions (intravenous sodium sulphate, increased plasma colloids, low blood pressure). Dogs poisoned by uranium, on the other hand, could not be made to excrete a concentrated urine under any circumstances.

In the present experiments, the effects of ureteral obstruction have been studied. Dogs subjected to adequate ureteral obstruction excrete a dilute urine, and cannot be made to concentrate by withholding food and water, nor by any methods tried. The daily urine volume is usually increased. Creatinine and urea clearances are markedly reduced. Blood pressure is not significantly elevated.

These changes in renal function are apparent as early as five days after obstructing the ureters. Histologically, such animals show tubular degeneration. This damage, however, is reversible, for if the ureteral obstruction is removed the animal recovers its ability to excrete a urine of high gravity.

Successful Management of Addison's Disease with Adrenal Cortex Extract. By W. O. THOMPSON and (by invitation) P. K. THOMPSON, S. G. TAYLOR, III, and W. S. HOFFMAN, Chicago, Ill.

We have been able to rehabilitate patients with typical Addison's disease and maintain them in good health for long periods by the administration of large doses of an adrenal cortex extract (10 to 20 cc. daily) without any other form of therapy. When typical symptoms of adrenal insufficiency develop during the administration of an inadequate dose of the extract, or following its omission, the patient may be revived by large doses of the extract alone, provided the insufficiency has not been allowed to develop too far. When a crisis is well marked the administration of sodium salts must be added to the treatment until nausea and vomiting disappear. While patients may be maintained for periods of several months by the administration of sodium salts alone or by combining this form of therapy with small doses of extract, the most desirable clinical condition is not produced unless an adequate dose of extract is given, and then supplementing with sodium salts is unnecessary. If the dose of extract is adequate, the potassium content of the diet may be ignored. While changes in the composition of the blood are important in diagnosis and as an index of the efficacy of treatment, the data show that, early in a crisis, there may be some discrepancy between the concentration of various substances in the blood and the clinical condition of the patient. When the crisis is well marked, the blood findings usually coincide with the clinical condition.

The Rôle in Growth and Development of Certain Potent Chemical Agents Found in Thymus Extract. By L. G. ROWNTREE, and (by invitation) ARTHUR STEINBERG, N. H. EINHORN, N. K. SCHAFFER and WILLIAM ZIEGLER, Philadelphia, Pa.

With freshly prepared solutions of glutathione, ascorbic acid and cysteine administered to parent rats, we have produced definite acceleration in the rate of growth and development of the offspring, in the second generation. These may be used singly or in combination. They are now being tried by way of substitution therapy in the retardation in growth and development incident to thymectomy, through successive generations of rats. Ergothionine, another iodine-reducing agent, is not present in the thymus extract. The effects of glutamic acid and glycine are under investigation.

The possibility of obtaining thymus effects from a synthetic extract containing glutathione, ascorbic acid and cysteine is being tried at present.

The Treatment of Diabetes Mellitus with Protamine Zinc Insulin. By S. SOSKIN, and (by invitation) R. LEVINE and M. D. ALLWEISS, Chicago, Ill.

There can be no doubt as to the greater efficacy and convenience of protamine zinc insulin, in the treatment of diabetes mellitus, as evidenced by a number of recent clinical reports. However, further experience has tempered our initial enthusiasm with certain practical considerations. Treatment with protamine zinc insulin was instituted under carefully controlled conditions in the Max Pam Metabolism Unit of the Michael Reese Hospital. After several weeks of hospital observation, these same cases were followed for many months in the outpatient dispensary. Our observations on these and other patients have led us to the following conclusions: (a) A single dose of protamine insulin may show some effect for as long as 48 hours in a fasting individual, but its clinically significant period of activity under the ordinary conditions of feeding is probably 16 to 20 hours. (b) Diabetes of the adult type can usually be well controlled with one dose of protamine insulin per day. (c) Diabetes of the juvenile type can be well controlled but usually requires two doses of protamine insulin per day. (d) Occasional severe juvenile diabetics cannot be well controlled throughout the 24 hours of the day by either protamine or ordinary insulin. (e) Because of its lesser effect on alimentary hyperglycemia, protamine insulin may be less effective than ordinary insulin in the treatment of the uncoöperative or unintelligent patient.

Indirect Calorimetric Study of the Oxidation of Glucose in Controlled and Uncontrolled Diabetic Men. By J. M. SHELDON (by invitation) and L. H. NEWBURGH, Ann Arbor, Mich.

The study consisted of a continuous four hour measurement by means of a respiration chamber of the amount of carbohydrate oxidized by normal men and by diabetics when they were controlled and uncontrolled. Standard, open circuit, indirect calorimetry was employed. All subjects were first studied while subsisting on a low carbohydrate, high fat type of diet. Insulin was not employed. The diets for all subjects were adjusted so that the blood sugars of the diabetics remained within the normal range. The energy of the diet was approximately maintenance. Subsequently, the oxidation of glucose by the same diabetics was studied while they were constantly hyperglycemic and glycosuric, due to the addition of sufficient carbohydrate to the diet (calories were kept constant by an isocaloric reduction of fat). The controls received the same diet. A typical example follows:

	Carbohydrate of preparatory diet	Glucose at beginning of indirect calorimetry	Glucose oxidized
	grams	grams	grams
Normals.....	50	50	22
Diabetic controlled.....	50	50	18
Normals.....	130	100	42
Diabetic uncontrolled...	130	100	20

The data indicate that the diabetic is unable to oxidize as much glucose as the normal control. A considerable increase in the dietary carbohydrate causes the normal to oxidize much more glucose but has no measurable effect upon the diabetic.

The Corpus Luteum Hormone in Pregnancy. By J. S. L. BROWNE, and (by invitation) J. S. HENRY and ELEANOR M. VENNING, Montreal, Canada.

Using a gravimetric method, the excretion of sodium pregnandiol glucuronide in the urine has been followed in nine apparently normal cases at various periods of pregnancy. This compound has been shown to be excreted during the luteal phase of the menstrual cycle and the authors regard it as an excretion product of corpus luteum hormone (progesterone) in human urine. The values are expressed as milligrams of pregnandiol excreted in 24 hours, and days are counted from the first day of the last menstrual period.

Up to the 60th day the values found in four cases have been from 4 to 10 mgm.; these are approximately the same as those found during the menstrual cycle. The rate of excretion began to rise from this level, in the cases studied, between the 80th and 100th day. By the 150th day in four cases it had reached a level of 40 mgm. The rate continued to rise and a peak was reached in the eighth month; in two cases 80 and 73 mgm. were excreted at this period. Within 24 hours of delivery the compound disappeared practically completely from the urine. In one case after removal of the ovary containing the corpus luteum at the fourth month, the compound continued to be excreted.

There are variations in the rate of excretion; but it is impossible to say at present whether or not these are of a cyclic nature or what are the limits of normal variability. The efficiency of the glucuronide synthesizing mechanism as well as the amount of progesterone produced is probably a factor in determining the rate of excretion of the glucuronide. The requirements of the body for corpus luteum hormone throughout pregnancy and the rôle of the placenta as a site of its production in the later months are discussed.

The Calorigenic Activity of Thyroid Iodine at Different Levels of Metabolism. By JACOB LERMAN and WILLIAM T. SALTER, Boston, Mass.

Several questions with regard to thyroid medication are in dispute. Does myxedematous (athyreotic) man respond to the whole thyroid iodine or only to thyroxine iodine? Does the athyreotic organism with normal or hypernormal metabolism respond in accordance with total thyroid iodine or with the thyroxine iodine only? As the normal organism becomes hyperthyroid in response to medication, does it respond in accordance with total thyroid iodine or with the thyroxine iodine only?

Our investigations in human myxedema have shown that the caloric response can be predicted more accurately in terms of the total thyroid iodine. In the artificial production of hyperthyroidism in man, however, our studies

indicate that *in this case* the thyroxine iodine is the better determinant. This result agrees with data obtained in normal guinea pigs by other investigators. In hyperthyroidism, artificially induced, the total thyroxine stored and the daily thyroxine need increase in roughly logarithmic fashion with the basal metabolic rate. Such data are illuminating in considering spontaneous hyperthyroidism. When thyroid medication is administered to man, the better index of its effectiveness is (a) the total iodine for the athyreotic individual and (b) the thyroxine iodine for the thyreotic individual.

The Prognostic Use of Iodine in Thyrotoxicosis. By S. HERTZ (by invitation) and J. H. MEANS, Boston, Mass.

In previous papers we have discussed the therapeutic and diagnostic use of the response to iodine in thyrotoxicosis. Evidence can now be presented which indicates that the character of the response also gives information of value in prognosis.

A follow-up study on patients treated in our clinic in 1930 by Thompson revealed that the patients who did well on prolonged iodine medication with but few exceptions showed a substandard basal metabolic rate at one time or other during their course of treatment. Patients who did not exhibit this type of response to iodine came to operation.

The animal experiments of Friedgood on the behavior of the basal metabolic rate of guinea pigs with anterior pituitary induced hyperthyroidism showed a similar behavior of the basal metabolic rate when the animals reached the refractory or remissive stage and iodides were administered coincidentally.

Upon the basis of such evidence we have taken the development of a substandard level of metabolism on iodine to indicate that the patient exhibiting it is approaching a spontaneous remission of his disease and therefore does not require operation. In an impressive number of cases this reasoning has proved sound.

Observations in Chronic Hypoparathyroidism. By WILLIAM T. SALTER and (by invitation) DOROTHY M. TIBBETTS, Boston, Mass.

The treatment of chronic hypoparathyroidism, whether idiopathic or postoperative, often presents a complicated therapeutic problem. In order to study the effect of various therapeutic agents, the calcium and phosphate metabolism was studied in four dogs whose thyroids and parathyroids had been removed. The observations extended, after operation, continuously over periods of 2, 14, 17, and 60 weeks, respectively: they comprised the effects of low and high calcium diets, of parathyroid extract in varied dosage, of thyroid hormone, and of vitamin D in various combinations. Similar observations were obtained also in two cats.

Among the results noted were the following: (1) During the continuous administration of minimal doses of parathyroid extract, thyroxine was ineffective unless high calcium was available in the diet, when the blood calcium rose. On a low calcium intake, thyroxine ag-

gravated tetany. (2) Parathyroid extract became progressively less effective as the animals' calcium reserves were depleted, as indicated by the calcium balance, but its effectiveness returned with high calcium intake. (3) Vitamin D with high calcium intake alone might preserve the normal status for long periods, but vitamin D without dietary calcium was ineffective even in tremendous dosage. However, after a recent repletion of calcium stores, vitamin D continued to be effective for several weeks after calcium was largely withdrawn from the diet. (4) "Withdrawal" tetany occurred after excessive doses of parathyroid extract were suddenly omitted. Indeed, with a rapidly dropping serum calcium, the onset of tetany was noted at levels of 14 to 12 mgm. per cent.

Conclusion. The thyroid hormone may elevate the serum calcium to normal levels if abundant calcium be supplied in the diet while parathyroid extract also is injected in small amounts. In other words, in relieving hypoparathyroidism, thyroxine does not act upon the residual parathyroid glandules, but upon some other mechanism of calcium mobilization. The beneficial effect of vitamin D is likewise dependent upon readily available calcium either from the diet or from recent storage as demonstrated by positive calcium balances.

Idiopathic Hypoparathyroidism. By FULLER ALBRIGHT, and WALTER BAUER, and (by invitation) BENJAMIN CASTLEMAN and TRUMAN G. DRAKE, Boston, Mass.

This report is based on five cases of hypoparathyroidism occurring spontaneously, and includes the autopsy findings on one of these cases. It is not so much concerned with the metabolic disorder resulting from the hypoparathyroidism as with the underlying cause of the hypoparathyroidism itself. It is pointed out that the disease usually starts in adolescence and that the time of onset can be approximately determined by certain changes seen in roentgenograms of the teeth. To the knowledge of the authors the autopsied case here reported is the first one in which the underlying pathology in the parathyroid glands in this rare condition has been studied. The disease is contrasted with hyperparathyroidism due to idiopathic hyperplasia. The possible rôle of the pituitary gland and of infection in the etiology is discussed.

Chronic (Spontaneous) Hypoglycemia in a Juvenile Diabetic with Marked Amelioration of the Diabetes. By PRISCILLA WHITE (by invitation) and ALEXANDER MARBLE, Boston, Mass.

Studies are reported on a young woman now 21 years old with onset of typical juvenile diabetes of marked severity at the age of 7.8 years. The patient has been under close medical observation from the date of onset until the present. Symptoms, blood and urine findings and course during this period leave no doubt even in retrospect that the patient had true diabetes mellitus of severe grade. In the summer of 1934 it was noted that her insulin requirement (previously 40 to 65 units daily) was becoming less and that hypoglycemic attacks con-

tinued despite progressive reduction in insulin dosage. In October 1935 on 8 units a day she was constantly aglycosuric while following her diet. "Breaking diet" caused only slight glycosuria. No menstrual period occurred between June and November 1935. During a hospital stay in February 1936 it was found that with no insulin whatever, hypoglycemic attacks occurred despite a liberal diet. She reentered the hospital in March 1936 for special studies. These showed a curious combination of mild diabetes and spontaneous attacks of hypoglycemia. No insulin was administered and yet no acidosis developed despite a diet which at times included as much as carbohydrate 300 grams, protein 130 grams and fat 120 grams a day. Ergotamine brought about in one hour severe hypoglycemia with a transient right hemiplegia. Pure carbohydrate seemed to provoke rather than to prevent hypoglycemia (after a period of transient hyperglycemia) whereas a mixed meal was more effective in preventing "reactions."

At home between April 1936 and February 1937, she was entirely without insulin. Attempts were made to keep her on a diet relatively low in carbohydrate but because of the easy tendency to hypoglycemia the diet as actually taken at home was high in all three food components. Consequently she gained 20 pounds in weight in the 10 months.

Further studies under controlled conditions were carried out in the hospital in February 1937. A blood sugar curve over a 24 hour period revealed a marked tendency to the development of low values when 2 or 3 hours had elapsed after the taking of food. After 100 grams of glucose there was an immediate rise to a level consistent with mild diabetes and then a precipitous fall to a hypoglycemic level with attendant symptoms.

These diagnoses have been thought most worthy of consideration: (1) Pancreatic islet cell adenoma; (2) Hypofunctioning of the pituitary; (3) Some disturbance of glycogen storage in the liver. Studies designed to demonstrate a pituitary tumor have been negative and although the liver is definitely enlarged, functional tests have given values within normal limits. The patient and her family have refused abdominal exploration.

The Reticulocyte Response to Liver Extract in Experimentally Induced Anemia. By B. E. HALL, G. R. HIGGINS and C. H. WATKINS (introduced by H. Z. Giffin), Rochester, Minn.

Macrocytic anemia, associated with hepatic cirrhosis, was induced in adult white rats by exposing the animals to inhalations of carbon tetrachloride for short daily periods over a span of two to three months, according to the method of Higgins and Stasney. Data with reference to erythrocyte and reticulocyte counts in normal and anemic rats were established and were compared with the data of the aforementioned workers. A group of normal rats were injected intraperitoneally with commercial liver extract. Separate groups of anemic rats were injected with: (1) single doses of liver extract intraperitoneally, (2) single doses of physiologic saline

solution intraperitoneally, and (3) repeated daily doses of liver extract intramuscularly for one week. In each instance the amount injected was arbitrarily chosen: 0.5 cc. per 100 grams of body weight. The normal rats receiving liver extract and the anemic rats which were given saline solution failed to show reticulocyte reactions. However, significant responses were observed in the anemic animals which received either one injection or repeated daily injections of fresh commercial liver extract. An attempt was made to control these experiments by eliminating other factors known to cause reticulocyte reactions.

The Etiology of Idiopathic Hypochromic Anemia. By W. M. FOWLER and (by invitation) ADELAIDE P. BARER, Iowa City, Iowa.

During the course of studies of iron metabolism on patients with hypochromic anemia certain observations pertaining to the etiology of "idiopathic hypochromic anemia" were made.

Determinations of iron balance show that patients with achlorhydria retain less iron from a normal dietary iron intake than do patients with a normal gastric acidity.

Although the patients with idiopathic hypochromic anemia denied excessive menstrual blood loss, it was found that the average loss for these individuals was considerably larger than the average for 100 normal women. It was also found that the amount of iron which these patients retained from a normal dietary intake was not sufficient to replace that lost by menstruation.

A daily iron intake of approximately 12 mgm. is apparently necessary to maintain a positive balance.

The patients with idiopathic hypochromic anemia retained as much iron and regenerated hemoglobin as rapidly while receiving medicinal iron as did patients with chronic hemorrhagic anemia, so that no evidence of faulty iron metabolism was apparent.

Blood Volume Changes in Pernicious Anemia. By J. G. GIBSON, 2D (by invitation) and WILLIAM P. MURPHY, Boston, Mass.

Changes in plasma and red blood cell volume occurring in patients with pernicious anemia treated by parenteral liver extract were studied by the method described by Gibson and Evans (*J. Clin. Invest.*, 1937, 16, 301).

In severe anemia the total blood volume is reduced, averaging 17.5 per cent below normal in six patients with red cell counts around 1,500,000. The diminution in red cell volume is offset to some extent by an increase in the plasma volume. The individual cell volume is high.

With clinical improvement there is a progressive increase in the total blood volume, the plasma volume tending to diminish as the red cell volume rises. With complete clinical recovery the red cell and total blood volume returns to normal limits. Changes in individual cell volume vary with individuals but the general trend is toward smaller cells as red cell volume rises.

During recovery, the relationship between changes in plasma and red cell volume is such that the degree of re-

turn in red cell volume to normal values is closely reflected by the degree of return to normal values of red cell counts, hemoglobin determinations and hematocrit values.

Certain evidence has been obtained which indicates that the response, in terms of percentage return to normal in red cell volume is slower following multiple small doses of liver extract than that which follows single large doses, even though a satisfactory reticulocyte response occurs in both instances.

The Maturation of Transfused Reticulocytes in the Rat. By A. J. CRESKOFF (by invitation) and THOMAS FITZ-HUGH, JR., Philadelphia, Pa.

Our previous study¹ of the reticulocytosis of fetal and nursing rats indicated the probability of peripheral reticulocyte maturation.

In the present experiments litters of young rats with high reticulocyte counts were used to supply donor-blood to a recipient group of adult rats with low reticulocyte counts. Just before transfusion, recipients were bled an amount equal to the volume to be transfused (average 5 cc.). In another group, anemic adult animals, with high reticulocyte counts induced by repeated bleedings, were used as donors. In both groups the donor blood was concentrated to an 8,000,000 erythrocyte count before transfusion. Control bleeding and transfusion experiments were made with normal adult animals.

In all of our experiments the transfused reticulocytes disappeared progressively over a period of 48 to 96 hours, at the end of which time the recipient's reticulocyte count had declined to pre-transfusion level without any concomitant change in the recipient's elevated post-transfusion erythrocyte counts. This we believe indicates peripheral reticulocyte maturation and suggests that the youngest reticulocytes (rat) require almost 4 days to "mature" in the peripheral blood. Our data suggest also that transfused erythrocytes survive for 5 to 8 days. Wistar-strain albino rats have no demonstrable intra-group hemagglutinins.

The Questionable Relationship of Staphylococcus Infection to Leukemia. By FRANKLIN R. MILLER, Cleveland, Ohio.

Infection has been considered frequently as an etiological agent in the leukemia group. In the past three years I have studied five leukemias, each of whom had at sometime one or more foci of infection caused by hemolytic staphylococcus aureus. Three of these cases were studied to see if the white cell count and the number of immature cells bore any relationship to the infections. Two of these cases were given antigen made from staphylococcus aureus, in the one case autogenous vaccine and in the other commercial staphylococcus toxoid. In each case the white cell counts were low at the start and as the doses of antigen increased, the level

¹ Fitz-Hugh, T., Jr., Creskoff, A. J., and Taylor, H. B., *J. Clin. Invest.*, 1936, 15, 468.

of the white blood cell count increased, and the increase was chiefly made up of immature cells. Following the use of toxoid in the one case, diphtheria toxoid was given in an immunizing dose with little or no increase in white blood cell level. The third case had a leukemic count at the start, but no demonstrable infection. However, hemolytic staphylococcus aureus was cultured from the patient's nasopharynx and, because of this, staphylococcus antitoxin was employed. After the start of the antitoxin, many bullous lesions developed over the buttocks, arms, back and face. These lesions contained pure cultures of hemolytic staphylococcus aureus. No beneficial change occurred in the white cell count or progress of the disease with the use of 70 cc. or 50,000 units of antitoxin.

The staphylococcus toxoid was used in immunizing doses on a fourth case of leukemia without infection, in which the white blood cell count was controlled with Fowler's solution. Here again the white blood cell count increased and immature cell forms were found in the blood smear.

The data is too meager to state that infection in these cases played any definite rôle in inducing or aggravating the leukemic process.

Erythrocyte Sedimentation. Clinical Significance and Evaluation as a Quantitative Procedure. By THOMAS HALE HAM (introduced by Clark W. Heath), Boston, Mass.

Variation in the stability of erythrocytes in suspension was found to be a non-specific phenomenon which was altered by: plasma fibrinogen, serum globulins, lipoids, viscosity, hematocrit, mean corpuscular volume of erythrocytes, anticoagulant, diameter of sedimentation tube and height of blood column. The sedimentation rate was a measure of the degree of erythrocyte instability and, as such, had no direct clinical importance. The clinical interpretation of the sedimentation rates depended upon the significance of the abnormal blood constituent, and not upon the altered suspension stability.

Employing the Rourke-Ernstene technique, 260 determinations of the corrected sedimentation "index" on 65 subjects showed linear correlation with the concentration of plasma fibrinogen only when there were normal values for serum globulins and in general for lipoids. The sedimentation rate of erythrocytes in defibrinated blood was observed with correction for variations in hematocrit in 72 subjects. These rates were extremely slow and almost a constant in normal subjects; they were slightly accelerated and variable in abnormal subjects with normal serum globulins and lipoids; but were strikingly elevated in instances of increased serum globulins or lipoids. The corrected defibrinated sedimentation rate showed no relation to the concentration of plasma fibrinogen.

The sedimentation techniques of Wintrobe, Westergren, Linzenmeier and Cutler produced less satisfactory correlation with plasma fibrinogen than the method of Rourke and Ernstene. However, none of the above techniques using whole blood, nor the technique employed

here for defibrinated blood, could be used as an accurate or specific method of estimating the concentration of any one blood constituent, such as plasma fibrinogen, serum globulin or lipoids, because of the influence of variations in any one of these substances on the suspension stability.

Neutropenia (Agranulocytosis). Fatigue as an Etiological Factor and Monocytosis as a Prognostic Sign. By PAUL REZNIKOFF, New York, N. Y.

Of the four etiological factors important in the causation of neutropenia—fatigue, drugs, menstruation and infection—fatigue previous to the onset of illness was found to be the most prominent predisposing factor in 11 of 13 patients. No inquiry was made into this feature in the 2 remaining cases. Drugs known to be of etiological significance in this disease were taken in 9 cases; in 3, no history of their use could be elicited. One patient who had never taken drugs before her attacks received 1.62 grams of amidopyrine as a sedative during her fourth attack and recovered. Menstruation was a factor in 3 of the 9 female patients; 6 had passed the menopause. Infections of possible importance in 6 patients; in 4, no history of infections could be elicited, and in 3, no previous infection could be found.

The most constant hematological sign of recovery was a pronounced monocytosis which usually appeared before any other evidence of improvement. Only a sporadic or slight monocytic response was present in the 3 fatal cases.

Plasma Proteins in Anemias. By CHARLES L. BROWN and (by invitation) I. W. GINSBURG, Philadelphia, Pa.

This report consists of a correlation study of the plasma proteins with the size and hemoglobin content of the red blood cells in ten cases of severe or moderately severe anemia and fourteen cases of mild anemia, other than pernicious anemia or anemia of pregnancy. These cases were classified as microcytic, normocytic, and macrocytic in accordance with the classification of Wintrobe.

Plasma protein studies included total serum protein, serum albumin, serum globulin, albumin globulin ratio and colloid osmotic pressure. Throughout the whole group of cases the total protein tends to be normal with the serum albumin lower than normal with resulting somewhat lowered albumin:globulin ratio. The colloid osmotic pressure, while varying over a considerable range shows no distinct constant variation referable to the microcytic or macrocytic cases.

These studies indicate that there is no constant relationship of the cell volume to the colloid osmotic pressure of the blood serum, and the increase in the size of the red blood cell cannot be explained alone on an osmotic basis.

The Longevity of Erythrocytes in Human Blood. By MATTHEW C. RIDDLE (by invitation) and RAPHAEL ISAACS, Ann Arbor, Mich.

From a study of the rate of blood formation in over 600 patients with various types of anemia, it is concluded

that the increase or decrease in the erythrocyte count per week (It) is equal to the difference between the number of new erythrocytes formed and the number destroyed ($P - D$) in a given weekly period (t). For pernicious anemia the weekly rate of destruction (D) = $0.22 + (0.176 \text{ times } E_0$, the initial red blood cell count). In normal individuals, in certain anemias (acute hemorrhage, iron deficiency, pernicious anemia during remission) and for transfused normal erythrocytes, $D = 0.22 E_0$. The average period of erythrocyte survival in pernicious anemia in relapse varies from 1.6 to 4.54 weeks, depending on the erythrocyte count. In the other conditions mentioned, the average duration is 4.54 weeks.

The theory is advanced that erythrocytes, being no longer living nucleated cells, persist "indefinitely" unless they are fortuitously destroyed by trauma. "Wearing out" then, is not in the order of "age," but in degree of trauma. Modifying factors are (a) total erythrocyte concentration, (b) shape, (c) size, (d) elasticity, (e) nature of the capillary bed, (f) velocity of the stream, and (g) chemical environment. Comparable tissues in this respect are the hair and nails.

The Effect of Intramuscular Administration of a Globulin Substance Derived from Normal Human Plasma in Hemophilia. By FREDERICK J. POHLE and F. H. L. TAYLOR (introduced by George R. Minot), Boston, Mass.

Patek and Taylor¹ have demonstrated the effectiveness of a single intravenous injection of a globulin substance derived from normal human plasma in reducing the coagulation time of the blood in hemophilia.

The present observations demonstrate that the globulin substance may be given intramuscularly with similar effectiveness. After either single intramuscular or intravenous injection there was a prompt reduction in the coagulation time followed by a gradual rise with return to the pre-injection level in 24 hours.

When injections were repeated by the intramuscular or intravenous route within 7 hours, it was not possible to maintain the coagulation time at the reduced level. This refractory period does not last longer than 24 hours after the last injection.

However, during this refractory period the plasma or blood of the injected hemophilic patient showed no loss of clot-promoting power when measured *in vitro* against a second control hemophilic blood. Therefore, the refractory phase in the injected patient cannot be explained on the basis of a deficiency of globulin substance alone.

Experiences with Insulin in Non-diabetic Individuals.

By REGINALD FITZ and (by invitation) BEN VIDCOFF, Boston, Mass.

A series of non-diabetic individuals were given ordinary glucose test meals with and without added insulin. Three types of curve were encountered. In the one,

insulin had its usual effect in lowering the blood sugar concentration after a test meal. In another group, no effect of insulin was demonstrable, the curves being essentially the same with and without insulin. In the third group of cases, the glucose tolerance after the administration of insulin appeared diminished; so that the resultant curve following insulin was a diabetic-like curve, whereas without insulin, the curve was such as is obtained in normal individuals after a glucose meal. That insulin in normal individuals under certain circumstances may appear to lower sugar tolerance already has been recognized. The reason for this finding is not altogether clear. In our experience, the activity of the thyroid gland is one certain factor. The size of the dose of insulin used is another factor in determining the type of sugar tolerance test obtained. Possibly the activity of the anterior lobe of the pituitary gland is a third factor, though our data on this score are not altogether convincing.

Parathyroid Diuresis. By CLARENCE L. ROBBINS (introduced by John P. Peters), New Haven, Conn.

Recent studies of the effect of injections of parathyroid extract on the excretion of electrolytes in urine indicate that the excretion of base and particularly sodium is increased in the first few hours after injection. Ellsworth and others had previously demonstrated the increased rate of excretion of phosphorus immediately following injection of parathyroid extract.

In the studies here reported an attempt was made to determine whether the parathyroid extract specifically influences the excretion rate of sodium and of phosphorus or whether the observed increases are simply a resultant of increased renal filtration. Human subjects who presented no evidence of renal dysfunction were used for control observations and for studies of excretion rates of sodium, chloride, phosphorus, pH changes and exogenous creatinine clearances before and after injection of parathyroid extract.

In the first hour and continuing for three hours after injection a significant rise in pH of urine and in the excretion rates of water, sodium and phosphorus occurred. Creatinine clearances remained unchanged. Chloride excretion was not significantly influenced.

It is concluded that parathyroid extract exerts a diuretic action by inhibiting tubular reabsorption and not by increasing glomerular filtration as measured by creatinine clearances. Molecular ratios of excess sodium to phosphorus greater than 15 suggest that phosphatemia, immediately following parathyroid extract may be entirely secondary to diminished reabsorption of sodium by the renal tubules.

Supra-Diaphragmatic Splanchnic Resection for Essential Hypertension: A Two Year Study of Results, Selection of Cases, and Physiological Considerations. By REGINALD H. SMITHWICK (by invitation) and ROBERT S. PALMER, Boston, Mass.

In thirty-four early or moderate cases of essential hypertension followed from a few months to two years,

¹ Patek, Arthur J., Jr., and Taylor, F. H. L., J. Clin. Invest., 1936, 16, 113.

a fall of blood pressure to within normal limits in two-thirds, and almost to normal in the remaining third occurred.

There is marked symptomatic improvement in all. No marked fall in blood pressure is obtained in cases of malignant hypertension and only a moderate fall in 50 per cent of the cases of late hypertension. Symptomatic improvement of moderate or marked degree is obtained in all of late benign essential hypertension, and likewise in all of 6 cases diagnosed malignant hypertension. Medical treatment causes a substantial fall in the blood pressure of over 50 per cent of mild and moderate cases, while 90 and 75 per cent respectively, either have no symptoms or are very much relieved. Medical treatment causes a substantial fall in the blood pressure in one-third of the late cases, and there are no symptoms, or symptomatic relief is obtained in slightly less than 50 per cent.

Experiments on the blood flow in the arm after novocaine block, indicate that vasomotor control is much diminished. We suggest that the basis of essential hypertension may be at first a vasomotor instability, gradually becoming conditioned to a state of "chronic emergency." By sympathectomy of a large area of the minute vessels the first barrier of the peripheral resistance is lowered. It is not expected that the capillary resistance depending on tissue needs is affected by this procedure. In the early vasomotor stage essential hypertension may be halted at its inception. Later it may be relieved by abolishing the variability so characteristic of essential hypertension, but it is unlikely that the level can be lowered to normal after arteriolar change resulting from long continued hypertension has taken place.

The Treatment of Polycythemia Vera by the Production of a Chronic Iron Deficiency State. By WILLIAM DAMESHEK and (by invitation) HENRY H. HENSTELL, Boston, Mass.

The treatment of polycythemia vera is eminently unsatisfactory. Phenylhydrazine is exceedingly difficult to control and probably damaging to the liver. Fowler's solution is not well tolerated. X-ray therapy has been disappointing. Occasional venesections apparently stimulate blood production.

In 5 well-controlled cases previously treated with the above methods, a state of chronic iron deficiency was induced by multiple venesections and a diet grossly deficient in iron. Venesections, usually 6 to 8 in number, of 500 cc. were done twice weekly until the hemoglobin reached about 70 to 80 per cent and the erythrocyte count about 5.0 million. The daily dietary iron content was reduced to less than 6 mgm. Frequent studies were made of the clinical status, the blood, hematocrit, blood volume, and viscosity.

With this method, the patients were maintained symptom-free from 6 to 9 months, and there have occurred: great reduction in the various features of the plethoric state, relatively low hemoglobin concentration with very

low color index and mean corpuscular hemoglobin concentration, low hematocrit with low mean corpuscular volume and small average red cell diameters, and reduction in the blood volume and blood viscosity to normal values.

Rising values after 6 to 9 months have been readily controlled by a few venesections.

A Delayed Disturbance of Nitrogen Metabolism Following Certain Infections. By HAROLD A. BULGER, St. Louis, Mo.

The mysterious relationship of infection to such local disturbances as arthritis or nephritis inspires an interest in any correlated metabolic changes. We have noted certain striking phenomena following some acute infections. They have occurred after an intervening period of one to several weeks of seemingly normal metabolism. The most notable change has been an extraordinary excretion of amino nitrogen. There has been at the same time a reversion to a negative nitrogen balance. Most cases of nephritis have shown a more or less marked increase in amino nitrogen excretion. Even more striking has been a great increase in the output of amino nitrogen of certain cases of arthritis. The magnitude of this change may exceed ten times the usual amounts. We have noted an immediate fall after removal of foci of infection. It should be noted that as a rule this phenomenon is not associated with any febrile reaction.

High Peripheral Venous Pressure. Its Lack of Relationship to Orthopnea and Dyspnea in the Absence of Congestive Failure. By EUGENE B. FERRIS, JR., and (by invitation) JOHNSON MCGUIRE, Cincinnati, Ohio.

There is considerable clinical and experimental evidence that the dyspnea and orthopnea of cardiac failure are not related to increased venous pressure. However, a number of observers have maintained that such a relationship does exist, either directly through the effect of high venous pressure itself; or indirectly through stagnation anoxemia which is assumed to occur with high venous pressure, or through the associated increased intracranial pressure.

We have observed thirteen patients having extremely high venous pressures in the upper part of the body resulting from superior vena caval obstruction and have been impressed by the absence of dyspnea or orthopnea in the majority of such patients. Blood gas studies of blood obtained from the internal carotid artery and from the internal jugular vein, spinal fluid pressures, simultaneous cubital and femoral venous pressures, and clinical observations have been made on five consecutive patients having superior vena caval obstruction.

Dyspnea and orthopnea were absent in all five patients, although venous pressures and spinal fluid pressures as high as 50 cm. of water were recorded. The cerebral blood flow was diminished in some cases and normal in others. Stagnation anoxemia, when present, was not accompanied by respiratory symptoms.

A Method for Determining the Minimal Infective Dose of Treponema Pallidum in Experimental Syphilis. By HUGH J. MORGAN and (by invitation) GEORGE P. VRYONIS, Nashville, Tenn.

Our method offers a means of quantitating the dose of virus necessary for establishing syphilis in the rabbit. At least, one can say how many visible organisms are in an inoculum which produces an infection. The results so far indicate that a certain minimal number are necessary before infection will occur. This is a matter of interest since many experiments in rabbit syphilis are based on the assumption that, if *any* organisms are present, an infection will occur. Moreover, the method may be of some value in considerations of the question of a ultramicroscopic virus in syphilis.

The Combination of Oxygen and Hemoglobin in the Blood of Patients with Liver Disease. By ANCEL KEYS (by invitation) and ALBERT M. SNELL, Rochester, Minn.

The occurrence of anoxemia in advanced hepatic dis-

ease has been reported previously, the available evidence indicating that ordinary pulmonary and circulatory factors are not responsible. Oxygen dissociation curves of the blood, calculated on the basis of an assumed pH, indicated a displacement of the curve to the right in some of these cases. The present study confirms the presence of oxygen unsaturation of the arterial blood in advanced cirrhosis. A study of the oxygen-hemoglobin combination in such cases, with measurement of pH_a and pH_e of the arterial blood as drawn and as equilibrated, shows an apparent decreased affinity of hemoglobin for oxygen. This decreased affinity persists over a range of from 30 to 80 per cent saturation and is sufficient to account for the observed anoxemia. The presence of hyperbilirubinemia alone is not a factor.

A study of laked blood, as contrasted to whole blood, in these cases, provides the necessary data to discriminate between alterations in the hemoglobin itself and abnormalities in the equilibrium across the cell membrane. The evidence obtained to date indicates that the hemoglobin itself, as in all pathological conditions which have been studied, is not physiologically altered.