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PRESIDENTIAL ADDRESS

THE MAN AND QUALITY IN CLINICAL INVESTIGATION

By THOMAS HALE HAM

The complete title of this address is as follows: The man and quality in clinical investigation; the allegory of the brackish water, *i.e.*, the clinical investigator as an estuarial species; or growth, common sense, and ethics. There is no doubt that the members of the American Society for Clinical Investigation have concerned themselves with the man and quality of investigation. It is appropriate, therefore, to look for those policies which may guarantee such quality in the future. Since judgment of the present is difficult and prophecy is treacherous, other methods of evaluation of potential future policies may be tried. From nature itself, and by the use of allegory, it may be possible to describe controversial problems in the quiet and objective language of the biologist. Thus the field of clinical investigation may be described allegorically in a timeless manner by study of the dynamic concepts of the botanist, Professor Merritt L. Fernald (1).

In the study of fresh tidal estuaries and shores, Fernald found that certain plants, such as genus *Lilaeopsis,* were distributed widely throughout the world. Critical observations of the plants and their environment led Fernald to a remarkable theory to explain the wide distribution and location of these species. First, these plants occurred only in brackish tidal estuaries, where the regular action of tide alternately flooded and left bare the inner shores of streams and inlets twice a day with essentially fresh water. Second, the plants which could tolerate such daily changes were limited in number. It was also apparent that continental shelves had been submerged and then elevated, which processes rendered certain areas dry or completely submerged in salt water. There always remained, however, a brackish tidal estuary in a new location and the same plant growth apparently migrated with the changing estuary. Thus, the concept is advanced by Fernald that the tidal estuary, in spite of its dynamic change in salinity twice a day, is a reproducible medium for plant growth that is more constant than land, which may be inundated by salt water, and more constant than the sea bottom, which may be elevated and left dry.

The application of this concept to clinical investigation is immediately apparent, as indicated in Figure 1. Thus, the clinical investigator is bathed daily in the salt water of clinical medicine and the fresh water of biology and other sciences. Relatively few choose to tolerate such daily changes in medium. Or, as expressed in old terminology, some like fresh, some like salt, some like brackish and millimols exalt. Accordingly, the medium for clinical investigation may well be defined as dynamic and brackish. If new discoveries submerge or elevate continental shelves of existing knowledge, there always remains an estuary where clinical medicine and biology meet, but in a new location. The faculty of the clinical investigator to work in a tidal estuary, to move promptly to the correct salinity develops (in this estuarial-species-of-scientist) remarkable degrees of hardiness, adaptability, humility, and considerable intellectual honesty.

To continue the allegoric analysis of clinical investigation, the hypothesis is here advanced that the finest quality of this research is produced, not by one estuarial species, but by the symbiotic growth of three closely related species. The total number of each species may be large in a research group. For simplicity, only a single symbiotic unit of three species will be considered here as related to function, selection, growth requirements, growth antagonists, and factors modifying quality of productive research.

A symbiotic unit is defined hypothetically as composed of three persons of integrity and ability whose major function in life is the production of outstanding clinical research. The administrator, at the base of the unit, is the most complex of the species and has roots in medicine, science, his institution, and the community. The senior investigator, supported by the functions of the administrator, is the major productive unit, but, in turn, is required to support the junior investigator who is maturing. Thus, the concept is advanced that the weight of the two investigative persons is supported by the administrator, as shown in Table I.

The administrator may be described by a variety of synonymous terms such as director, leader, soul of the clinic (2), guardian of freedoms, professor, etc. He may conduct research himself. However, his administrative role is indeed a responsible one, since it concerns recruitment of capable investigators and advising them on their own growth (or careers). The administrator may indicate fields for research by the choice of investigators whose interests are known. He then gives freedom for the conduct of research but judges the quality of results and of men. The cultivation of growth of investigation and of the investigator, *without* directing the research, is probably the most delicate metabolic equilibrium of the symbiosis. Further, the administrator is concerned with the environment, or culture medium, for growth of investigators and investigation, the translation of research

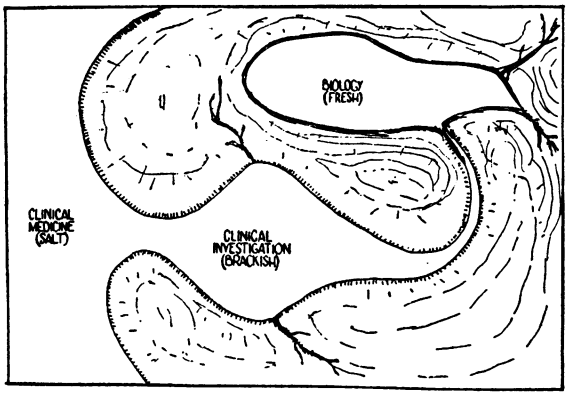

FIG. 1. THE ALLEGORY OF THE BRACKISH WATER OR THE CLINICAL INVESTIGATOR AS AN ESTUARIAL SPECIES

men and their true results to the community and the translation of the community to the investigators.

It is manifest that the selection of the junior investigator who will grow into a productive senior investigator is a major responsibility. For this reason, the natural history of this species is reviewed. First, selection is made, after a span of 25 to 30 years, from a knowledge of a man's past integrity, endowment, education, and inquiry, and his current abilities as a beginning investigator, physician, teacher, and leader. The species is characterized in large part by an endowment of inquiry and enthusiasm. On these criteria, a plan for the future is begun in which a period of 35 to 40 years is envisioned for optimum growth and productivity in the brackish area of clinical investigation. Many candidates do not choose or have opportunity to make a career as an estuarial species. For those who do continue in clinical investigation, however, the span of 65 years is indeed a long-term phenomenon that requires a long-term plan and long-term support.

TABLE I

Hypothesis of symbiotic structure required for growth of quality in clinical investigation (persons of INTEGRITY and ABILITY)

Note delicacy of balance

Junior investigator	
Senior investigator	
Administrator	
Science Medicine	Institution Community

Beginning, then, with a junior investigator of integrity and ability, it is important to examine the requirements for his growth that will lead to quality of results. The following requirements appear essential. There must be a clear responsibility to produce research of quality. This is one biologic stimulus that relates to survival of the species. Manifestly, time and scholarship are required for productivity. For normal growth of the species, certain freedoms appear to be essential, such as freedom to speak the truth, freedom to choose research problems, associates, and institution; freedom to teach and to care for patients. In addition, stimulating colleagues contribute indefinable growth factors of catalytic nature.

Potential growth antagonists are readily recognized of both quantitative and qualitative variety. Quantitatively, growth and productive investigation are inhibited by lack of time for research and scholarship, and by financial distress. Growth may be adversely influenced by requirement to publish substandard or incomplete results. Some of these data can be plowed back into the culture medium as fertilizer. Growth that is abnormal, bizarre, or neoplastic, and research that is substandard may be related to an attempt to obtain wealth through practice, by selection of a research problem because of ease of financial support or by the sequelae that may result from misrepresentation of data in order to obtain support. Another group of factors that appear catalytic in producing *abnormal* growth in investigators include: ectopic administrative demands, traces of regimentation, unpredictable and unexplained changes in environment, command performances, fund raising, and politics.

One factor requires special definition since it appears to influence development of the investigator and especially the kind of research he chooses. This factor is the duration of support of the investigator. Research can be arbitrarily divided into three kinds, as follows: (*1*) short-range problems with small risk—these may be easily described in advance; (*2*) medium-range problems with

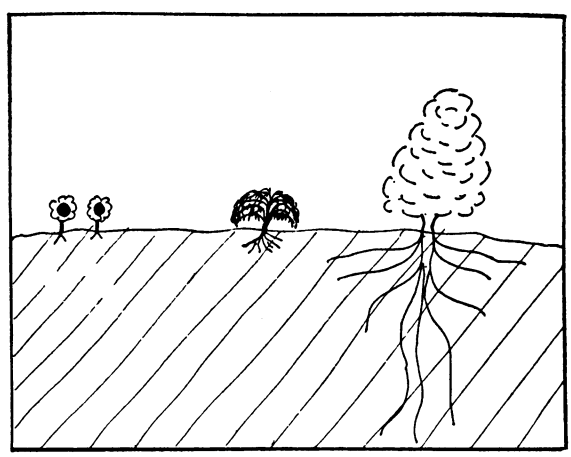

FIG. 2. ROOTS OF VARYING DEPTH ALLOWING PRODUCTIVITY OVER A RANGE OF FROM ONE YEAR TO MANY YEARS FOR FULL FRUITION

moderate risk—these may be difficult to describe in advance; (*3*) long-range problems with large risk—these may be impossible and undesirable to describe in advance. The hypothesis is advanced here that an investigator will have maximum opportunity for mature growth and productivity if all three kinds of research are proceeding simultaneously. It is observed, however, that short-term support tends to encourage short-range problems at the expense of other kinds. Thus, the duration of support to be optimum would permit growth of roots of varying depth, so that productivity may be planned over a range of from one year to many years for full fruition, as shown in Figure 2.

In summary, an attempt has been made to describe the field of clinical investigation in terms of the brackish mixture of clinical medicine, biology, and other disciplines. Although data obtained by allegoric analysis can not be interpreted in great detail, it is believed that the quality of clinical investigation begins and ends with men of high integrity, ability, and inquiry. Similarly, it is the *man* that requires selection and support for his long-term growth. It is proposed that the organization of clinical investigation may be described as a symbiotic unit of at least three persons serving, respectively, as administrator, senior investigator, and junior investigator. The functions of each of these are considered as related to the proper growth of the investigators so that the finest quality of research is possible.

The following conclusions are generic. If the allegoric analysis has virtue and if it is true in part, then, from the objective language of the biologist, policies may be evolved that are constructive and based on common sense. And, if ethics represent a codification of common sense, one may develop a sound ethical basis for evaluating the controversial problems of today that will influence the quality of clinical investigation of the future.

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ABSTRACTS

Observations on Brain Embolism with Special Reference to the Mechanism of Hemorrhagic Infarction. RAYMOND D. ADAMS, Boston, Mass., (Introduced by William G. Lennox).

Brain infarction is of 2 types, anemic in which the necrotic tissue is pale, and hemorrhagic in which a large part of the necrotic tissue is stippled with small hemorrhages.

In the postmortem examination of 351 brains with vascular occlusion, the infarcts were hemorrhagic in 66. Of the latter in all except 3 there was pathological evidence of embolism. Two of the 3 exceptions were cases of internal carotid artery thrombosis and 1 was a probable but unproved middle cerebral artery thrombosis. It seems reasonably well established therefore, that nearly all cases of hemorrhagic infarction are embolic.

In contrast to anemic infarcts where an embolus or thrombus usually can be demonstrated just proximal to the lesion, in hemorrhagic infarcts the embolus cannot be found or it occupies more distal branches of the vessel, often at the apex of anemic portions of the infarct. This relationship has been demonstrated in 8 of our last 10 cases.

It is hypothecated, therefore, that blockage of an artery by an embolus causes infarction of the tissues supplied by that vessel. Later, due to relaxation of local vascular spasm or to fragmentation of the embolic material, the embolus moves from its original position into more distal branches. This exposes the necrotic tissue to the force of arterial blood pressure with resulting hemorrhages from damaged capillaries. Parts of the brain supplied by vessels which are still occluded remain anemic. The relative importance of vascular spasm and migration of the embolus cannot be assessed.

Brain embolism is conceived as a dynamic process in which the embolic material may change form and position with the induction of local or diffuse arterial constriction. Some of the transient clinical phenomena of embolic apoplexy are related to these events. This mechanism explains the unique morphology of hemorrhagic infarction.

Effect of Cortisone, Adrenocorticotropic Hormone (ACTH), and Desoxycorticosterone Acetate (DOCA) on Serum Lipids. DAVID ADLERSBERG, LOUIS E. SCHAEFER and RHODA DRITCH, New York, N. Y., (Introduced by George Baehr).

In the course of studies on hormonal regulation of the serum lipid partition, the effects of cortisone, ACTH, and DOCA were investigated.

Cortisone, injected in doses of 60 to 200 mgm. daily over a period of six to 17 days, usually produced a gradual elevation of serum phospholipids (Sperry modification of the method of Fiske and Subbarow) with a slower concomitant increase of serum cholesterol (Schoenheimer-Sperry method). This alteration of serum lipids occurred regardless of the underlying pathological condition: disseminated lupus erythematosus, acute or chronic glomerulonephritis, polyarteritis nodosa, scleroderma. The elevation of serum phospholipids ranged from 19 per cent to 61 per cent in eight out of ten instances. In the remaining two cases (acute myeloblastic leukemia, Hodgkin's disease) there was no significant change. The increase of serum cholesterol ranged from 4 per cent to 53 per cent in eight out of ten instances. While eight of the ten patients received a diet containing adequate amounts of fat, two of them were maintained on a fat-free diet (Kempner regimen). The latter two showed an increase of phospholipids of 27 per cent and 34 per cent, and an increase of cholesterol of 11 per cent and 8 per cent, respectively.

Essentially similar changes in the lipid partition were observed after injection of ACTH in doses of 75 to 100 mgm. daily over a period of seven to ten days.

DOCA, in contrast to cortisone and ACTH, did not produce an elevation of serum lipids. Of seven patients (rheumatoid arthritis, scleroderma, thyrotoxicosis) who received 10 mgm. a day for seven days, four presented a decrease of serum phospholipids from 2 per cent to 27 per cent, while two remained unchanged, and one showed a moderate elevation. The cholesterol level of these individuals exhibited a drop of 3 per cent to 16 per cent in five, and no change in two.

The clinical significance of these observations will be discussed.

Coagulation Defect in Hepatic Disorders: Deficiency of Prothrombin-Conversion Accessory Substances. BENJAMIN ALEXANDER* and ROBERT GOLDSTEIN, Boston, Mass.

Hepatic disease is known to cause defective blood coagulation and hemorrhage as a result of hypoprothrombinemia and/or fibrinogenopenia. Evidence is presented, which indicates that two other abnormalities also occur: deficiency of a prothrombin-conversion accessory factor in plasma and of the autocatalytic accelerator in serum.

Four patients with severe liver pathology—hepatoma, acute and subacute yellow atrophy, and alcoholic cirrhosis—showed, in addition to hypoprothrombinemia refractory to vitamin K, diminished plasma Labile Factor (L.F.) and decreased serum prothrombin conversion accelerator (SPCA). L.F. varied between 10–50 per cent of normal, and was most depressed in the subject with acute yellow atrophy. In the patient with subacute

* Member.

yellow atrophy, L.F. returned to normal with the earliest clinical evidence of improvement in her condition. Plasma prothrombin increased simultaneously.

One subject (alcoholic cirrhosis) whose plasma Ac-globulin activity was studied, also exhibited marked decrease in this entity. Ac-globulin deficiency has also been observed in hepatic damage (chloroform) in dogs. The parallel reduction of L.F. and Ac-globulin lends support to the concept, already substantiated by many other observations, that the two factors are identical.

The low SPCA in all the patients was comparable to that observed in congenital, or dicumarol induced, hypoprothrombinemia, indicating that its formation is related to the plasma prothrombin convertible to thrombin.

L.F. or Ac-globulin is essential for the rapid conversion of prothrombin to thrombin by thromboplastin plus calcium. SPCA, arising during coagulation, accelerates this reaction further. Deficiency of these factors may contribute to the hemorrhagic phenomena of hepatic disorders. Because L.F. or Ac-globulin is labile, the indication for *fresh* blood or plasma in the treatment of pathological bleeding in these conditions is clear.

Concentration of Sodium in Thermal Sweat in Patients with Mental Disease. M. D. ALTSCHULE * and HENRY GRUNEBAUM, Boston, Mass.

Thermal sweat, collected from the hands, has been studied in patients with mental disease. The sweat sodium concentration is above the normal range in most psychotic patients, irrespective of their clinical diagnoses, who have been ill for more than three years. Patients ill for shorter periods may show either normal or high values. Elevated sweat sodium concentrations fall to normal during insulin therapy, electroshock therapy, and spontaneous remission. These observations suggest that diminished production of hormones controlling the electrolyte balance is frequent in psychosis and that treatment stimulates production of these hormones. These findings support other evidence which suggest that abnormal function of the adrenal cortex occurs in mental disease. On the other hand, there is no absolute correlation between fall in sweat sodium and recovery during therapy; also, administration of hormones which lower sweat sodium, such as ACTH and desoxycorticosterone, do not cause remission of mental disease. Accordingly, it is concluded that changes in sweat sodium in psychosis and after treatment indicate alterations in adrenal cortical function which are not of primary importance.

A Study of Pyruvic Acid in the Blood, Spinal Fluid and Urine of Patients with Liver Disease with and without Hepatic Coma. DONALD S. AMATUZIO and SAMUEL NESBITT, Minneapolis, Minn., (Introduced by Richard V. Ebert).

To investigate the possibility of impaired intermediary carbohydrate metabolism in hepatic failure, pyruvic acid was determined by the modified Lu method in blood, spinal fluid, and urine. Controls included 16 surgical patients with mechanical disability and 31 patients with various diseases exclusive of liver disease. Thirty-six patients with liver disease included 12 with viral hepatitis and 24 with portal cirrhosis. Fourteen were observed in hepatic coma (9 cirrhosis, 5 hepatitis). Pyruvic acid levels in the hepatitis group (excluding those in coma) were normal. The group with simple decompensated cirrhosis had moderately elevated values on admission which returned to normal within a few days. The highest values were found in hepatic coma in which group the pyruvic acid was constantly elevated. Serial determinations showed an abrupt rise during coma and a decline with improvement. Spinal fluid values were elevated in 10 and normal in 4. Mean blood, urine (mgm. %) and spinal fluid values in the coma group were significantly higher than values in the cirrhosis group without coma ($t=4.4$, $P<0.01$) and in the control group ($t=6.7$, $P<0.01$). A series of patients with pulmonary emphysema (arterial oxygen saturation of 51.1 per cent to 93.3 per cent) gave normal blood and urine values. This would exclude hypoxia (reported to occur in cirrhosis) as a cause of elevated values. The degree of elevation of blood pyruvic acid would appear to depend upon the degree of hepatic failure. We suggest that this may result from an inability of the liver to assimilate pyruvic acid to form the dicarboxylic acids necessary for the Kreb's cycle. Thus failure of cellular aerobic metabolism may well explain the neurological manifestations and oliguria so characteristic of hepatic coma.

Molecular Weight Distributions of the Globulins in the Nephrotic Syndrome. S. H. ARMSTRONG, JR.,* B. G. NELSON, L. A. PARNESS and RUTH SIGHTS, Chicago, Ill.

Recent studies using electrophoretic methods have shown that the proteins in the urine of the nephrotic stage of glomerulonephritis contain, in addition to albumin of molecular weight 69,000, gamma globulins of molecular weight up to 180,000.

In that the serum of nephrotic patients is well known to be low both in albumin and gamma globulin and high in alpha and beta lipoproteins, it becomes of interest to determine the average molecular weight of these beta lipoproteins in order to ascertain whether a matter of renal permeability to various molecular particle sizes is the basis of the lipoproteinemia seen in the nephrotic syndrome and whether, indeed, this is a teleological mechanism in the prevention of complete loss of plasma osmotic pressure in this situation.

To this end, the average molecular weight of the globulins has been determined by osmotic pressure methods in a group of patients in various states of nephritic and nephrotic edema, and these molecular size distributions have been compared with the normal human globulins and the albumin present in nephrotic urine. The results indicate extraordinarily large particle size, molecular weights between 300,000 and 500,000 for the nephrotic lipoprotein globulins and molecular weights characteristic of albumin for the urinary proteins in this state. The

spectrum of molecular weight distribution tends to return toward normal with the amelioration of the disease.

The implications of these factors in the metabolic and renal contributions to the nephrotic syndrome are considered.

Clinical Evaluation of Crude and Highly Purified Preparations of Corticotrophin (ACTH) Obtained in Good Yield by Simple Laboratory Procedures. E. B. Astwood,* M. S. Raben, R. W. Payne and A. P. Cleroux, Boston, Mass.

An efficient method involving glacial acetic acid extraction of pig pituitary powder (Wilson), followed by fractional precipitation, yielded a dry powder which upon solution in water was found suitable for therapeutic use. Twelve grams of crude extract of potency twice that of the Armour standard was derived from 100 grams of dry pituitary. Of eight patients treated with extracts of whole pituitary, three exhibited reactions from contaminating pressor and oxytocic principles, whereas all forty patients treated with similar preparations made from anterior lobes failed to show any such reactions.

The conditions treated included ten cases of rheumatoid arthritis, two of rheumatoid spondylitis, four of asthma, four of regional enteritis, one of allergic rhinitis, one of eczema, two of neurodermatitis, and one of lupus erythematosis. These responded to treatment satisfactorily. Of ten cases of leukemia treated, only four of lymphatic leukemia in children showed clear objective improvement, while a further two showed temporary symptomatic benefit. One case each of scleroderma, psychosis, chronic nephritis, candida meningitis, and asthma with emphysema showed no improvement.

The duration of treatment varied from two days to seven weeks and averaged two weeks. The maximal dosage used, 20 mg. every six hours, was probably excessive; 20 mg. every eight hours was fully effective while 20 mg. twice daily was sometimes suboptimal. Single daily doses of 20 or 40 mg. gave inferior results. Infants and children received 10 to 40 mg. daily in divided doses. The most prominent side effect observed was water retention, sometimes with edema, and two children treated with the largest doses developed convulsions.

Purification of the active substance by chromatographic fractionation yielded a colorless amorphous powder with thirty times the potency of the Armour standard. Used in six patients suffering from rheumatoid arthritis, this material proved effective in divided doses totaling 2 mg. daily.

Congenital Adrenal Hyperplasia Associated with the Adrenogenital Syndrome: an Attempt to Correct Its Disordered Hormonal Pattern. Frederic C. Bartter, Anne P. Forbes and Alexander Leaf, Boston, Mass., (Introduced by Fuller Albright).

It is established that stimulation of the normal adrenal cortex with adrenocorticotropic hormone (ACTH) results in sequelae which fall into three groups: (a) sodium and chloride retention, potassium loss, and alkalosis; (b) decrease in the number of circulating eosinophiles, glycosuria, and increased excretion of nitrogen and "reducing steroids"; and (c) increased excretion of 17-ketosteroids, acne and hirsutism. Cortisone, on the other hand, may reproduce these first two groups of sequelae of ACTH while decreasing the normal excretion of 17-ketosteroids of adrenal origin.

In the adrenogenital syndrome resulting from adrenal hyperplasia, 17-ketosteroids are excreted in excess, acne, hirsutism and virilism develop, but there is no other evidence of excessive ACTH production.

If the disorder arises from the stimulation of a normal adrenal by an abnormal pituitary, one would expect administered ACTH to produce its usual effects on salt and carbohydrate metabolism (groups a and b), whereas administered adrenal hormones might fail to inhibit the abnormal pituitary. Conversely, if the disorder arises from an abnormal adrenal response to a normal pituitary, one would not expect administered ACTH to produce its usual effects, whereas administered adrenal hormones might succeed in inhibiting the pituitary.

Metabolic studies are reported in patients with the adrenogenital syndrome which show that (1) administered ACTH does not produce the first two groups of sequelae; (2) cortisone does produce changes characteristic of the first two groups of sequelae and may reduce the excretion of 17-ketosteroids to normal values.

These findings suggest that the adrenogenital syndrome results, not from an abnormal pituitary stimulation of the adrenal, but from an abnormal adrenal response to a normal pituitary.

The therapeutic implications are discussed.

Studies on Portal Circulation and Alimentary Absorption Using Superficial Portal Anastomotic Veins. William B. Bean,* Murray Franklin and James Embick, Iowa City, Iowa.

The occurrence of large portal anastomotic veins, direct communications between the portal venous tributaries and the superficial abdominal portion of the systemic venous circulation, provides an opportunity to study directly (1) portal venous pressure, (2) portal blood gases, (3) circulation times and (4) to compare the changes in portal and systemic blood following the ingestion of carbohydrate, fat, amino acids and vitamins. Such anastomotic veins were found in two patients who had cirrhosis; and although cirrhosis complicates the evaluation of the data it is an inevitable concomitant.

Venous pressure in the abdominal vein of the two subjects was 22 and 19 cm. of water at a time when it was 11 and 9 cm. in the antecubital fossa. Circulation times were 16 and 17 seconds from arm to tongue, but only 11 and 14 from abdominal vein to tongue. Because the abdominal venous blood was brighter red than that from the arm oxygen studies were done in one subject and revealed abnormally low oxygen saturation in systemic veins while blood from the anastomotic vein had a higher degree of saturation. Four series of tests on dextrose absorption,

three on protein and amino acids and lipids, and two on fructose, urea nitrogen, ascorbic acid, thiamine, vitamin A and carotene were done after oral administration of a test meal containing in various combinations 60 grams of protein (dry skim milk), 80 grams of fat, 50 grams of dextrose, 50 grams of fructose, ½ gram of ascorbic acid, 10,000 units of vitamin A and 5 mg. of thiamine.

This method permits a direct approach to the problem of alimentary absorption and an indirect approach to investigation of metabolic and circulatory functions of the liver.

The Effect of ACTH and Cortisone on the Metabolism of Ascorbic Acid. J. C. Beck, M. M. English, J. W. Hackney and K. R. Mackenzie, Montreal, Can., (Introduced by J. S. L. Browne).

Andreae and Browne observed a fall in blood and urinary ascorbic acid in traumatized previously healthy individuals. Accompanying this fall was a marked rise in the urinary corticoids. It was therefore felt desirable to observe changes in ascorbic acid metabolism associated with the administration of ACTH and Cortisone. Urinary and blood ascorbic acid levels were observed in chronically diseased patients on intakes varying from 75 to 100 mg. of ascorbic acid per day during ACTH and Cortisone administration. It was generally observed that a sharp increase in the urinary excretion of ascorbic acid occurred in the first 24 hours of the administration of 75 to 100 mg. of ACTH in four divided doses. No such increase was observed during the administration of 100 to 300 mg. of Cortisone acetate in two divided doses per 24 hours. The relationship of these changes have been compared with alterations in urinary corticoids and other metabolic data studied in the University Clinic by others of our group and with the clinical response of the subjects. Possible interpretation of these results will be discussed.

The Effect of Intravenous Digoxin on the Dynamics of the Circulation in Congestive Heart Failure. Richard A. Bloomfield,* Garth K. Graham, Henry Kraus and Paul H. Pfeiffer, Boston, Mass.

Six patients in combined right and left heart failure were given digoxin intravenously in doses of 1.0 to 1.25 mgm. Prior thereto, and for a period of one hour thereafter, measurements were made of peripheral venous, right auricular and systemic arterial pressures with electromanometers. Control and at least three follow-up determinations of cardiac output were made by the direct Fick method, by means of right auricular catheterization.

There was marked variation in the control value of cardiac output and index as well as in venous and auricular pressures. Following digoxin there was in all six patients a fall in right auricular and peripheral venous pressure and a rise in cardiac output. However, there was no consistent relationship between the heights of the auricular and venous pressures and the levels of cardiac output or index either before digoxin or after. Thus, during intervals without change in venous or auricular pressure distinct changes in cardiac output were noted. Conversely, significant changes in venous and auricular pressure were accompanied by only slight changes in cardiac output. There was no correlation between heart rate or rhythm and either degree of heart failure indicated by decreased cardiac output or degree of elevation of venous or auricular pressure. There was no correlation between changes in heart rate and the observed hemodynamic responses.

No evidence was noted for a peripheral venous site of action of digoxin. The measurements suggested that digoxin acts directly upon the myocardium and that the drug's chief mode of action in patients with congestive heart failure is to increase the minute volume output of the heart. The decrease in venous and auricular pressures are the result of transfers of blood from these reservoirs to and through the lungs to the systemic arterial channels.

Effects of ACTH in Patients with Liver Disease. A. M. Bongiovanni, S. H. Blondheim, W. J. Eisenmenger, and H. G. Kunkel, New York, N. Y., (Introduced by Thomas M. Rivers).

ACTH was administered to 7 patients with various types of cirrhosis of the liver for periods of 6–21 days in doses of 50 or 100 mg. per day. The patients with biliary cirrhosis and severe alcoholic cirrhosis with ascites did not show significant improvement. Four women under the age of 35 with cirrhosis of undetermined etiology, characterized by a marked increase in serum gamma globulin, demonstrated a fall in serum bilirubin which persisted for at least 6 weeks after therapy was stopped. A marked rise in serum albumin occurred in each of the latter patients which was demonstrated by 4 different techniques for determining albumin including the immunological and electrophoretic methods. The rise in albumin continued after cessation of therapy. A fall in total protein and gamma globulin was also found but these effects were difficult to quantitate because of an increase in plasma volume as determined by T1824.

The patients in general showed high initial urinary reducing corticoids and low 17-ketosteroids which rose following therapy. Eosinophil counts were low and were further reduced following ACTH.

Marked side reactions were encountered in 4 of the more severely ill patients; bloody ascites in 2, and elevation of fasting blood sugar above 250 mg.% in 2 others. Blood sugar values returned to normal within 24 hours after stopping therapy. These results indicate variable effects of ACTH in patients with cirrhosis, with the apparent improvement in albumin synthesis by the liver in one type of cirrhosis being the most striking.

The Relationship of Sodium Depletion to Carbohydrate Metabolism. John J. Bookman, Raymond S. Megibow and Herbert Pollack,* New York, N. Y.

Previous studies suggest that the glucose tolerance of humans and of animals may be decreased by sodium restriction. We have reported that hypertensive patients

exhibit a rise in the uric acid creatinine ratio and a fall in the circulating eosinophiles following accelerated sodium depletion induced by diet and by mercurial diuretics. In view of recent reports concerning the intimate relationship of ACTH/cortisone to glucose tolerance, it was felt that a study of carbohydrate metabolism following sodium depletion was indicated. Accordingly the glucose tolerance was determined in nine patients before and after sodium depletion. Four patients were hypertensive; one patient was hypertensive and diabetic; one patient had a Kimmelstiel-Wilson syndrome; one patient suffered from rheumatoid arthritis complicated by diabetes; and two patients had rheumatoid arthritis.

Average blood sugar levels of the glucose tolerance curve were slightly though probably not significantly higher after sodium depletion in the uncomplicated hypertensive group. The patient with the Kimmelstiel-Wilson syndrome developed increased glycosuria and increased insulin requirements after sodium depletion. These alterations were reversed by the administration of sodium chloride. The remaining four patients revealed significant increases in the blood sugar levels of their glucose tolerance curves after sodium depletion. Two of these patients were resalted subsequently, following which their glucose tolerance returned to the control levels.

It is believed that sodium depletion induces definite alterations in carbohydrate metabolism, and that this effect may well represent another aspect of pituitary adrenal axis stimulation in the presence of diminished sodium intake.

The Evolution and Significance of the Hepatic Granuloma in Experimental Brucellosis. A. I. BRAUDE, Minneapolis, Minn., (Introduced by John M. Adams).

Experiments have been conducted in animals to clarify the significance of the granuloma observed repeatedly in this clinic in the liver and bone marrow of patients with culturally proved brucellosis. In mice infected with *Br. abortus,* brucella were seen in polymorphonuclear neutrophiles of the blood about 90 minutes after intraperitoneal inoculation. In 3 hours, brucella were present in the sinusoids of the liver in numerous polymorphonuclears as well as Kupffer's cells. In 24 hours the polymorphonuclears were greatly diminished and Kupffer's cells swelled with organisms. Parasitized Kupffer's cells then formed focal aggregations within the sinusoids. By five days these foci had increased in size to become granulomas composed almost exclusively of epithelioid cells. In guinea pigs, these granulomas fused to form larger granulomas, which underwent central hyaline degeneration at about 3 months. After 6 months, the granulomatous process usually began to subside with a reduction in the number of cells in the focal lesion. By the end of one year, the granuloma had disappeared without demonstrable scar. This nonsuppurative granuloma reflected a good defense mechanism against *Br. abortus* and the infected animals remained in good condition. In infections due to *Br. suis,* on the other hand, the suppurative granuloma was prominent and the animals were in poor condition.

The cells of the newly formed granuloma were those which had removed brucella from the body fluids. As focal collections of phagocytic cells increased in size, intracellular organisms became less numerous. A predominance of mononuclear cells in the granuloma was associated with a favorable balance for the host. The continued activity of polymorphonuclears with abscess formation represented a less effective defense mechanism against a more virulent species of brucella.

Osmotic Diuresis in Diabetes Insipidus. W. A. BRODSKY and S. RAPOPORT,* Cincinnati, Ohio.

A widely current hypothesis holds that about ⅞ of the glomerular filtrate is reabsorbed isotonically in the proximal, while ⅛ is reabsorbed in the distal renal tubule. The distal water reabsorption is under hormonal influence of the hypothalamic-hypophyseal region. Thus, the diuresis of diabetes insipidus is due to failure of distal water reabsorption owing to lack of hormones. Presumably, salt reabsorption proceeds normally since the patients conserve salt in a normal manner.

In order to test this hypothesis, osmotic diuresis was produced, by mannitol loading, in a 12 year old, dwarfed boy with severe diabetes insipidus. After a 4 hour period of water deprivation, the urine flow stabilized at a value of 7.6 cc./min./1.73 M^2, with an osmolarity of 113 m.Osm./L. Loading at 2 levels resulted in a progressive increase of urine flow to 15 cc./min., with an osmolarity of 200 m.Osm./L. The mannitol clearance remained constant. The urinary load increased from a pre-loading level of 0.86 to 3.04 m.Osm./min. Another loading test with the patient on pitressin gave an essentially normal response.

These data are difficult to explain by the present theory. A tentative analysis was made on the assumption that there exists in diabetes insipidus a basal dilute urine flow, possibly largely a secretion of the distal tubule. With loading an increased amount of proximal isotonic fluid is added to the urine without affecting the basal flow, or being acted on by the distal tubule. The increment of urinary load, divided by the plasma osmolarity, gives a calculated value for the proximal fluid added to the urine. Calculated and observed urine flows were in reasonable agreement.

The Use of Abdominal Supports in Patients with Angina Pectoris as Selected by the Ballistocardiogram. HERBERT R. BROWN, JR., MARVIN J. HOFFMAN, MARVIN A. EPSTEIN and VINCENT DE LALLA, JR., Rochester, N. Y., (Introduced by Howard B. Slavin).

A total of 250 patients with definite or suspected coronary insufficiency were studied with the ballistocardiograph. From this series certain cases were selected to wear a special abdominal support, and were followed clinically and with ballistocardiograms.

The method of selection was the comparison of the

control ballistocardiogram pattern with that when the abdominal support was applied. The usual criterion for such a selection was the demonstration of a significant improvement in the pattern with the support. During expiration these patients usually show a marked reduction in the amplitude of the ballistocardiogram complexes and frequently some irregularity of the pattern. A support was recommended only when these abnormalities were shown to be reversed, at least in part, with the belt. In the entire series there were but 15 per cent of the cases studied who were found to be suitable candidates for treatment.

For the past 18 months these 40 selected cases have been followed closely; 92 per cent of this group showed definite symptomatic improvement and increase in exercise tolerance. Eight-five per cent of the 250 patients originally studied in this series were eliminated because they failed to show any change in the ballistocardiogram pattern with the abdominal support. Patients with hypertension or chronic pulmonary disease rarely show improvement in pattern and constitute the major portion of the rejected group.

In this study an integrated approach to the problem of angina pectoris has been stressed. In attempting to explain the favorable results in these selected cases, it was necessary to consider body stature, the circulation of the blood as a whole, the effect of respiration on the circulation, and the role of the splanchnic and pulmonary pools as blood reservoirs.

Relationships of Mixed Alveolar-Arterial Oxygen and Carbon Dioxide Gradients to Exercise Performance in Patients with Diseases of the Heart or Lungs. ROBERT A. BRUCE, FRANK W. LOVEJOY, JR., PAUL N. G. YU, MARION E. MCDOWELL, with technical assistance of JOHN VERNARELLI, Rochester, N. Y., (Introduced by Nolan L. Kaltreider).

An index of physical fitness for moderate exertion (treadmill walking) has been formulated from the least variable characteristics of circulatory and pulmonary functions in both normal and pathological subjects. Fitness scores have been shown to vary inversely with the *observed* mid-capacity (mixed alveolar)–mixed arterial pO_2, and directly with the estimated mean capillary pO_2 of the peripheral tissues *during rest.* Continuous sampling of arterial blood, in addition to comprehensive respiratory measurements, during the adaptation to and recovery from *exercise* has revealed changes in the observed oxygen and carbon dioxide gradients of the lungs which are of fundamental importance. The relationships of these gradients to shunting of blood, collateral pulmonary circulation, and fitness for exertion, or working capacity are surveyed.

The Problem of Human Radiocarbon Fixation. AUSTIN M. BRUES,* Chicago, Ill.

Because of the long half-life of carbon^{14} (5700 years) and its deposition in bone carbonate and in organic constituents of soft tissue, this radioisotope has been considered potentially hazardous and has not yet realized its usefulness in clinical investigation.

Experiments have been done to determine the degree and duration of fixation of C^{14} from inhaled CO_2 or injected bicarbonate. While radiocarbon dioxide is being inhaled, a large proportion of the isotope is absorbed and distributed throughout the blood and tissue bicarbonate-CO_2 system at a specific activity approaching that of the alveolar CO_2. A small proportion of the absorbed radiocarbon is exchanged with other carbon compartments of the body. That portion exchanged with bone carbonate is probably critical in determining safe absorption levels. Due to exchange within the body, the rate of loss of CO_2 containing the isotope, after exposure is ended, is appreciably slower than the rate of uptake.

Bicarbonate C^{14} injected into rats and mice is rapidly lost in expired CO_2. At the end of 24 hours, about 1 per cent remains. The residue is lost more and more slowly, since it comes from increasingly slowly metabolized compounds. Between 2 and 9 months after injection the concentration of C^{14} in bone decreased by only about 50 per cent, but was less than 1/1000 of the body concentration at the time of injection.

Due to the lower rate at which the human being clears his bicarbonate compartment through CO_2 excretion from the lungs, it is expected that fixation will be somewhat greater in man; but due to the complexity of carbon metabolism the degree of difference cannot be predicted. It is therefore important that some clinical observations be made.

The Effect of Previous Immunization and X-Irradiation upon the Disposition in Vivo of Protein Antigens Labelled with Radioactive Iodine. SAMUEL C. BUKANTZ,* F. J. DIXON and G. J. DAMMIN, St. Louis, Mo.

Proteins tagged with radioactive Iodine (I^{131}) are of established stability in vitro and have proven useful in investigations of anaphylaxis, tissue localization of antibody, and quantitative precipitation. The initial objectives of the present study were to determine distribution of such antigens in relation to the cellular reactions of hypersensitiveness and sites of antibody formation.

Bovine Gamma Globulin (BGG) and Bovine Serum Albumin (BSA) were iodinated and traced by a modification of Warren and Dixon's technique. The 200 rabbits studied to date were in three groups: (a) immunized 20 days before tracer dose; (b) given 500–600 r. total body x-irradiation 2 days before; or (c) controls. Activity levels of blood, 24-hour urine, and tissues were determined periodically for 9 days.

Results indicate: (1) Rapid loss of radioactivity from the blood of all animals, most rapid in immunized. Only 34 per cent of injected activity remained in the blood of animals dying in anaphylactic shock within 5–10 minutes, while 65 per cent remained in comparable controls. At 96 hours less than one per cent of original activity remains in the blood of BGG sensitized animals, while controls and x-rayed rabbits had 8 per cent and 6 per cent,

respectively; with BSA, sensitized and control animals had 5 per cent and 14 per cent, respectively. (2) Appearance of non-protein bound I^{131} in urine, accounting for 75 per cent of total activity in immunized animals and 50 per cent in the others. Partition papergrams identify practically all of this activity as inorganic iodide and diiodotyrosine. No significant qualitative or quantitative difference in excretion products as determined on simultaneous papergrams was encountered among the groups. (3) Accelerated disappearance of activity from blood after the fourth day in controls, not encountered in x-rayed animals. (4) Quantitative reduction in concentration of immunologically active protein in plasma parallels decline in radioactivity. (5) Tissue localization was not selective to lymphoid structures.

The Urinary Excretion and Biologic Decay Period of Radiomercury Labeling a Mercurial Diuretic in Normal and Diseased Man. GEORGE BURCH,* THORPE RAY, SAM THREEFOOT, FRANK KELLY and ARTHUR SVEDBERG, New Orleans, La.

The ordinary mercury and radiomercury ($Hg^{203,205}$) labeling a mercurial diuretic administered intravenously to control subjects and to patients with chronic congestive heart failure, chronic nephritis and miscellaneous disease states were excreted more rapidly in the control subjects than in the patients with chronic congestive heart failure. The patients with impaired renal function excreted the element slowly. The mean $C_{1/2}$ values (time for plasma concentration to reach one-half initial level after attaining a steady state) were 2.2 and 4.0 hours respectively for the control subjects and the patients with heart failure, the mean $U_{1/2}$ values (time for one-half the radiomercury to be excreted in the urine) for the former being 2.3 hours. The urine counts reached background in approximately 27 and 44 hours respectively in the control and heart failure subjects. The $C_{1/2}$ value was 45 hours, with the urine reaching background in 191 hours in a subject with renal insufficiency and congestive heart failure. These and other biologic decay values were obtained.

Chronic congestive heart failure tended to diminish the rate of excretion, although individual variations were wide. There was overlapping of the values for the control subjects and for those with chronic congestive heart failure. The state and phase of the failure influenced the rate of excretion.

The rate of excretion of the radiomercury was considerably impaired by renal insufficiency, the degree of impairment may be great enough to result in accumulation of toxic quantities of mercury with frequent administration of the drug. The importance of this impairment in excretion during clinical therapy is evident.

Detailed biologic decay rates, rates of clearance and other excretory factors are to be presented.

Studies on the Mechanism of Resistance to the 4-Amino Antagonists of Pteroylglutamic Acid in Leukemia. JOSEPH H. BURCHENAL, New York, N. Y., (Introduced by C. P. Rhoads).

There is general agreement that the remissions induced in patients with acute leukemia by the 4-amino derivatives of pteroylglutamic acid (PGA) are temporary, and that the disease eventually becomes resistant to this form of therapy. An analogous situation has been demonstrated in mouse leukemia Ak4 in which, although the survival time of the treated mice may be more than doubled, all eventually die of the disease despite continued therapy with the 4-amino derivatives of PGA.

It has been possible, by methods somewhat similar to those used in producing drug fast strains of bacteria, to develop a subline of leukemia Ak4, designated Ak4R, completely resistant to therapy with 4-amino-N^{10}-methyl-PGA. This was accomplished by several serial passages of the leukemia thru treated mice. In this subline (Ak4R) no significant increase in survival time could be produced by therapy with any of the 4-amino derivatives which were chemotherapeutically effective against the sensitive strain Ak4. This characteristic of resistance has remained fixed despite ten passages thru untreated animals. The mechanism of this resistance to these drugs has been studied.

Four theoretical explanations exist for this resistance. They are the ability of the resistant leukemic cell to synthesize its own PGA, to deaminate the anti-metabolite at the 4 position of the pteridine ring, or to methylate the 4-amino group, or an increased ability of the host organism to detoxify the compound. Evidence regarding each of these possible mechanisms will be reported.

The Measurement of Total Body Potassium by the Radioisotope Dilution Technique. B. A. BURROWS and J. H. SISSON, Boston, Mass., (Introduced by Francis C. Lowell).

The measurement of total body potassium by the radioisotope dilution technique ("exchangeable potassium") has been studied in normal subjects and in patients with chronic illness. In some instances the subjects were shown to be in potassium balance; the others were, for the most part, eating normally and assumed to be in a stable state as far as potassium balance was concerned.

Where duplicate determinations of "exchangeable potassium" were made in the same subjects, even several weeks apart, agreement was generally within 10 per cent. The calculated "exchangeable potassium" after an equilibration period of 20 hours generally varied less than 10 per cent from that calculated at 36 hours, indicating that sufficient time was allowed for equilibration. In the group of normal subjects the "exchangeable potassium" (expressed as mEq./kilo of body weight) varied between 40 and 50 mEq./K., with an average value of 43.9 mEq./K.

The diseases studied included poorly controlled diabetes, intractable asthma, congestive heart failure, chronic alkalosis due to vomiting, hepatic cirrhosis, severe renal insufficiency with acidosis, Addison's disease, and Cush-

ing's syndrome. Most patients were not obviously malnourished or excessively obese. In no instance were there symptoms of potassium depletion. The "exchangeable potassium" in this group ranged between 34.7 and 16 mEq./K., or from 20 per cent to over 50 per cent less than the normal average. The serum potassium concentration in this group was in most instances normal. In a few cases, however, it was high or low, with no correlation with the observed "exchangeable potassium."

It is apparent from these observations that in chronic illness there is a reduction in either intracellular potassium concentration or total cell mass, or both, as measured by this technique. The implications of this will be discussed.

Urinary Corticoids in Acute Leukemia (Receiving ACTH and Compound E) and in Cushing's Syndrome. ROBERT B. BURTON, ALEJANDRO ZAFFARONI and E. HENRY KEUTMANN, Rochester, N. Y., (Introduced by Lawrence E. Young).

By the method of paper chromatography utilizing nonaqueous solvent systems previously reported, corticosteroids may be identified in neutral urinary extracts. Preliminary paper chromatograms remove interfering pigments and furnish fractions containing $C_{21}O_5$, $C_{21}O_4$, and $C_{21}O_3$ corticosteroids. These are then re-chromatographed and the steroids located with suitable color reactions. For final identification, chemical and chromatographic properties are matched with those of known steroids.

The normal persons studied excreted in the $C_{21}O_5$ fractions, Kendall's Compounds F and E, 20 to 40 micrograms of each daily. Occasionally very small amounts of material (designated "MSF") of slower mobility than Compound F were detected, but characterization is incomplete. Most normals excreted no $C_{21}O_4$ compounds. Occasionally traces insufficient for characterization were noted. In no specimen in this study was desoxycorticosterone (the only $C_{21}O_3$ corticoid) detected even in ten-day aliquots.

In specimens from two patients with Cushing's syndrome with pituitary adenomata Compounds E and F were present. One patient excreted moderately increased amounts of each. The concentration of these compounds in the other patient's specimen, which had been stored for four years, approached normal. Both excreted MSF in moderate amounts. One patient's $C_{21}O_4$ fraction contained two compounds incompletely characterized.

A 21-year-old female with acute myeloid leukemia excreted normal amounts of F and E and slightly increased amounts of MSF. No $C_{21}O_4$ compounds were detected in 71-hour aliquots. On 100 milligrams of ACTH daily, there was a moderate increase of Compound E and MSF, but a much greater increase of F.

A three-year-old boy with acute lymphatic leukemia, receiving 50 milligrams of Compound E daily, excreted F, MSF, and E, all in amounts several times those during a control period, suggesting conversion of E to the others.

The Use of the 24-Hour Endogenous Creatinine Clearance as a Clinical Measure of the Functional State of the Kidneys. AUGUSTO A. CAMARA, Ann Arbor, Mich., (Introduced by L. H. Newburgh).

The hourly urea clearance test requires such precise timing that values reported in most hospitals are quite commonly unsatisfactory or even misleading. Furthermore, the wide range of results from persons with normal kidneys (75 per cent to 130 per cent of the average value of 75 c.c. per minute for maximal clearance or 54 c.c. per minute for standard clearance) makes the test of little value in doubtful cases.

Even though glomerular filtration rate can be measured accurately by inulin clearance, the duration of the actual test is necessarily limited to such short periods that there is no assurance that such values hold true for the overall unrestricted 24-hour cycle. Furthermore the test is technically too difficult for routine clinical use.

Twenty-four hourly clearances can be performed by means of either urea or endogenous creatinine. Since the former gives different values due to changing reabsorption of urea and to changing concentration of BUN, a test based on endogenous creatinine which is not reabsorbed and whose serum concentration does not vary significantly throughout the 24 hours is more satisfactory. This use of creatinine is, however, exposed to an error of about 10 per cent in far advanced kidney disease because part of excreted creatinine may be the result of tubular secretion. However, the resulting slight increase in the calculated value of glomerular filtration is of no significance in the clinical evaluation of the patient. Furthermore, the technical procedure for determining creatinine is much simpler than that for urea N.

Our average normal value for endogenous creatinine clearance corrected to body surface of 1.73 sq.m. is 150 liters per 24 hours; range 139 to 159 liters. The 76 clearances on 23 patients, corrected to body surface of 1.73 sq.m. ranged from 122 to 0.37 liter per 24 hours.

A Prolonged Outbreak of Infectious Hepatitis in Nurses Due to a Group of Small Children Serving as a Reservoir of the Virus. RICHARD B. CAPPS,* ALFRED M. BENNETT and JOSEPH STOKES, JR., Chicago, Ill.

This study concerns an outbreak of infectious hepatitis in an orphanage for infants and small children. Over a 7-year period 73 cases were recognized in student nurses and 1 each in a resident and an adult female patient. Analysis of the epidemiological data suggested that the children between 6 and 24 months who were largely on one floor were infected with the virus and were transmitting it to the nurses by direct contact. In this age group the children play together but are not toilet trained so that fecal-oral transmission is facilitated.

This hypothesis was supported by an investigation of the children. Approximately one-third were found to have markedly abnormal liver function tests including the thymol turbidity, cephalin cholesterol flocculation, scarlet red, gamma globulin flocculation, choline esterase and

alkaline phosphatase. This was associated with hepatomegally and symptomatology consistent with infectious hepatitis. Bilirubinemia was observed only once. The significance of these findings was established by observing a group of new student nurses on the floor. Seven developed hepatitis with jaundice. Subsequent to the institution of proper nursing technique no further cases have developed in nurses.

It can be concluded that the children served as a reservoir for the virus and as a focus for the nurses. The continuous presence of contagious children over a period of years was apparently provided by an adequate turnover of patients as well as a prolonged period of contagiousness. The diagnosis was not suspected because of the lack of jaundice. This is believed to be the first description of an epidemic of infectious hepatitis of this sort as well as the first time it has been possible to recognize and describe hepatitis without jaundice in children of this age.

The Role of the Reticulo-Endothelial System and the Adrenal Cortex in the Regulation of the Plasma Iron Level. G. E. CARTWRIGHT,* L. D. HAMILTON, C. J. GUBLER, W. J. KUHNS and N. M. FELLOWS, Salt Lake City, Utah.

Studies in patients with chronic infections have revealed a pronounced alteration in iron metabolism as evidenced by a persistent hypoferremia and rapid removal of injected iron from the plasma to the liver and spleen. To determine if the avidity of the tissues for iron could be satisfied and then the anemia and hypoferremia overcome, large doses (1.0–2.0 grams) of iron in the form of saccharated oxide of iron were administered intravenously to patients with the anemia of infection. It was found that even these doses were ineffective in overcoming the hypoferremia and anemia.

The mechanism of this diversion of iron has been studied in dogs. It has been found that a variety of agents (histamine, epinephrine, fracture, anaphylactoid shock, adrenal cortical extract and the adrenocorticotrophic hormone), in addition to bacterial or sterile turpentine abscesses, are capable of producing hypoferremia. In the adrenalectomized dog the hypoferremia caused by mild stress and by ACTH is abolished; the hypoferremic effect of epinephrine is significantly decreased but not abolished. Intravenously administered iron is removed rapidly from the plasma of intact dogs given ACTH and more slowly from the plasma of adrenalectomized dogs. The administration of colloidal thorium dioxide abolishes the hypoferremic effects of turpentine.

It is postulated that the level of plasma iron is regulated by the reticulo-endothelial system, and that the functional activity of its cells is influenced by the adrenal cortex. A variety of factors stimulate the reticulo-endothelial system to increased phagocytic activity; the accompanying discharge of the pituitary-adrenal system provides the cortical hormone which makes possible increased function. With impairment of the pituitary-adrenal system the cells of the reticulo-endothelial system can still react to stress but their functional activity is reduced. In this way the adrenal cortex plays an accessory role in iron metabolism.

Measurement of Blood Flow and Effects of Cardiodynamics with a Venous Shunt in Mitral Stenosis. DON W. CHAPMAN, R. A. HUGGINS and W. G. GLASS, Houston, Texas, (Introduced by James A. Greene).

An attempt to determine some of the physiological effects of venous shunts between the inferior pulmonary vein and the azygos vein of artificially produced mitral stenosis is presented.

Dogs were anesthetized with sodium barbital and an open chest preparation was used in connection with alternating positive air pressure. Anastomoses were effected between the azygos vein and a large tributary of the right pulmonary vein by means of cannulization and a rotameter inserted to measure the blood flow. Aortic pulse contours were obtained by inserting a sound connected to an optical manometer down the left carotid artery. Cardiac output was calculated from the contours and expressed in liters per square meters of body surface. Right ventricular pressures were measured by inserting a sound through the right jugular into the right ventricle and connecting it with an optical manometer. Stenosis of the left pulmonary artery was obtained by clamping the artery. Mitral stenosis was experimentally produced by a modification of the method of Katz and Siegel.

The cardiac output was diminished with either procedure and opening or closing the shunt had no effect. The rate of flow through the shunt could be increased two to threefold either by occlusion of the left branch of the pulmonary artery or by constricting the left atrium. In only two animals with constriction of the left atrium was there evidence of right heart strain by rise of initial tension in the right ventricle. Further opening of the shunt gave no evidence of additional strain on the right heart.

A patient with mitral stenosis and repeated attacks of pulmonary edema with high right ventricular and pulmonary arterial pressure as determined by the intravenous catheterization of the heart was subsequently anastomosed with apparent improvement and will be presented.

Multiple-Balloon-Kymographic Recordings of the Comparative Action of Banthine (Ethyl Dimethyl Beta-9-Xanthine Carboxylate Ethyl Ammonium Chloride) Placebos, and Tincture of Belladonna on the Motility of the Upper Small Intestine in Man. WILLIAM P. CHAPMAN,* ARTHUR B. FRENCH and PHYLLIS S. HOFFMAN, Boston, Mass.

Eighteen tests have been made in nine healthy young male adult subjects to determine the action and minimal effective dosage of the oral administration of Banthine on propulsion contractions and "tone" of the upper small intestine. The drug was administered after a 45-minute control period and its effect studied for an average of

four hours. In comparable studies nine other subjects received tincture of belladonna (0.4 cc.) and 18 subjects, four of whom were given Banthine, received placebos. In all instances any form of suggestion was avoided as far as possible. Alterations in propulsive contractions were assessed by visual inspection and changes in "tone," by measurements of the average distances between the resting level of contractions and the baseline of the tracings.

The administration of Banthine in the six subjects receiving 100 mgm. orally was followed in 35–50 minutes by an almost complete cessation of propulsive contractions. As estimated by visual inspection, this action represented in each subject about a 90 per cent decline in propulsive activity. This maximal effect was maintained for the remainder of the four-hour post-medication period, was twice as marked as the apparent spontaneous decline in activity noted after the administration of placebos and slightly more marked and sustained than the effect of tincture of belladonna. The minimal effective oral dosage of Banthine was 50–100 mgm. Its effect in reducing "tone" was only questionably greater than that noted in the placebo or tincture of belladonna studies. Banthine caused minimal dryness of the mouth and slight tachycardia. There was, however, a striking increase in heart rate noted in three subjects upon standing at the completion of the test. These results indicate that Banthine has an anti-parasympathicomimetic action and is equal to or possibly more effective in decreasing intestinal contractions than tincture of belladonna.

The Effect of Nitrogen Mustard on Renal Manifestations of Human Glomerulonephritis. HERBERT CHASIS,* WILLIAM GOLDRING and DAVID S. BALDWIN, New York, N. Y.

Nitrogen mustard (HN_2) prevents the development of experimentally induced Schwartzman phenomenon, Arthus reaction, and glomerulonephritis. Since human glomerulonephritis may be the result of immunological alteration, HN_2 was administered to 8 patients with glomerulonephritis in whom the duration of the disease was at least 5, 5, 6, 8, 8, 14, 18, and 32 months.

After HN_2, the 24-hour urinary protein showed a significant reduction for 3 to 13 days in 25 of 28 courses. Glomerular filtration rate measured 16 times at the time of maximal diminution of protein excretion, was increased over the immediate control on 6 courses, unchanged in 8, and decreased in 2. HN_2 was administered 16 times to 6 patients with edema. Following 6 courses there was prompt and marked diuresis with loss of 10 to 40 pounds, and in 3 patients there was complete disappearance of edema.

Of the 8 patients treated with HN_2, 2 have died, 3 are still under treatment, and in 3 striking improvement has persisted for 7 months, 1 month, and 8 months. In one of these the possibility of spontaneous remission after 6 months of the disease cannot be fully excluded.

It appears from our data that HN_2 induces a temporary return of glomerular function towards normal in patients with glomerulonephritis as manifested by concomitant decrease in proteinuria, unchanged or increased filtration rate, and diuresis. In 3 patients repeated induction of these temporary changes was followed by persistent improvement in these manifestations of the disease.

A Study of Gastric Secretion of Pepsin and Pepsin Inhibitors in Peptic Ulceration. A. B. CHINN, D. T. BOOK and A. J. BEAMS, Cleveland Ohio, (Introduced by R. F. Parker).

Twelve hour nocturnal and one and a half hour insulin induced hypoglycemia gastric secretion was collected by constant suction under standardized conditions, from patients with active duodenal ulcer, patients who had had vagal resection for duodenal ulcer, and from persons without gastro-intestinal disease. The pepsin content of the secretions was assayed by modification of the method of Anson and Mirsky using beef hemoglobin solution as a substrate.

Crystalline pepsin equivalent values in gastric secretion were determined by extrapolation from a curve constructed by incubation of varying quantities of crystalline pepsin with the substrate in the same manner as the gastric juice. Pepsin inhibition by the gastric juice was determined by (1) incubating with gastric juice and substrate a standard amount of crystalline pepsin and (2) extrapolation of these results from a curve constructed by addition of the standard amount of crystalline pepsin to incubation mixtures of substrate and varying amounts of crystalline pepsin. The "gastric juice plus pepsin" determinations were made in the exact same time relationship as the "pepsin plus pepsin" curve was constructed.

There is no significant difference in the secretion of pepsin by patients with duodenal ulcer and by the controls except as it relates to total secretion volume. In the patients with duodenal ulcer secretion volume was larger than the controls. Pepsin is materially reduced per unit of volume, however, in those patients with vagal resections as compared to the controls. No inhibition of crystalline pepsin incubated with gastric juice was demonstrated in secretions from patients with duodenal ulcer, patients who had vagal resection and persons without gastro-intestinal diseases.

Oxygen Uptake and Blood Flow in the Human Kidney. JOHN K. CLARK, HAROLD G. BARKER, ARCHER P. CROSLEY, JR., and ALVIN J. CUMMINS, Philadelphia, Pa., (Introduced by Isaac Starr).

Renal oxygen consumption (Q_{O_2}) is commonly thought to vary directly with changes in blood flow, the arteriovenous oxygen difference [(A–R) O_2] remaining relatively fixed. In the body as a whole and other organs, changes in blood flow are associated with reciprocal changes in arteriovenous difference.

Measurements of renal oxygen consumption (Q_{O_2}) renal arteriovenous oxygen concentration difference [(A–R) O_2], renal whole blood flow (RBF), glomerular filtration rate

(GFR), and rate of diuresis (V/T) have been made in 24 subjects who had no known renal disease. These patients were then subjected to various experimental procedures allowing the determination of 64 measurements. In five the RBF was increased by administering intravenous albumin, in four the RBF was decreased by tilting the subject, and in the remaining 15 the kidneys were subjected to test procedures which did not alter RBF. Such measurements during water diuresis, osmotic (mannitol) diuresis, and saturation of the tubular excretory mechanism for PAH were made in five subjects each.

In the group of 24 patients as a whole a highly significant negative correlation was obtained between (A–R) O_2 and RBF and a highly significant positive correlation between RBF and Q_{O_2}. Thus renal oxygen uptake does indeed vary with changes in RBF but not in complete proportionality. We interpret these findings as indicating that the kidney has certain basal needs for oxygen regardless of its blood flow or functional activity at the time and that this basal quantity is measurable by the techniques used. In addition, however, the oxygen uptake above and beyond the basal requirement seems to vary with RBF for some unknown reason.

The Relation of "N," "S" and "Salt" Hormone Effects to the Manifestations of Rheumatoid Arthritis. WILLIAM S. CLARK, Boston, Mass., (Introduced by Walter Bauer).

The administration of adrenocorticotrophic hormone to patients with rheumatoid arthritis in doses which favorably affect the disease produces profound physiological effects. Many of these alterations are attributable to the so-called "N," "S" and "Salt" hormones of the adrenal cortex and can be simulated by the administration of Testosterone, Cortisone and Desoxycorticosterone. The possible relationships of these metabolic effects to the hormone-induced remissions of rheumatoid arthritis have been investigated in a 43-year-old male subject with the characteristic manifestations of this disease. During a long-term study, the following hormones were administered for periods of eight to twelve days: testosterone propionate, cortisone acetate, desoxycorticosterone glucoside, desoxycorticosterone glucoside plus cortisone acetate, adrenocorticotrophic hormone, testosterone suspension, testosterone suspension plus cortisone acetate, and desoxycorticosterone acetate. In addition to careful clinical evaluation, the following studies were made: electrolyte and nitrogen balances, serum electrolyte and fasting and postprandial glucose determinations, 17-ketosteroid and 11-oxysteroid urine values, synovial fluid analyses, electrophoretic measurements of serum proteins, sedimentation rates and hematological studies.

Cortisone and ACTH produced comparable clinical effects while desoxycorticosterone and testosterone were without effect. In similar experiments on other subjects desoxycorticosterone glucoside in very large doses produced no unfavorable changes in the disease. The administration of desoxycorticosterone or testosterone with cortisone did not measurably influence the action of the cortisone on the disease. The metabolic phenomena resulting from the administration of these agents will be analyzed to demonstrate what, if any, relationships they have to the clinical manifestations of rheumatoid arthritis.

Veratrum Viride in the Treatment of Hypertensive Vascular Disease. WALTER S. COE and MAURICE M. BEST, Louisville, Ky., (Introduced by J. Murray Kinsman).

Recent favorable reports of the use of veratrum alkaloids in the treatment of essential hypertension suggest the need for revaluation of the drug.

Twenty-five ambulatory patients with sustained hypertension, ranging in age from 30 to 60, received extensive studies in an attempt to eliminate those with hypertension of known etiology.

All patients received Veratrum Viride. Each tablet contained 10 Craw units; maximum daily dose varied from 60 to 120 Craw units. Duration of treatment was from 12 to 30 weeks. Following Veratrum therapy, 23 patients received Placebo tablets for at least one month. With Veratrum therapy 2 patients (8%) had a sustained fall of greater than 30 mm. of Hg systolic, and no patients had a fall of greater than 20 mm. diastolic. Improvement in hypertensive symptoms occurred in 16 of 25 patients (64%) with Veratrum and 14 of 23 patients (60.8%) while on Placebo tablets. A toxic reaction to Veratrum was noted in 16 patients (64%). Four patients had improvement in their electrocardiogram, and 3 patients had a reduction in size of the heart while on Veratrum.

Veratrum Viride in the form used in this study proved to be an unsatisfactory drug for the treatment of the ambulatory patients.

Non-uniformity of Alveolar Gas in Patients with Pulmonary Disease. J. H. COMROE, JR.,* and W. S. FOWLER, Philadelphia, Pa.

A technique requiring only a single breath of oxygen has been devised to study the uniformity of distribution of inspired oxygen in the functional residual gas. After a deep expiration the patient inhales oxygen and then expires maximally; the concentration of nitrogen in the expired alveolar gas is measured continuously by the Lilly nitrogen meter and the volume of expired gas is measured simultaneously by a flow meter. If the inspired oxygen mixes instantly and uniformly with the alveolar gas, the alveolar gas expired (after wash-out of the respiratory dead space) should have a constant nitrogen concentration. A rising nitrogen concentration during continued expiration indicates that some areas of the lung are hypoventilated (have received little inspired oxygen and hence have a high nitrogen concentration) and empty relatively later in expiration than the better ventilated areas. The slope of this rise can be measured, expressed as an Uniformity Index, and used to detect and quantitate deviations from normal.

A comparison of this test with the seven minute pulmonary emptying rate of Cournand, Baldwin, Darling

and Richards has been made in 100 patients with pulmonary disease. The single breath technique has been found to be considerably more sensitive than the seven minute test; abnormal records were obtained in 32 patients who had a normal seven minute pulmonary emptying rate. This test is not influenced greatly by the rate or depth of breathing or by the volume of functional residual air as is the seven minute test; furthermore, this test avoids difficulties in obtaining a representative sample of alveolar air. Most marked deviations from normal occurred in patients with emphysema or with pulmonary cysts; less marked abnormalities were present in patients with carcinoma of the lung, asthma, pulmonary sarcoidosis, silicosis, bronchiectasis and congestive heart failure.

B_{12} Activity of the Urine of Normal Subjects and of Patients with Pernicious Anemia Following Oral and Parenteral Administration of the Vitamin. C. LOCKARD CONLEY, CALVIN A. LANG, BACON F. CHOW and CHARLES E. ELLICOTT, Baltimore, Md., (Introduced by A. McGehee Harvey).

No appreciable B_{12} activity, as measured by microbiological assay, was detectable in the urine of normal human subjects or of patients with untreated pernicious anemia. Administration of a diet presumably rich in vitamin B_{12} did not increase the B_{12} activity of normal urine. After intramuscular injection of a solution of crystalline vitamin B_{12}, there was prompt appearance in the urine of B_{12} activity. This response appeared to be the same in normal subjects and in patients with pernicious anemia in relapse. The B_{12} activity of the urine was maximal during the first 8 hours following the injection, after which it rapidly decreased to the pre-injection level. The B_{12} activity of the urine was equivalent to that of a high proportion of the injected B_{12}. This observation suggests that when vitamin B_{12} enters the body fluids, it is promptly excreted by the kidneys, even in the presence of a deficiency state.

Oral administration of vitamin B_{12} in single amounts as large as 500 micrograms was not followed by the appearance of vitamin B_{12} activity in the urine of normal subjects or of patients with pernicious anemia. This can be interpreted to indicate that vitamin B_{12} is poorly absorbed from the gastro-intestinal tract even by normal individuals. However, other explanations of this result can be suggested. For example, vitamin B_{12} might be altered in some way during absorption by the gastro-intestinal tract so that it is not excreted by the kidneys. Or B_{12} might undergo some change during its absorption which would render it ineffective in meeting the nutritive requirements of the organism employed in the assay.

The Relation of Cell Metabolism to Radiation Susceptibility. W. E. CORNATZER, DAVID CAYER,* GEORGE T. HARRELL * and CAMILLO ARTOM, Winston-Salem, N. C.

The present investigation is a part of a more extended study concerning the susceptibility of mammalian tissues to radiation and factors which might modify it. Groups of mice were maintained on experimental diets adequate in vitamins and minerals in which the protein and fat content were varied. They were injected with a single dose of radiophosphorus (6 microcuries per gram of body weight) after at least 5 days of the diet. Control animals not given radiophosphorus survived and grew without gross lesions.

With a diet low in fat (5%) and in protein (10%) the time of 50% of deaths, the percentage of survival at the 21st day and the average survival time were 16 days, 40% and 16 days respectively.

When the level of fat (32%) and protein (25%) were increased in the diet, the data were significant ($P < .01$), being 12 days, 3% and 12 days respectively. These findings may perhaps be related to an increased metabolism due to the specific dynamic action of dietary components especially protein and therefore would be consistent with the concept that susceptibility to radiation parallels the rate of cell metabolism.

Indeed, young and growing tissues have been shown to be more sensitive to radiation than old or resting tissues. The effects of radiation on the animals seem to be more severe in conditions causing an increase in the general metabolism such as exposure to cold or after receiving thyroxine. Studies on the effects of other dietary factors such as choline, folic acid, B_{12}, and inorganic phosphate on the susceptibility to radiation are in progress and will be discussed.

A Grass Polysaccharide as an Index of Decreased Glomerular Permeability in Renal Diseases. A. C. CORCORAN,* J. BEATTIE and IRVINE H. PAGE, Cleveland, Ohio, and London, England.

Observations in dogs on the renal clearance of a levan with a molecular weight of about 8000 prepared from Italian rye grass, indicated that it did not freely permeate glomerular capillaries, since the ratio of levan to thiosulfate clearance ranged from 0.7 to 0.5 or less.

We have now compared renal plasma clearances of levan (C_L) to simultaneous mannitol clearances (C_M) in human beings. In 30 observations on 5 normal subjects the ratio C_L/C_M averaged 1.12 with a standard deviation of ± 0.0766. In 5 patients with essential hypertension of varying severity, 30 observations yielded a mean C_L/C_M of 0.999 ± 0.118. The difference between normals and hypertensives is highly significant (difference/standard error of difference $= 4.9$). In 2 patients in the nephrotic phase of chronic glomerulonephritis, the ratios averaged 0.68; in 1 patient with renal amyloidosis, the ratio was 0.83 and in 1 recovering from acute glomerulonephritis, it was 1.06.

We conclude: (1) that the normal human glomerulus, in contrast to that of the normal dog, is freely permeable to the levan since C_L/C_M is equal to inulin clearance/C_M, heretofore determined; (2) that, since the levan seems to lie close to the limit of glomerular permeability, it might serve as an index of this function; (3) that the low ratios in patients with active glomerulonephritis and in

the patient with renal amyloidosis bear out this suggestion, since the lesions in these conditions are such as to interfere with glomerular permeability; (4) that difference between normal subjects and patients with hypertension indicates that essential hypertension also results in impaired glomerular permeability, although the defect is not nearly as severe as it is when the glomeruli are the primary seat of disease.

The Relation of the Clotting Mechanism and the Hemolytic System in Paroxysmal Nocturnal Hemoglobinuria. WILLIAM H. CROSBY, Boston, Mass., (Introduced by William Dameshek).

It has been shown that the red blood cells in paroxysmal nocturnal hemoglobinuria (PNH) are sensitive to hemolysis by a normal plasma or serum constituent. The exact nature of this factor has not previously been demonstrated.

Native normal plasma was clotted and quickly defibrinated in the cold, yielding a serum which was then acidified (pH 6.8) and incubated (15′ at 37° C.) with red cells from patients with PNH. It was observed that such a serum when tested at intervals became increasingly hemolytic during two or three hours after clotting. This suggested that the coagulation system might be involved in PNH. The various known coagulation factors were examined for possible activity in the PNH hemolytic system.

Thrombin powerfully activated the hemolytic activity of fresh serum but was not itself hemolytic. A close parallelism was found however between the hemolytic activity of serum and the ability of serum to accelerate coagulation. Seegers' purified serum Ac globulin dissolved in saline was hemolytic against PNH cells but not against normal cells.

In two patients with PNH a sharp increase in serum accelerator activity occurred at the time of hemolytic crisis. Dicumarol was administered to one patient. The accelerator activity of the serum was suppressed and hemolysis became reduced. When dicumarol was stopped the patient developed a short hemolytic crisis.

The normal plasma factor which is capable of destroying the abnormal PNH cells appears to be the activated coagulation accelerator. This globulin exists in plasma as an inert proenzyme which may be activated by thrombin.

Observations on the Administration of Ammonium Cation Exchange Resin to Patients with Cardiac Edema. JAMES H. CURRENS, TIMOTHY COUNIHAN and MARGARET ROURKE, Boston, Mass., (Introduced by Edward F. Bland).

Four patients have been observed in the hospital while receiving ammonium cation exchange resin, two of whom have had electrolyte balance studies. All patients had clinical edema and three demonstrated varying degree of refractoriness to mercurial diuresis. The diets were normal except for moderate restriction of sodium.

Fluid retention was observed to occur during control periods. All patients were observed to lose fluid while receiving the resin in dosages varying from 15 grams twice a day to 40 grams three times a day between meals.

Significant increase of serum chloride and decrease of serum carbon dioxide were observed. Serum potassium decreased slightly. Serum sodium and calcium were not appreciably altered.

The striking observations from the balance studies were the loss of potassium and retention of chloride. One patient was observed to be in positive sodium balance and the other patient observed to be in negative sodium balance during the administration of resin. During the overall balance studies when resin and control periods altered, the former patient remained in sodium balance while losing appreciable edema fluid. The latter patient manifested a remarkable positive sodium balance while losing relatively little edema fluid. A negative calcium balance was observed in one patient.

Clinical improvement in the signs of congestive circulatory failure was noted in all patients. Patients receiving the greater amounts of resin manifested considerable generalized weakness. Constipation was a minor complication during the resin administration.

Carboxylic Cation Exchange Resin Studies in Animals and Humans. T. S. DANOWSKI,* L. GREENMAN, F. MATEER, J. H. PETERS, F. A. WEIGAND, H. MERMELSTEIN and C. E. CLARKE, Pittsburgh, Pa.

Concentrations of serum constituents, stool and urinary excretions of Na^+, K^+, Cl^-, and N and internal balances of Na^+ and K^+ were determined in dogs and humans during periods of measured diet up to 11 days in length with and without intake of cation exchange resin (National Drug) ranging up to 60 grams daily. Ingestion of a hydrogen cycle resin in 14 animals increased, as indicated by balance studies, stool losses of K^+ and Na^+, but not of Cl^- or N, to values significantly greater than those in 23 controls. The validity of these effects is further supported by the demonstration in 4 other experiments covering 28 days that replacement of the H^+ of the resin with Na^+ before ingestion did not increase stool losses of Na^+ and K^+.

In 10 complete balance studies including control periods with ordinary, moderately increased, and markedly restricted intakes of Na^+ in 4 human subjects during 87 days it was observed that the carboxylic exchange resin (H^+ cycle): increases stool excretion of ingested Na^+ and K^+, removes Na^+ and K^+ from gastro-intestinal secretions, and induces prompt diuresis of edema when used in conjunction with low Na^+ (Lonalac) regimen. Diuresis was attributable to marked Na^+ restriction, gastrointestinal loss of extracellular Na^+, and acidifying effects associated with the administration of the H^+ cycle resin. The last is based on decreases in serum CO_2 content and pH in certain subjects, and development of acidosis with overbreathing in 1 patient with renal failure. Losses of K^+ in stools increased significantly in animal and human subjects during resin therapy. This was frequently asso-

ciated with losses of body K^+ and slight decreases in serum K^+ concentrations.

Competitive Inhibition of Metabolites: a Mechanism for Integration of Biosynthesis. BERNARD D. DAVIS,* New York, N. Y.

Wild-type *E. coli* fails to excrete any amino acids during growth. The cell must therefore possess regulatory mechanisms to insure economical synthesis of these compounds in proportion to their relative requirements for growth. One mechanism for this integration is suggested by the following experiments.

It is known that a mutant blocked at a certain stage in isoleucine synthesis accumulates an intermediate which competitively inhibits an enzyme essential for synthesis of the structurally related compound, valine; the mutant therefore requires both isoleucine and valine. If such internal inhibition is a pathological exaggeration of a normal mechanism of enzyme control, one could predict that a mutant blocked at an earlier stage in isoleucine synthesis would fail to make this governing intermediate, and hence might excrete valine. Experiment confirms this prediction. Considered alone, this predicted excretion also allows alternative explanations. Only competitive inhibition, however, seems compatible with the further observation that an excess of the required nutrilite (isoleucine) abolishes excretion of the structurally related compound (valine), presumably through restoring the governing compound by reversal of the normal synthesis. The theory is further supported by similar observations on certain tyrosine-requiring mutants that excrete the related compound phenylalanine, and phenylalanine-requiring mutants that excrete tyrosine.

This conception implies metabolic integration through mechanisms controlling not only the number of molecules of each enzyme per cell, but the activity per molecule. Furthermore, the pharmacological principle of competitive inhibition is extended by this work to physiology, with a dual role for certain metabolites: substrate for one enzyme, and governor for another. Such integrative mechanisms are surely not restricted to bacteria, but probably enter into normal and disturbed growth regulation in animal cells.

Studies on the Life Cycles of Spirochetes. EDWARD D. DELAMATER, Philadelphia, Pa., (Introduced by Francis C. Wood).

Previous studies have demonstrated the presence of the complex life cycle in both the pathogenic treponema pallidum as it occurs in the experimental rabbit and in two of the nonpathogenic strains of treponema pallidum as they grow in culture. The present studies have been carried out by means of the phase contrast microscope and by means of impression smears stained with the newly developed method for demonstration of spirochetes. Syphilomas in the rabbit testis have been studied from the time of their development through their course and involution. The form and morphological configuration of the spirochete has been followed by means of these two techniques. The organism has been demonstrated to reproduce vegetatively by means of transverse division and by means of the production of minute gemmae or buds which eventuate into unispirochetal cysts. In addition, large cystic forms have been observed which eventuate into multispirochetal cysts. Photomicrographs of these structures are presented.

Increased Sodium-retaining Corticoid Excretion in Edema, with Some Observations on the Effects of Cortisone in Nephrosis. QUENTIN B. DEMING and JOHN A. LUETSCHER, JR.,* San Francisco, Calif.

The failure of normal excretion of sodium and water by edematous patients with nephrosis and heart failure can be correlated with reduction of glomerular filtration rate in many cases, but some striking exceptions suggest that alterations in tubular function may play an important part in the accumulation or release of edema. Since tubular reabsorption of sodium is believed to be governed by the adrenal cortex, a bio-assay method has been devised for the quantitation of sodium-retaining steroids, using desoxycorticosterone as a standard. The activity of lipid extracts of normal urine has been defined. A greatly increased sodium-retaining activity has been demonstrated in the urine of patients with heavy edema due to nephrosis or heart failure.

These findings suggested the administration of cortisone to patients with nephrosis. Although the return of the sodium-retaining activity to a normal level has not yet been demonstrated, perhaps because of the interfering effect of the administered cortisone, some interesting clinical results have been observed.

The effects have varied from negligible changes to a complete remission of the nephrotic syndrome. Patients vary widely in their sensitivity to the cortisone. Cortisone may reduce the excretion of sodium and may increase the proteinuria during the initial days of treatment. On longer administration or after the end of a short course of treatment, there may be a sharp fall in proteinuria. Endogenous creatinine clearance is increased, and the serum creatinine concentration falls. Plasma albumin and total protein concentrations are increased variably. The best result following cortisone has occurred in a child, who showed elimination of edema, disappearance of proteinuria, and increase of total protein and albumin concentrations to nearly normal levels. Follow-up has been too short to define the duration of such a remission.

The Urinary Excretion of Hormones in Men with Liver Disease. F. C. DOHAN,* E. M. RICHARDSON, LEWIS BLUEMLE and P. GYORGY, Philadelphia, Pa.

Animal experiments indicate that the liver is probably of major importance in the inactivation of estrogens. This "inactivation" has been attributed to: (1) Conjugation with acids, (2) Production of less active forms (estriol), (3) Degradation, and (4) Excretion into the

intestine. Other investigators have reported an increased urinary excretion of unconjugated estrogens in patients with severe liver disease. To examine further the effect of liver damage on mechanisms (1) and (2) above, and their possible clinical correlations, the urines of ten patients with cirrhosis or chronic hepatitis have been tested for free and conjugated "total estrogens"; and in 14 patients, the free and conjugated portions of "the estrone, estradiol, and estriol fractions" of 17 urine collections were examined. Five normal controls were tested. Six to nine day urine collections were extracted and fractions separated by the method of Friedgood, Garst, and Haagen-Smit. Final bioassays were performed by the vaginal smear method at two dose levels for both standard and unknown. Twenty mice per dose level were used for the standard. In most unknowns 5 to 20 mice per dose level were used depending on the amount of estrogens available, as determined by preliminary assay.

To date, there is no apparent correlation between the severity of the chronic liver disease, the presence of gynecomastia, skin spiders, or testicular atrophy and the absolute values of the estrogens or their fractions. Nor is there apparent correlation with the gonadotrophin excretion. A moderate decrease of urinary 17-ketosteroids is found in the patients with the most severe chronic liver disease. Part of this may be due to the greater age of this group and the non-specific effects of prolonged illness.

Circulatory Dynamics in Atrial Septal Defect. JAMES W. DOW and LEWIS DEXTER,* Boston, Mass.

Seventeen patients with defective atrial septa have been studied by the technique of cardiac catheterization. Pressures have been measured in the pulmonary artery, right ventricle and right atrium in all patients, left atrium and pulmonary capillaries in several. Flows through pulmonary and peripheral circuits have been estimated by the Fick principle. The results have been compared with control observations made in patients with intact septa.

Pulmonary "capillary" pressures are known to offer an index of left atrial mean pressures in the dog and in man. When the septa are intact, pulmonary "capillary" and therefore left atrial mean pressures exceed right atrial mean pressures. Since stroke volumes are normally equal, the right ventricle must be more readily distensible than the left. When there is a large atrial septal defect left and right atrial pressures are equal. Shunting must therefore be due at least in part to greater filling of the more distensible right ventricle than of the thicker and stronger left ventricle from a common pressure source.

The outputs of right and left ventricles were correlated with atrial pressures. Systemic flows were smaller in the cases with the higher atrial pressures, while right ventricular outputs tended to be larger as atrial pressure increased. Decreased output of a ventricle at high atrial pressure represents obstruction to ventricular filling or ventricular malfunction. Common atrial pressure consequently seems to depend upon left ventricular rather than upon right ventricular function.

Physiological Studies in Pre and Postoperative Mitral Stenosis. ARTHUR J. DRAPER, RICHARD J. BING,* ALLAN FRIEDLICH, RAY HEMIBECKER and JOHN F. DAMMANN, Baltimore, Md.

Patients with clinical diagnosis of isolated mitral stenosis were studied during rest and exercise by cardiac catheterization. Several of these were restudied following splitting of the mitral commissures and observations were made three months following the operation. *Preoperatively,* the cardiac output was below normal in the majority, rising only slightly during exercise. The increase in the A–V oxygen difference was proportionally greater than that in the oxygen consumption. The oxygen consumption per liter of ventilation fell from rest to exercise. Pulmonary artery and pulmonary capillary pressures were elevated, increasing during exercise. The pulmonary arteriolar resistance calculated from cardiac output and the gradient between the pulmonary artery and pulmonary capillary pressure or a maximal pulmonary vein pressure of 35 mm. was elevated in only half the patients. Due to a rise in pulmonary capillary pressure the pulmonary arteriolar resistance decreased during exercise, in several patients.

Following operation, the resting cardiac output rose as the A–V oxygen difference decreased. The oxygen consumed per liter of ventilation increased from rest to exercise. Resting pulmonary artery pressure fell to 50 per cent of its preoperative value, but rose with exercise. Resting pulmonary capillary pressure remained elevated. Pulmonary arteriolar resistance decreased markedly.

The observations show that pulmonary arteriolar resistance is not always elevated in mitral stenosis. Splitting of the mitral commissure and exercise may result in a lowering of pulmonary resistance, indicating that pulmonary resistance may not be fixed.

The Treatment of Chronic Idiopathic Ulcerative Colitis with Adrenocorticotrophic Hormone. CHARLES H. DUTOIT, Boston, Mass., (Introduced by Marian W. Ropes).

The response of two patients with idiopathic ulcerative colitis to adrenocorticotrophic hormone therapy was studied. During the forty-seven days of treatment the following measurements were made at frequent intervals: serum sodium, potassium, chloride, carbon dioxide, specific gravity, non-protein nitrogen, uric acid, cholesterol, cholesterol esters, calcium, phosphorus, phosphatase and vitamin C; fasting and postprandial blood sugars; urine 17-ketosteroids, reducing steroids and glucose; hematological studies including total eosinophil counts. The fluid intake and output, caloric intake, body weight and the number, volume and character of stools were recorded daily. Frequent proctoscopic observations were made. Barium enemas were done initially and with the termination of treatment.

The patient with the more acute form of the disease experienced an immediate disappearance of the constitutional symptoms and a gradual subsidence of bowel symptoms and abnormalities seen on proctoscopy. She has subsequently remained free of symptoms, although minimal proctoscopic findings persist. The other patient's disease was more chronic in nature with fewer constitutional symptoms. While it seemed possible to correlate periods of improvement with periods of eosinopenia, the net improvement as judged by symptomatic or objective criteria was very slight.

Ill effects consisted of water retention, Cushing's disease-like facies, hirsutism, acne, pigmentation, a tendency to spontaneous ecchymosis and glycosuria. Edema, present early in the treatment, was seemingly controlled by a low sodium, high potassium diet. In the patient with chronic disease the ill effects occurred early and to a more alarming degree, thus preventing the use of as large doses as were employed in the acute case.

Although adrenocorticotrophic hormone exerts a favorable effect on the course of idiopathic ulcerative colitis, it does not eradicate the disease process.

Renal Function and Edema in Acute Glomerulonephritis. DAVID P. EARLE,* SAUL J. FARBER and JOHN D. ALEXANDER, New York, N. Y.

Edema of non-cardiac origin in acute glomerulonephritis is usually attributed to capillary damage. That the kidneys contribute to nephritic edema is demonstrated by serial observations on renal functions and electrolytes in 13 patients. Glomerular filtration rate (GFR) was usually reduced out of proportion to renal plasma flow (RPF) and to maximum tubular ability to reabsorb glucose (TmG) or to excrete p-aminohippurate (TmPAH). Acute reduction of filtered load observed in these patients, in the presence of relatively normal tubular reabsorptive capacity for sodium, could account for retention of this ion and edema. However, there are also tubular effects in acute nephritis. Thus, urea clearance was reduced out of proportion to GFR and urine flow in 4 patients during edema. In addition, urea clearance increased more than could be explained by changes in GFR or urine flow in 7 of 10 patients who diuresed. These findings represent increased urea back diffusion across tubular walls probably damaged by nephritis. Furthermore, loss of edema took place without increase in GFR in 2 of 3 patients observed before and during diuresis, and in 5 first observed during early diuresis. Five others, during more protracted edematous phases, exhibited definite increases in GFR without diuresis.

Whether changes in tubular functions or in GFR and its relation to tubular are more important in particular circumstances, there is a renal basis for edema and diuresis in acute glomerulonephritis. In this view, peripheral capillary damage, if it exists, is relegated to the secondary role of contributing to the localization of edema fluid.

Curiously, the renal functional pattern of acute glomerulonephritis with a low filtration fraction (FF) persisted in 2 patients who developed complicating congestive heart failure, a condition ordinarily characterized by a high FF. Loss of edema in 1 was associated with increased GFR and FF.

The Effect of Chemotherapy on the Tissue Response to Tuberculous Infection as Observed in vivo. R. H. EBERT * and W. R. BARCLAY, Chicago, Ill.

Using the rabbit ear chamber technique a study has been made of the effect of streptomycin and para-aminosalicylic acid on tuberculous infection as observed *in vivo*. The ear chamber provides a transparent layer of living vascularized tissue 40 to 50 μ thick which can be observed daily under the highest magnifications.

Eight animals were studied in detail in the following groups: (1) 4 animals, streptomycin-treated, (2) 2 animals treated with para-aminosalicylic acid, and (3) 2 animals treated with a combination of para-aminosalicylic acid and streptomycin. Small numbers of animals were used because the method was laborious and the purpose was to determine the manner in which the pathological process was modified rather than the relative efficacy of the drugs. All animals except one were sensitized prior to inoculation of the chamber. The chamber was infected directly via a removable plug with an average dose of .004 mg. of virulent bovine tubercle bacilli. The animals were treated for 6 to 8 weeks, the average daily dose being 100 mg. of streptomycin and 900 mg. of para-aminosalicylic acid.

Conclusions: 1. There was no modification of the fundamental tissue response as the result of treatment. Extension by thrombosis of small vessels and infarction of tissue and healing by growth of new capillary loops into necrotic regions were of the same type as described in untreated animals. There was considerably more evidence of healing in all treated animals, however, than in untreated.

2. It was common to observe simultaneous healing and extension in different portions of the same tubercle.

3. Often there were cyclic periods of extension followed by periods of healing.

4. Even when treatment was begun prior to inoculation of the chamber, the initial necrotizing response was not inhibited. It should be noted, however, that the infecting dose was large.

Electrokymographic Studies of Postural Alterations in the Cardiac Cycle and in the Ventricular Diameter. E. E. EDDLEMAN, KATHRYN WILLIS and HOWARD E. HEYER, Dallas, Texas, (Introduced by Carl A. Moyer).

In healthy young males the change from recumbency to sitting is accompanied by the following changes in antero-posterior ventricular diameter: (1) Decreased systolic excursion. (2) Increased systolic diameter. This is apparently the result of less complete emptying consequent to elevated peripheral resistance. (3) Decreased diastolic filling. This is apparently due to diminished inflow as the effect can be reproduced by trapping blood

in the legs with tourniquets. (4) The diastolic diameter usually increases but may decrease depending on whether the decreased systolic emptying or the decreased diastolic filling predominates. (5) Reduction of the duration of the ejection phase of systole. The cause of this change is uncertain. (6) Prolongation of the early rapid filling phase of diastole. This is apparently due to decline in the pressure gradient between auricle and ventricle at the onset of filling.

The Comparative Metabolic Effects of ACTH, Cortisone Acetate, and "Compound F" Acetate in a Patient with Chronic Lymphatic Leukemia. LEONARD P. ELIEL, OLOF H. PEARSON and FREDERICK C. WHITE, New York, N. Y., (Introduced by Edward C. Reifenstein, Jr.).

Observations have been made on a 58-year-old male with chronic lymphatic leukemia, on a constant dietary intake, who was given cortisone acetate, 100–200 mg. daily for 18 days; adrenocorticotrophic hormone, 100 mg. daily, for 27 days; and compound F acetate (17-hydroxycorticosterone acetate), 100–200 mg. daily, for 8 days. Marked shrinkage of lymph nodes and spleen occurred on both ACTH and cortisone. Slight shrinkage of cervical lymph nodes occurred with compound F. A definite increase in circulating lymphocytes was seen with ACTH and cortisone only. Eosinopenia, and an increase in reticulocytes and platelets, were observed with all three substances. Regrowth of tumor tissue and splenic enlargement occurred after stopping ACTH and cortisone. No regrowth has been observed 8 days after stopping compound F.

A comparison of the first eight days of treatment showed that ACTH produced the greatest increase in excretion of nitrogen and phosphorus, compound F produced the least, while cortisone was intermediate. Similar rises in potassium excretion occurred with ACTH and cortisone but a smaller rise was observed with compound F. Marked retention of sodium and chloride occurred with both ACTH and cortisone. A relatively greater retention of sodium than of chloride was exhibited on ACTH. Compound F, however, produced losses of both sodium and chloride. Metabolic alkalosis and hypopotassemia eventually resulted during ACTH therapy but were not observed with cortisone or compound F.

Increased excretion of phosphorus occurred under treatment with all three hormones which was about twice that expected from the increased nitrogen excretion. Analyses of lymphoid tumor and muscle tissue revealed a P/N ratio in the former three times that in the latter. These data suggest that tumor tissue as well as muscle tissue was being destroyed as a result of the administration of these agents.

Intracellular Cation Exchanges in Metabolic Alkalosis. J. R. ELKINTON,* R. D. SQUIRES and A. P. CROSLEY, JR., Philadelphia, Pa.

Nine patients with elevated serum concentration of bicarbonate and low concentration of potassium were studied by the balance technique during replacement therapy. Five of the patients had undergone extensive loss of gastrointestinal fluid, two had been on potassium-free intakes due to starvation or casein hydrolysate therapy, and in two hyperfunction of the adrenal cortex was induced by ACTH administration or was the result of an adrenocortical carcinoma.

During the first 2 or 3 days of therapy when the serum bicarbonate concentration was still elevated, the increment of chloride needed to raise the serum chloride and lower the serum bicarbonate to normal, exceeded the urinary excretion of chloride in only three of the seven patients exhibiting normal urine flow. In the other four patients factors other than the rate of administration of water and chloride conditioned the renal regulation of these extracellular ions. In all patients the balance of chloride greatly exceeded that of sodium. Assuming chloride to be mainly extracellular, sodium was lost from the intracellular phase, and potassium was retained in excess of nitrogen in amounts up to 15.6 meq. per kilogram. In three of the patients during the preliminary administration of NH_4Cl, the serum bicarbonate concentration was brought to and maintained at normal levels in association with a definite loss of intracellular sodium and when no potassium was taken up by the cells. If there is an obligatory relationship between extracellular bicarbonate concentration and intracellular cation transfers as postulated by Darrow, the dissociation produced in these patients would link the former more directly with transfers of cellular sodium rather than with those of potassium. In the patients other than the two with hyper-adrenocortical function due to ACTH or adrenal carcinoma, no convincing evidence could be adduced of such hyperfunction at the time of the studies.

Studies on Pregnancy Complicated by Thyrotoxicosis or by Myxedema. W. W. ENGSTROM and E. B. MAN, New Haven, Conn., (Introduced by D. M. Kydd).

Scattered reports are available on the use of thyroid-depressant drugs in a few cases of thyrotoxicosis complicated by pregnancy. In this study, propylthiouracil or thiourea were used to control hyperthyroidism during 11 pregnancies in 7 women. Eight normal children were delivered; these children were normal one month to three years after delivery. One miscarriage occurred when the thyrotoxicosis was uncontrolled; another pregnancy is in progress at the seventh month. One child, whose mother probably had hypothyroidism induced by propylthiouracil early in pregnancy, was born with a diffuse goiter which disappeared by the third month. While induced hypothyroidism in the mother poses a hazard to the fetus, large doses of goitrogen need not be avoided if these are needed to control the thyrotoxicosis.

The serum precipitable iodine (SPI) is known to rise during normal pregnancy without producing symptoms of thyrotoxicosis. When the supply of thyroid hormone

is largely, if not entirely exogenous, as in treated myxedema, the occurrence of pregnancy does not effect an appreciable rise in SPI. This was observed in two patients with frank myxedema and two who probably had incomplete hypothyroidism. It can be surmised that the physiological rise of SPI observed in normal, uncomplicated pregnancy requires an intact thyroid gland and is not due to an altered rate of disposal or destruction of thyroid hormone. Pregnancy did not appear to influence significantly the severity of hyperthyroidism or hypothyroidism. If pregnancy alters the "effectiveness" of thyroid hormone on peripheral tissue, the influence is slight. The nature of the rise of SPI in normal pregnancy remains unexplained. In the patients with thyroid disease early miscarriage did not necessarily occur if SPI failed to rise to levels usually seen in normal pregnancy.

An Epidemic of Q Fever Among Employees of a Rendering Plant in Syracuse, New York. HARRY A. FELDMAN,* A. CLEMENT SILVERMAN and CHARLES V. ADAIR, Syracuse, N. Y.

In October, 1949, several employees of a Syracuse, New York, rendering company were ill with a disease suggestive of Q fever. In retrospect, the first patient had become ill on September 16th, and the last on December 7th. . Complement-fixation tests were performed on the sera of 86 of the 130 (an inconstant number) people employed at this plant. Titers of 1 : 40 or greater were present in 33 and 2 were positive at 1 : 20. Definite antecedent illnesses had occurred in 30 of the 35, whereas the remaining 5 were detected during a serological survey of the plant personnel. The clinical manifestations among serologically proven cases ranged from very slight to severe illnesses. Only 9 of the patients were hospitalized, and these were distributed among 5 different hospitals. Clinical diagnoses included upper respiratory infection, atypical pneumonia, typhoid fever and miliary tuberculosis. Treatment regimens varied from none for 6 individuals to different combinations of antibacterial substances. Five men received aureomycin only and responded rapidly to this therapeutic agent. Five others received aureomycin after failing to respond to other therapeutic agents, and the disease seemed to be interrupted abruptly by the aureomycin. One patient received chloramphenicol after failing to respond to sulfadiazine and penicillin, while another received chloramphenicol after responding to, but developing nausea with, aureomycin. Variations in clinical manifestations, as well as the reaction to different forms of therapy will be demonstrated. Evidence will be presented which suggests that this epidemic of Q fever, a disease hitherto not detected in this part of the country, could have been induced by Q infected guinea pig carcasses discarded with other experimental animals and shipped to this rendering plant from a research institution not located in Syracuse.

Lack of Avitaminosis among Chronic Alcoholics. Its Relation to Fortification of Cereal Products and the General Nutriture of the Population. W. F. FIGUEROA, FREDERICK SARGENT, II, and ROBERT M. KARK,* Chicago, Ill.

Since 1946 only one patient ill with beri-beri has been found in the University of Illinois Hospitals. To obtain suitable cases for catheterization studies, in 1948–1949 approximately 16,000 alcoholic inmates of the Bridewell were screened for classical deficiency syndromes, 451 newly admitted alcoholics were studied during the "pellagra-season" and detailed, serial, physiological and biochemical observations were made on 24 selected alcoholics, before and during therapy. Although 23 per cent were grossly underweight, among all these men were found only two with pellagra, one with beri-beri, three with florid ariboflavinosis, one with Wernicke's encephalopathy and seven with possible nutritional polyneuropathy. Among those studied, hemoglobin and total protein averaged 15.3 and 6.9 gm./100 ml. respectively, and urinary thiamine and riboflavin were within the normal range.

To explain the unexpectedly low post-war incidence of avitaminoses among a population notoriously subject to nutritional disturbances, pre- and post-war comparisons were made of incidence of deficiency states among alcoholics in Cook County and Boston City Hospitals. Data from various agencies were analyzed and field observations were made in "Skid Row", Chicago. All these show no change in the environment, eating habits, appetite, alcoholic consumption or economic status of the alcoholic. Vitamin pills and nutrition education have by-passed him. The alchemy of fermentation and distillation is traditional and liquors are not vitamin fortified.

The only innovation since 1938 which bears on the alcoholic's nutrition has been vitamin enrichment of bread, started in Chicago in 1940–41. Alcoholic pellagra disappeared from Cook County Hospital in 1942–43 when niacin, for flour enrichment, was first made by the ton. The alcoholic eats mainly fortified bread, and we conclude that this has been the most significant factor contributing to the present surprising lack of avitaminoses among chronic alcoholics. On the basis of observations on the alcoholic's diet, we take the position that primary avitaminoses are uncommon among the population of the United States.

Studies on the Functional State of the Adrenal Cortex During and Following ACTH and Cortisone Therapy. PETER H. FORSHAM, GEORGE W. THORN,* THOMAS F. FRAWLEY and LAWRENCE W. WILSON, Boston, Mass.

The status of adrenal cortical function has been investigated in a variety of diseases prior to and following ACTH and Cortisone therapy. Criteria of adrenal cortical activity and reserve chosen for this study were the daily 17-ketosteroid excretion, the four hour eosinophil response to a single injection of 25 mg. of ACTH and the rise in 17-ketosteroid excretion during a forty-eight hour period of ACTH administration, (10 mg. q. 6. h.).

In chronic disease although the 17-ketosteroid excretion was low initially, ACTH produced a satisfactory response suggesting low adrenal cortical activity with latent but adequate reserve function. A wide variation in the final response of the adrenal cortex was noted in patients given forty-eight hours of ACTH or prolonged therapy. Functional regression occurred within four days following discontinuance of ACTH (40–200 mg. daily). Adrenal cortical activity returned to but did not fall below the pre-treatment level. In contrast Cortisone therapy (100–200 mg. daily) suppressed both adrenal cortical activity and the response to ACTH for up to ten days after therapy.

When Cortisone (100–200 mg. daily) was added to ACTH therapy (100 mg. daily) there was an additive effect on 17-ketosteroid excretion rather than its suppression found with 100 mg. of Cortisone daily alone. When only 40 mg. of ACTH was used daily, 100 mg. of Cortisone a day failed to show a rise in 17-ketosteroid excretion. This suggests that Cortisone acts through pituitary ACTH inhibition rather than through any inhibitory effect on the adrenal cortex itself. The clinical implications of these findings in the therapeutic use of ACTH and Cortisone in a variety of disease states will be discussed.

The Phenomenon of "Congestion Collapse"; Its Pathogenesis and Significance. EDWARD D. FREIS, JOSEPH R. STANTON, FRANK A. FINNERTY, JR., CHARLES E. RATH, JR., and ROBERT W. WILKINS,* Washington, D. C., and Boston, Mass., (Introduced by Harold J. Jeghers).

When the thighs and one arm of normal or hypertensive supine subjects were congested by cuffs placed proximally and inflated to pressures of 80–100 mm. Hg there was little change in arterial pressure over a 5-minute period. However, the prior administration of sodium nitrite, DHO, dibenamine, C6 or TEA usually resulted in a marked fall in arterial pressure and collapse in the supine position within a few minutes of such congestion.

The phenomenon was not caused by diminution of venous tone since estimation of the blood pooled in the congested extremities, using T–1824, and of limb volume, using plethysmography, indicated that the excess amount of blood trapped in the limbs was essentially the same (200–500 cc.) after as compared to before the administration of sodium nitrite or sympatholytic agents. The cause of congestion collapse appeared to be rather a failure of compensatory vasoconstriction in regions other than the congested limbs, following moderate degrees of blood loss. Whereas, prior to drug the arterial pressure in the supine position remained essentially unchanged during venesection of 500 cc. of blood, after sodium nitrite, DHO or C6 the arterial pressure fell perceptibly with each 50–100 cc. of blood removed. This stepwise decrease in arterial pressure was reversed by returning the blood to the circulation.

These results suggest that normally circulatory adjustments occur to degrees of blood loss as small as 2–5 per cent of the total blood volume. Following blockade of the homeostatic vasoconstrictor mechanisms, hypotension and collapse may occur after withdrawal of only moderate amounts of blood from the general circulation.

A Quantitative Study of Renal Excretion of Digitoxin in the Normal and Cardiac Subject. MEYER FRIEDMAN,* RENÉ BINE, JR., and SANFORD O. BYERS, San Francisco, Calif.

Renal excretion of digitoxin was studied by means of the embryonic duck heart method in normal and cardiac subjects.

The average renal excretion of digitoxin in 14 young subjects after oral administration of 1.2 mgm. of the drug was 60 mcg. in 24 hours, or 5 per cent of the dose given. Renal excretion after ingestion of smaller amounts was proportionally less, continuing to be about 3 to 5 per cent of the given dose. In 10 old subjects (over 60) renal excretion was 17 mcg. in 24 hours or 1.4 per cent of the dose given. Renal excretion (first 24 hours) in 5 subjects after intravenous administration of digitoxin (1.2 mgm.) was significantly less (41 mcg. in 24 hours) than after oral administration of same amount of drug.

The quantitative extent and duration of renal excretion of digitoxin was studied in 9 subjects after a single initial dose of 1.2 mgm. Six of the 9 persons ceased excreting digitoxin 21 days, and all 24 days, after ingestion. It was estimated that approximately 42 per cent of the administered dose was excreted over the entire period.

The average daily renal excretion of digitoxin was determined in 7 normal subjects given 1.2 mgm. of the drug initially and then 0.1 mgm. daily. A similar study was done on cardiac patients who had been digitalized for many months. The renal excretion rate in both the digitalized normal and cardiac person was 35–50 mcg. per 24 hours. The renal excretion rate in subjects manifesting signs of "digitalis toxicity" was 72–132 mcg. daily.

These observations indicate that digitoxin is excreted by the human kidney at a rate dependent upon (1) age of subject, (2) method of administration of drug, and (3) quantity of drug given. The therapeutic implications of the findings will be discussed.

Changes in Antipyrine, T1824 Spaces and Total Body Chloride Following the Rice Diet. HERMAN F. FROEB, New York, N. Y., (Introduced by Robert W. Berliner).

Changes in body fluid compartments following the rice diet were studied on two separate groups of hypertensive patients. Body water was measured as antipyrine space and plasme volume as T1824 space. The total body chloride was calculated from the bromide and thiocyanate spaces.

In one group of 17 patients, the following changes took place after an average of 7 weeks on the rice diet. All but 5 lost more body water than weight, the mean water loss being 3.3 liters and the mean weight loss being 2.1

kilos. All patients lost total body chloride as calculated from the bromide space, the mean being 0.36 equivalents.

In the second group of 21 patients, the following changes took place after an average of 5 weeks on the rice diet. All but 2 patients had a reduction in their plasma volumes which averaged 0.30 liters. The mean weight loss was 2.4 kilos. Thirteen patients in whom total body chlorides were calculated from thiocyanate determinations showed a loss which averaged 0.36 equivalents. The addition of one to three grams of salt to the basic diet of 5 patients for a period of 3 weeks reversed the above changes in every case.

It appears that those patients who lost more body water than weight were gaining fat. In many instances this was apparent clinically. Those patients who had the largest reductions in their plasma volumes and total body chlorides were cardiacs. The reductions in plasma volume and total body chloride seem to be dependent on the low salt content of the rice diet. None of the data correlated with the reductions in arterial pressures observed in the patients while on the rice diet.

The Relation of the Adrenal to Thyroid Function. J. LESTER GABRILOVE and LOUIS J. SOFFER,* New York, N. Y.

Following the administration of epinephrine, there is a decreased uptake of I_{131} by the thyroid gland of the intact rat, but an increased collection by the thyroid of the adrenalectomized animal. If 17-hydroxy-11-dehydrocorticosterone is administered concomitantly with epinephrine to the adrenalectomized rat, the collection of I_{131} by the thyroid is similar to that noted in the intact rat given epinephrine alone.

The administration of 5 milligrams of adrenocorticotropin a day for twelve days to rats fed on a diet to which propylthiouracil has been added results in a significantly smaller increase in thyroid weight than ensues if animals on such a propylthiouracil enriched diet are untreated or treated with 5 milligrams of 17-hydroxy-11-dehydrocorticosterone or one milligram of desoxycorticosterone daily.

Although the uptake of I_{131} by the thyroid is unchanged in rats for one to three days following sham adrenalectomy, on the sixth and tenth postoperative days there is an increased collection of I_{131}. In adrenalectomized rats, the thyroid collection of I_{131} on the third postoperative day is markedly reduced as compared to that in the sham operated animals. No such significant difference is noted on the sixth postoperative day.

Hepatic Cirrhosis. Factors Contributing to the Failure to Excrete Urinary Sodium during the Accumulation of Ascites and Edema. GEORGE J. GABUZDA, JR., HENRY S. TREAGER and CHARLES S. DAVIDSON,* Boston, Mass.

Previous studies have shown that patients with hepatic cirrhosis fail to excrete urinary sodium while accumulating ascites and edema. It is also established that ascites and edema formation may be controlled by a diet containing 10 mEq. of sodium daily. To define some of the factors responsible for these phenomena, five such patients requiring frequent paracenteses were observed for 2 to 4 weeks with dietary sodium intakes of 113 mEq. daily, and subsequently for 2 weeks while ingesting diets rigidly restricted in sodium (10 mEq. daily). Daily fluid intakes were relatively constant throughout each study.

The daily losses of sodium (mEq.) were approximately 2 in urine, and 20 extrarenal (estimated) throughout each study, and 90 into ascitic fluid which was subsequently removed by paracentesis during periods of sodium ingestion.

During sodium ingestion, ascites and edema accumulated at a rate (as measured by weight gain) approximating that expected were 1000 ml. of water retained for each 140 mEq. of dietary sodium. Likewise, with the low sodium diet urine volumes increased by amounts approximating the daily weight gains observed during previous periods of sodium ingestion.

However, the retention of sodium and water in isotonic proportion was not observed in some patients immediately following paracentesis. During this period while body weight and ascites were rapidly increasing, edema decreased. Moreover, hematocrits increased while urine volumes were reduced (fluid intakes constant). Hyponatremia, although usually present, was also most marked immediately following paracentesis. These observations indicate that during this period there was reduction of plasma volume and retention of water in excess of sodium.

It is concluded that the following contribute stimuli for the renal conservation of sodium: 1) loss of large quantities of body sodium by repeated paracentesis, 2) hyponatremia, and 3) reduction of plasma volume following each paracentesis.

The Demonstration of Hemolysins in Acquired Hemolytic Anemia. FRANK H. GARDNER and JOHN W. HARRIS, Boston, Mass., (Introduced by John G. Gibson, 2nd).

Studies made on patients with acquired hemolytic anemia at a time when the hemolytic process was in an accelerated phase demonstrated a *direct* serum hemolysin in 3 patients—that is, the fresh serum hemolyzes homologous erythrocytes at 37.5° C. Although some activity was found at a physiological pH, this serum hemolysin was more active at pH 6.3 to 6.8.

In the subacute phase of acquired hemolytic anemia, such a *direct* serum hemolysin may not be found. However, if the patient's serum and normal homologous erythrocytes are incubated 1 hour at pH 6.3 to 6.5, hemolysis occurs when the cells are subsequently suspended in *active* absorbed guinea pig serum (complement) diluted one part in three with saline. In 1 instance hemolysis was immediately demonstrable when the patient's washed erythrocytes were suspended in guinea

pig serum. In the 3 patients the previously described erythrocyte agglutination at pH 6.5 to 6.7 and the direct Coombs test persisted after disappearance of the hemolysin.

In the 3 patients a significantly low titer of serum complement was found at a time when the hemolysin was directly demonstrable, probably because of complement utilization in the intense hemolytic activity. In the subacute or chronic phase of the hemolytic process the complement titer returned to the normal range.

In 1 of the patients absence of the direct Coombs test was observed, although the indirect Coombs test was positive after exposure of homologous erythrocytes to patients' serum at pH 6.3 to 6.7; and agglutination and direct hemolysis at lowered pH were found.

It is suggested that during active phases of erythrocyte destruction in certain patients with acquired hemolytic anemia, a direct serum hemolysin accompanied by an agglutinin, both activated by low pH, cause significant erythrocyte destruction.

A Study of Spatial Vectorcardiography: a Comparison of Three Lead Systems for Representing the Electrical Forces of the Heart in Three Dimensions. A. GENECIN, W. R. MILNOR, S. A. TALBOT, and E. V. NEWMAN,* Baltimore, Md., (Introduced by J. L. Lilienthal, Jr.).

Spatial vectorcardiograms (VCG's) projected in the frontal, sagittal and transverse planes of the body were recorded with a cathode ray oscillograph from normal subjects and patients with heart disease by three systems of placing the electrodes on the body. The leads were placed according to 1) the Einthoven-Wilson tetrahedron system, 2) the Sulzer-Duchosal system, in which leads are placed on the torso, and 3) the Milovanovich V_2–V_6–V_7 system.

The resultant spatial VCG's demonstrate significant dissimilarities, most marked in the sagittal and transverse plane projections. There is close agreement between the results from the tetrahedron and the Sulzer-Duchosal systems; these differ greatly from the VCG of the Milovanovich system. These differences include amplitude, direction, and the angles between QRS and T loops and therefore cannot be due to the unequal distances of the electrodes from the heart alone. This casts serious doubt on the validity of the Milovanovich method which assumes that the precordial leads (V_2, V_6) can be used as components of the spatial VCG.

The relation of the precordial V leads to the vectorcardiogram projections in three dimensions has been further studied by comparison of actual precordial electrocardiograms (V leads) with the "electrocardiograms" derived by calculation from the spatial vectorcardiograms. A comparison is made between the details of the precordial QRST configurations obtained from actual precordial leads and from the VCG projections on the precordium.

The problem of whether spatial vectorcardiograms obtained by leads at a distance from the heart give all the information which can be obtained from unipolar exploring leads on the surface of the body near the heart is discussed.

The Effects of Repeated Streptococcal and Pneumococcal Pulmonary Infections in the Cardiovascular System of the Rat. ROBERT J. GLASER, GUSTAVE J. DAMMIN and W. BARRY WOOD, JR.,* St. Louis, Mo.

Previous studies have shown that repeated pulmonary infections with group A streptococci result in the development of arterial lesions in the rat heart. In this investigation, the effects of repeated pulmonary infections with pneumococci were compared with those obtained in earlier studies with streptococci.

In one group of albino rats, repeated pulmonary infections were induced at two to three week intervals, using two different types of group A streptococci alternately; in a second group of animals, two types of pneumococci were employed in a similar manner. In both series, beginning eighteen hours after the onset of infection, a course of penicillin therapy was given in amounts known to effect cure. Two weeks after the last infection, the animals were sacrificed and their hearts subjected to microscopic study. Sections of the hearts of normal rats, maintained under similar environmental conditions, were examined to determine the incidence of spontaneous cardiovascular lesions.

Slight to moderate arteritis and periarteritis of the coronary and/or myocardial arteries occurred in about thirty per cent of animals infected repeatedly with streptococci. The incidence of such changes in the pneumococcal series was nine per cent and in the normal controls three per cent.

Pleomorphic cellular foci in the myocardium were observed in fifty-four per cent of the streptococcal group, thirty-four per cent of the pneumococcal series, and twenty-two per cent of controls.

Valvular abnormalities, chiefly thickening and mononuclear cell infiltration occurred in all groups with essentially the same frequency.

This study demonstrates that significant cardiac arterial lesions occur in thirty per cent of rats subjected to repeated group A streptococcal infections. Since rats subjected to pneumococcal rather than streptococcal infections and normal rats exhibit lesions with significantly less frequency, it is concluded that the streptococcus plays an important role in the pathogenesis of these changes.

Blood Lipoproteins and Atherosclerosis. JOHN W. GOFMAN, Berkeley, Calif., (Introduced by John H. Lawrence).

Investigations have been made of the physical-chemical and chemical properties of the cholesterol-containing blood lipids and lipoproteins in an effort to determine whether any of these molecules might have any bearing on the development of atherosclerosis in animals and man. Using ultracentrifugal techniques improved by the authors it has been possible to devise a system for

studying the blood lipids and lipoproteins as individuals and to apply this technique to the study of the serum of individual patients and normals. The data show that there is present in the sera of certain normals and practically all patients with proven atherosclerosis certain lipid and lipoprotein fractions bearing cholesterol. These lipoprotein and lipid fractions may be present even though the blood cholesterol was in the normal analytical range. In fact, aside from the observation that in general the so-called abnormal components are present more frequently when the total blood cholesterol is over 200 milligrams per cent, there is no real relationship between blood cholesterol level and the concentration of the lipids and lipoproteins which are believed to be associated with atherosclerosis. Studies of the effect of low cholesterol-low fat diets with and without the use of thyroid hormone, lipotropic factors and sex hormones on the blood concentration of the particular lipids and lipoproteins in which we are interested indicate that the blood levels of these components can definitely be modified by such measures. Detailed data on the occurrence of these molecules in various normals and diseased groups and on the effect of the various measures discussed above will be presented.

Pheochromocytoma and Essential Hypertension. MARCEL GOLDENBERG and HENRY ARANOW, JR., New York, N. Y., (Introduced by Robert F. Loeb).

The clinical data on 18 patients with pheochromocytoma and persistent hypertension were reviewed, and correlations made with the nor-epinephrine and epinephrine contents of the 10 tumors from this group, which were analyzed by chemical means. Four tumors from patients showing paroxysmal hypertension were similarly analyzed. The tumors ranged in weight from 21 to 790 Gm. Nor-epinephrine concentration ranged from 0.95 mg. to 7.2 mg. per gram of tumor tissue, and this amine constituted from 14 per cent to more than 97 per cent of the total catechol content; epinephrine made up the remainder, and was present in concentrations from 0.03 mg. to 9.1 mg. per gram of tumor.

The study indicated that, aside from paroxysmal hypertension, three types of hypertensive syndrome are associated with pheochromocytoma: 1) When the tumor contains epinephrine predominantly, or a very large amount of nor-epinephrine, the picture is characterized by hypertension, tachycardia, hyperhidrosis, hypermetabolism, and frequently, hyperglycemia. Benzodioxane tests are positive. 2) When the tumor is small and contains, for practical purposes, nor-epinephrine only, the syndrome of essential hypertension is very closely mimicked. Moderate increase in BMR may be present, and the benzodioxane test is positive. 3) Hypertension persisted after the removal of the pheochromocytoma in 7 of 12 patients for periods ranging from months to years. Benzodioxane tests were negative and BMR's normal in patients who prior to operation had elevated BMR's and positive benzodioxane tests. In one case this secondary hypertension mechanism could be observed even before removal of the tumor. This indicates that neither epinephrine nor nor-epinephrine was circulating in excessive amounts in these cases, and that the persistent blood pressure elevation was due to some secondary mechanism, perhaps set in action by the prolonged presence of these amines in the circulation, but not dependent on their continued presence for its maintenance. We were unable to distinguish the hypertension shown by these patients from essential hypertension, but it disappeared in several of them after varying lengths of time. Further analysis of this mechanism may add to the understanding of essential hypertension.

The Effect of Fasting and Cardiac Failure upon Heart Muscle Metabolism in Man. WALTER T. GOODALE, ROBERT E. OLSON and DONALD B. HACKEL, Boston, Mass., (Introduced by James P. O'Hare).

Coronary sinus catheterization, technically successful in 15 of 21 subjects, revealed significantly lower glucose, lactate and pyruvate concentrations in coronary venous blood than in arterial bood, reflecting extraction, and presumably utilization of these metabolites by the myocardium. Expressed as coronary arteriovenous difference, the myocardial extraction of each metabolite was related directly to its own arterial level. At average *non-fasting* arterial glucose, lactate and pyruvate levels of 103, 7.5 and 1.3 mg. per cent respectively, average coronary arteriovenous differences were 10.7, 2.7, and 0.4 mg. per cent respectively. The myocardial R. Q. was 0.86–0.93. Left ventricular coronary blood flow, measured by a modified nitrous oxide method, was 94–110 cc./100 Gm. of myocardium/min. Complete oxidation of the three metabolites extracted could together account for 90–100 per cent of the simultaneous oxygen extraction. At low *fasting* arterial levels, glucose, lactate and pyruvate extractions were small or negligible, with the myocardial R. Q. near 0.7, suggesting dependence of the myocardium upon fat or other non-carbohydrate sources of energy during fasting, or at blood sugar levels below 70–80 mg. per cent. Exercise tolerance is well known to be greatly increased by high carbohydrate feeding, and decreased by fasting, hypoglycemia, or high fat diet. These results suggest that liberal glucose administration may benefit the failing heart.

Six patients with multivalvular heart disease showed decreased coronary venous oxygen saturation, and elevated myocardial oxygen extraction directly correlated with estimated ventricular dilatation. This finding confirmed in man that aspect of Starling's law relating myocardial oxygen extraction to diastolic fiber length. Left ventricular blood flow and oxygen consumption *per 100 Gm.* were normal, but were undoubtedly increased in their total amount in direct proportion to the amount of cardiac hypertrophy. Myocardial glucose, lactate and pyruvate extractions were normal. Effective left ventricular work was reduced. Thus, there was no apparent defect in aerobic oxidative energy production, but rather a failure to convert oxidative energy to effective mechanical work.

Physiologic Method for Calculation of Cross-Sectional Area of the Mitral Valve. RICHARD GORLIN and FLORENCE W. HAYNES, Boston, Mass., (Introduced by Eugene C. Eppinger).

Data obtained by cardiac catheterization in 15 adult patients with uncomplicated mitral stenosis has been utilized in calculation of the cross-sectional area of the mitral valve. Cardiac outputs were measured by the direct Fick method and mean pressures recorded in the pulmonary "capillaries" ("PC"). Assuming "PC" pressure to approximate left atrial mean pressure, left ventricular diastolic pressure to equal 5 mm. Hg, and measuring diastolic filling time for the pressure tracing, cross-sectional area (A), in cm.^{2}, of the mitral valve was calculated from the standard orifice formula derived as follows:

$$(1)\ V = C_v\sqrt{2g(P_1 - P_2)};$$

$$(2)\ V = \frac{F}{C_e A};$$

$$(3)\ C = C_v \cdot C_e$$

substituting (2) in (1), solving for A, and substituting (3):

$$A = \frac{F}{C\sqrt{2g(P_1 - P_2)}}$$

where V = velocity of blood through valve; $g = 981$ cm./sec.^{2}, $P_1 - P_2$ = "PC" − 5, C_v = coefficient of velocity, $F = \frac{\text{cardiac output (cc./min.)}}{\text{diastolic seconds/min.}}$, diastolic seconds/minute = duration of diastole (sec./min.), C_e = coefficient of orifice contraction, C = discharge coefficient = 0.70.

Measured valve areas at autopsy were available in three patients, and intracardiac digital estimations of valve area at operation were obtainable in two others. The calculated area for each patient was within 0.1–0.2 cm.^{2} of the observed area.

In mitral stenosis, valve areas varying between 0.4 cm.^{2} and 2.4 cm.^{2} have been derived. The calculated decrease in cross-sectional area, correlated well with severity of respiratory symptoms. In cases of essentially uncomplicated mitral stenosis, calculation of valvular cross-sectional area may be useful in relating the degree of anatomic stenosis to other factors in this disease and in evaluating the effects of operative procedures on the mitral valve.

Assuming this calculation to be correct and knowing that the size of the mitral orifice in normal adults is between 4 and 6 cm.^{2}, it can be calculated that, at rest, there is a pressure gradient of 1–2 mm. Hg across the normal mitral valve.

An Experimental Study of Alternating Constipation and Diarrhea. WILLIAM J. GRACE, New York, N. Y., (Introduced by H. G. Wolff).

An experimental study was carried out on 25 subjects with symptoms of "mucous colitis" and "irritable colon". These individuals had experienced separate episodes of diarrhea, on the one hand, and constipation, on the other. Each one was subjected to extensive personality study and was then followed from day to day with observations on mood, preoccupation, dreams, associations, talk and behavior. At intervals an assessment of colonic function was made by means of fluoroscopic and X-ray examinations and by kymographic tracings recorded from the sigmoid colon.

It was found that episodes of constipation coincided with periods of sadness and dejection in which the individuals continued to strive and work in the face of a hopeless attitude. The general reaction of these subjects was one of grimly "hanging on". Diarrhea, on the other hand, occurred during situations to which the subjects reacted with fear, anxiety, guilt and resentment. The general reaction at such times was one of being overwhelmed and unable to fight back.

The significance of these striking temporal coincidences was reinforced by short-term experiments in which stress was applied by a discussion of significant personal conflicts while observations of colonic activity were being recorded. During sadness and dejection the colon became slack, elongated and hypomotile. Also, sustained voluntary contraction of the perineal muscles was associated with a diminution in contractibility of the colon. During experimentally induced periods of anxiety, guilt and resentment, however, the colon became contracted, shortened and hypermotile.

In the patients' daily behavior their moods were found to alternate from one of grimly "hanging on" to one of despair and desperation. The changing moods were accompanied by alternating hypofunction and hyperfunction of the large bowel.

The Cause of Enhanced Cervical Venous Pulsations During Inspiration in Subjects with Congestive Heart Failure. ROBERT P. GRANT and JOSEPH T. DOYLE, Atlanta, Ga., (Introduced by Paul B. Beeson).

The neck veins are frequently observed to pulsate with strikingly increased vigor during inspiration in subjects with congestive heart failure. This phenomenon has been studied in normal subjects and subjects with heart failure by electronically recording venous pulses at various points in the venous system and right heart.

Normally, and in mild left ventricular failure, mean venous pressure falls during inspiration while the amplitude of the C and V waves increases. That is, at all points in the venous system and right atrium, the pressures at the time of the peaks of the C and V waves remain unchanged when the patient inspires while the pressures at the time of the troughs fall.

In subjects with severe congestive heart failure and those with clinically "right-sided" failure, the mean pressure falls slightly during inspiration while the amplitude of the C and V waves is much more strikingly increased than in the normal subjects. This was seen as an absolute increase in the pressures at the peaks of the C and V waves when the patient inspires with only a slight change in the pressures at the troughs of these waves.

It is concluded that the increased cervical venous pulsations during inspiration in subjects with heart failure is an exaggeration of a normal response. The greater amplitude of C and V waves in the normal subject would appear to represent increased excursions of the atrioventricular valves due to the inspiratory increase in right ventricular stroke volume described by others. The exaggeration of this phenomenon in subjects with "right sided" failure would appear to be due to an actual regurgitation of blood through an insufficient tricuspid valve. These experiments illustrate the extraordinarily delicate balance of pressure gradients governing blood flow in the venous system and right heart in subjects with congestive heart failure.

Circulatory Changes in Pulmonary Arterio-Venous Fistulas. FRANK D. GRAY, JR. and PAUL R. LURIE, New Haven, Conn., (Introduced by Robert H. Green).

Changes in pulmonary circulation were studied in four patients having pulmonary arterio-venous fistulas. All had clubbed fingers, a continuous bruit over the lesion, and X-ray evidence of a fistula. Three were cyanotic.

In this disease the chief circulatory change is a right-to-left shunt carrying unoxygenated blood from the pulmonary artery into the pulmonary vein, where it mixes with oxygenated blood. A similar circulatory pattern has been demonstrated in patients with tetralogy of Fallot in which there is an intracardiac right-to-left shunt and in patients with chronic pulmonary disease in which blood is shunted through poorly ventilated alveoli. In both of these instances the development of an important collateral circulation between the bronchial and pulmonary arteries has been demonstrated. It seemed of interest, therefore, to determine whether such collateral flow existed in cases of pulmonary arterio-venous fistulas.

Arterial oxygen saturation studies before and after breathing pure oxygen demonstrated right-to-left shunts if pure oxygen breathing failed to raise the arterial saturation to 100 per cent. A comparison of the pulmonary artery blood flow, determined by applying the Fick principle to data obtained from cardiac catheterization, with the accessible pulmonary capillary blood flow, estimated by an indirect method involving carbon-dioxide equilibration, indicated the volume of blood shunted around the capillary bed and the collateral flow added to the alveolar capillaries.

A right-to-left shunt was found in each case. In one, a resting arterial oxygen saturation of 95 per cent represented complete compensation by the development of a collateral circulation found to be four times greater in volume than the shunt. The other cases revealed unsaturation of the arterial blood. Although collateral flow was undoubtedly present, it had not developed sufficiently to compensate for the shunting of venous blood into the arterial system.

The Tagging of Red Blood Cells and Plasma Proteins with Radioactive Chromium. SEYMOUR J. GRAY and KENNETH STERLING, Boston, Mass., (Introduced by Clifford L. Derick).

A method was developed for determining the chromium content of tissue which was accurate for amounts as low as 3–5 γ. The presence of chromium in normal human red blood cells and plasma was established by chemical and spectrographic analyses. The chromium content of normal red cells was found to be 20 γ per cent, and plasma contained 14 γ per cent.

A new biological tracer, radioactive chromium (Cr^{51}) with a half-life of 26.5 days, was applied to the study of the chromium-binding capacity of red cells and plasma.

When anionic hexavalent chromium ($Na_2Cr^{51}O_4$) was injected intravenously into animals, the red blood cells exhibited a marked and persistent affinity for the radioactive chromium, while the radioactivity of the plasma fell rapidly. The addition of $Na_2Cr^{51}O_4$ to red blood cells *in vitro* resulted in a similar rapid tagging of the red cells. More than 90 per cent of the added radioactive chromium was bound to the red cells within two hours. The cells retained their radioactivity without significant loss to the plasma for periods of one day or longer after injection.

This principle has been applied to the determination of circulating red cell volume in animals and humans. Results were confirmed by hemorrhage or transfusion of known volumes of blood with agreement within 5 per cent or less. There was no significant exchange of radioactive chromium between the red cells and the plasma. Preliminary studies suggest abnormal uptake of $Na_2Cr^{51}O_4$ by pathological human red cells.

In contrast to anionic hexavalent chromium, the cationic trivalent form ($Cr^{51}Cl_3$), when added to blood *in vitro* or injected intravenously, was not taken up by the red cells, the radioactivity remaining in the plasma. This form of the isotope is bound firmly to proteins, including plasma proteins, even after prolonged dialysis.

Vasomotor Tone in the Lesser Circulation, and its Inhibition by Tetraethylammonium Chloride. DAVID G. GREENE and IVAN L. BUNNELL, Buffalo, N. Y., (Introduced by John H. Talbott).

Pulmonary arterial pressure has been measured in man through a cardiac catheter, using a Hathaway blood pressure recording system, before and after autonomic blockade with tetraethylammonium chloride (TEAC). The TEAC was constantly infused intravenously at rates of 0.35 to 0.60 mgm./kg./min. for approximately 45 minutes.

Pulmonary arterial pressure fell in almost every instance. Changes in cardiac output measured by the direct Fick method were insufficient to account for the fall. This suggests that neurogenic vasoconstrictor activity in the pulmonary arterial tree was diminished. Further evidence of nervous control of these vessels was obtained from a study of the pulmonary arterial pressure changes consequent to the Valsalva maneuver. It is generally known that when the increased intrathoracic pressure is released in this maneuver, the pressure in the brachial

artery falls and then quickly rises to a peak higher than any previous level. This "overshoot" is generally interpreted as the result of an increased left ventricular output against an actively constricted systemic arterial tree. TEAC abolishes this "overshoot". We have observed a similar sequence of pressure changes in the pulmonary artery. During the expiratory effort of the Valsalva maneuver, the net pulmonary arterial pressure falls, as estimated by subtracting the expiratory pressure measured at the mouth from the recorded pulmonary arterial pressure. When the expiratory effort is stopped, the intrathoracic pressure and the recorded pulmonary arterial pressure both fall, to be followed immediately by a sustained rise in pulmonary arterial pressure. TEAC abolishes this "overshoot" as well. The mechanism suggested is much the same as that generally accepted for the "overshoot" in the brachial artery, namely increased right ventricular output against active neurogenic vasoconstriction in the pulmonary arterial tree.

Observations Using Adrenolytic Drugs and Surgery for Tumors of the Adrenal Gland. K. S. GRIMSON,* C. KEITH LYONS, J. T. WORTHAM and E. C. HAMBLEN, Durham, N. C.

Three patients with active medullary tumors of the adrenal glands have been studied observing cardiovascular effects of single doses of Benodaine and of 2(N, p–tolyl–N (m′ hydroxyphenyl)–aminoethyl)–imidazoline hydrochloride or C–7337. The test dose of C-7337 was 0.08 mgm./kg. which is much less than that found necessary to block injected epinephrine. In each patient blood pressure was reduced by either drug. Effects of continuous treatment during several hours and subsequently during operation have been observed using C-7337. Using intermittent intravenous injections of C-7337 blood pressure was reduced to normal levels. This reduction was maintained during operation. Consecutive injections of 0.16 mgm./kg. prevented or controlled elevations of pressure during manipulation of the tumor and following its removal vasomotor collapse thought possible from adrenalin withdrawal did not occur. In another patient with uremia both C–7337 and Benodaine reduced blood pressure though subsequent autopsy revealed no tumor. Studies in other patients indicate that at least 2 adrenolytic drugs should be employed to check a positive reaction.

Using a new surgical approach in 7 additional patients with symptoms attributable to tumor or hyperplasia of the adrenal gland, effects of removal of tumor or of part or all of one adrenal gland and a major portion of the other have been observed. 17-ketosteroids determined before and after operation were often abnormal before and values decreased afterward. Several months later, however, in the patients with hyperplasia values again rose. Effect upon gonadotropine were also obtained in several of these patients with subtotal adrenalectomy but depression was followed by recovery. There was, however, some evidence of symptomatic improvement. Results seem to indicate that amount of adrenal tissue removed for disturbances of function without tumor must become more extensive if possible and yet avoid deficiency states of steroids controlling salt and potassium metabolism.

Effect of Tilt on Cerebral Oxygen Metabolism in Patients with Arterial Hypertension. JOSEPH H. HAFKENSCHIEL, CHARLES W. CRUMPTON, JOHN H. MOYER, HERBERT WENDEL, HENRY A. SHENKIN, NELLY J. KEFFER and WILLIAM A. JEFFERS,* Philadelphia, Pa.

Cerebral blood flow and oxygen consumption were measured (nitrous oxide) in 19 patients with hypertension before and during 20° head-up tilt. This procedure was used as a means of inducing hypotension in the cerebral arterial system. The cerebral hemodynamic and metabolic alterations were compared with the results of a similar test in five patients with normal arterial pressure.

In the hypertensives tilt reduced mean effective cerebral arterial pressure from an average 147 mm. Hg to 122 mm. Hg. Cerebral vascular resistance decreased from 2.5 to 2.2. Cerebral blood flow dropped from 62 to 58. Cerebral oxygen uptake remained constant as cerebral arteriovenous oxygen difference increased. The oxygen content of the internal jugular vein was lowered from 10.7 to 9.9 volumes per cent. Three of these patients, having been immobile 15 minutes in the head-up position, developed sweating, bradycardia, nausea, marked hypotension and syncope. The second flow measurement in these three was made after return to the horizontal position. The mean response of normals was similar to that of the hypertensives except that it showed a significantly smaller decrease in the oxygen content of internal jugular vein blood with tilt.

These data suggest a cerebral hemodynamic adjustment both in hypertensive and normotensive subjects when passively semi-erect by a release in cerebral vascular resistance. In the patients having a normal arterial pressure, cerebral metabolic (oxygen) homeostasis was adequate, since cerebral oxygen uptake and tension did not change. The oxygen uptake of the brain of the patients with hypertension remained constant during the tilt, but at the cost of a lowered cerebral oxygen tension sufficient to be associated with collapse in three instances.

Radioactive Iodine Uptake of the Thyroid and Plasma Protein Bound Iodine in Subacute Thyroiditis. HENRY E. HAMILTON, WALTER M. KIRKENDALL and S. B. BARKER, Iowa City, Iowa, (Introduced by Willis M. Fowler).

The plasma protein bound iodine levels and the uptake of radioactive iodine were studied in four cases of subacute thyroiditis of the non-suppurative type. The protein bound iodine was at a high normal or definitely elevated level in early stages of the disease, whereas the radioactive iodine uptake was extremely low. The former fell to normal or slightly below normal levels later in the course of the disease while the uptake of I^{131} increased to normal values. The high protein bound

iodine value indicated a large amount of circulating thyroid hormone and suggested that the patients were hyperthyroid. The uptake of I^{131}, however, demonstrated that the thyroid was not taking up or not binding iodine in the normal manner. From a clinical standpoint, the patients were euthyroid or only slightly hyperthyroid at this early stage of the disease. BMR values were normal.

Three of the four patients were treated by X-ray irradiation to the thyroid with a good clinical response. The protein bound iodine returned to normal levels three to four weeks after treatment by X-ray irradiation. The uptake of radioiodine returned to normal in two to three months.

It is suggested on the basis of these data that early in the course of subacute thyroiditis the inflammatory reaction in the substance of the gland prevents normal function of the acini resulting in decreased uptake and binding of iodine. The high protein bound iodine values may be explained on the basis of colloid being released into the circulation by the disease process.

The Destruction of Thyroid Tissue in the Rat by the Halogen, Astatine. JOSEPH G. HAMILTON,* C. W. ASLING, W. G. GARRISON, K. G. SCOTT, B. JUE, P. C. WALLACE and H. R. HAYMOND, Berkeley, Calif.

The selective accumulation of the halogen, astatine, (Element 85), by the thyroid is comparable to iodine. The radioisotope employed, which emits alpha particles and has a half-life of 7.5 hours, is At^{211}. In a series of ten rats, the thyroid uptake averaged 3 per cent at 4 hours and 5 per cent at 18 hours. Sixteen rats were divided into groups and given intravenously the following amounts: 1.2, 6, 30, 40, 80, and 160 microcuries. The animals were sacrificed 41 days later and the thyroids removed for histological study. At the 3 highest dosage levels, skin, muscle, small intestine, stomach, spleen, lymph nodes, pancreas, adrenals, kidney, gonads, heart, lungs, parathyroid, salivary and lacrimal glands, brain, and pituitary were removed for histological preparation. Blood studies were done with these 3 groups. Essentially complete thyroid destruction was seen at dosages of 30 μc and above. Minimal structural changes were noted in some of the thyroids from the 1.2 and 6 μc groups. A marked but transient depression of the leukocytes with a reversal of the ratio of lymphocytes to polymorphonuclear cells was seen in the 80 and 160 μc groups. A slight histological effect was noted at 40 μc. Except with the thyroid destruction, no significantly apparent hematological changes were observed in any of the other tissues examined. Comparable studies indicate equivalent amounts of ionization from radio-iodine beta rays produced far less thyroid damage than astatine alpha particles. The short range alpha particles from astatine suggest its possible clinical application to thyroid disorders.

Increased Resistance to Osmotic Lysis as an Acquired Change in the Erythrocytes of Patients with Hepatogenous Jaundice or Biliary Obstruction. JOHN W. HARRIS and ROBERT F. SCHILLING, Boston, Mass., (Introduced by W. B. Castle).

The erythrocytes of some patients with jaundice due to extra- or intrahepatic disease show an abnormally increased resistance to lysis by hypotonic salt solutions. Whether this characteristic is due to the production of abnormal cells by the bone marrow or is the result of an effect upon the circulating erythrocytes has been a disputed point.

Heterologous normal erythrocytes transfused into 3 jaundiced recipients were found to acquire the osmotic characteristics of the recipients' erythrocytes within 2 to 14 days. The technique employed involved counting the total number of intact erythrocytes surviving in each of the various hypotonic solutions of sodium chloride used in the regular osmotic fragility test. Then, after agglutination of either the donor or recipient erythrocytes with powdered serum, the number of unagglutinated cells in each solution was counted. From these data, and the percentage of hemolysis in each tube of hypotonic salt solution, the proportion of the hemolysis contributed to each tube by donor and recipient cells respectively was calculated; and osmotic fragility curves of both types of cells were plotted.

In 2 patients as the jaundice subsided following relief of biliary obstruction or recovery from hepatitis, the patient's erythrocytes reverted to a normal range of osmotic resistance within 18 days.

These observations indicate that changes in resistance to osmotic lysis are not necessarily the result of the production of erythrocytes with different osmotic properties, but that plasma and/or tissue factors may cause such effects after delivery of the erythrocytes to the circulation. Attempts to produce these changes in normal cells by contact with serum from jaundiced patients, in vitro, have so far been unsuccessful.

Observations on the Origin of the Electrocardiogram: Potential Variations of Single Heart Muscle Fibres in Situ. HANS H. HECHT,* LOWELL A. WOODBURY, J. WALTER WOODBURY and R. CHRISTOPHERSON, Salt Lake City, Utah.

Variations in electrical potentials of single heart muscle cells have been obtained in the intact frog through capillary glass electrodes 0.5 to 2 micra in diameter which were inserted into the cell interior. An indifferent electrode was placed in the extracellular space.

The records demonstrate that during diastole a constant voltage (membrane resting potential) exists across the cell membrane with the inside of the heart muscle fibre negative to the outside by approximately 70 millivolts. This varies with temperature, ionic composition of the extracellular fluid, and other factors. Onset of systole is marked by a rapid disappearance and then reversal of this potential with the inside of the cell becoming positive to the outside by about 30 millivolts. This process of "depolarization" coincides with QRS of simultaneous surface records. It represented the begin-

ning of the action potential. The total amplitude of this deflection averages 100 millivolts as compared to a maximum QRS in normal human precordial electrocardiograms of about 5 and in standard limbleads of about 3 millivolts.

"Depolarization" is followed by a process of recovery (repolarization) which slowly restores the potential across the cell membrane to its previous resting value. It consists of a rapid, a slow, and a second rapid phase, which may change independently of each other. The last phase of the recovery process coincides with the T wave of surface records.

Changes in ionic concentration of the extracellular space modify shape, voltage and duration of the action potential. As expected, voltage and length of the excitatory process of closely adjacent cells may differ significantly.

Surface electrocardiograms in the frog may be interpreted in terms of the components of these monophasic action potentials. The theoretical concept which views an electrocardiogram as a distant representation of changes in depolarization and in various phases of recovery of single cells and of cell groups is supported by these observations.

Modifying Effect of Steroid Hormone Therapy of Human Neoplastic Disease as Judged by Radioactive Phosphorous (P^{32}) Studies. SAUL HERTZ,* Boston, Mass.

The encouraging results obtained in the application of P^{32} to the therapy of leukemia and polycythemia aroused the hope of utilizing this isotope in the treatment of cancer of other organs. Unfortunately, the few attempts which have been made in this direction have been limited by the failure of sufficiently selective concentration by the cancerous tissues to take place. With exception of certain brain and breast cancers the differential uptake has been of such small order as to discourage any wide application of P^{32} in this connection.

We have, therefore, set out to attempt to modify the P^{32} uptake by tumors. We selected hopeless cases of advanced metastatic cancer of several types for our experiments. P^{32} was administered as sodium-acid-phosphate; carrier free as separated by the Atomic Energy Commission laboratories at Oak Ridge, Tennessee. Dosage varied from 1–10 millicuries of P^{32} and was given orally to 12 patients of this type. Radioassay of excreta, biopsy and post-mortem material were carried out. External Geiger-Mueller counts utilizing a single thin-walled G-M tube (Victoreen) gave rough estimates of the distribution of P^{32} in vivo.

Radioautographic studies will be presented in correlation with the above tracer data to indicate that pretreatment of patients by testosterone and oestrogens promotes positive balance of PO_4 in the body of these subjects; and provides concentration factors of $P^{32} = 15$ to 20 times by neoplastic tissues as compared with 2 to 3 times by normal control tissues.

Preliminary therapeutic experiences encountered in these subjects utilizing this principle of hormonal modification of tumor metabolism of P^{32} will be discussed. The direction of our projected and current work utilizing ACTH for this purpose will be indicated.

The Regulation of Breathing During Severe Exercise. J. B. HICKAM,* W. W. PRYOR, E. B. PAGE and R. J. ATWELL, Durham, N. C.

It is generally agreed that the stimuli which produce hyperpnea during exercise are of both reflex and chemical origin, but the relative importance of the two is debated.

An investigation has been made of the nature and relative importance of some of the factors controlling respiration during severe treadmill exercise. Before, during, and after exercise, observations have been made of the respiratory rate and volume, the arterial blood oxygen and carbon dioxide contents, the arterial pH, the CO_2 tension (calculated), and of the effect of inhaling tank oxygen, 15 per cent oxygen, and a 5 per cent CO_2–21 per cent O_2 mixture.

The results show much variation among individuals in the importance of different respiratory stimuli during exercise. Inspiration of 15 per cent oxygen during severe exercise causes a definite, sometimes great increase in ventilation. Conversely, tank oxygen, as reported elsewhere, causes a fall in ventilation. This effect increases with severity of exercise. During severe exercise, there is a slight fall in arterial oxygen saturation. Apparently arterial oxygen is often more important in the regulation of breathing during exercise than at rest. In most subjects, inhalation of 5 per cent CO_2 causes a marked increase in ventilation, but the effect is variable. In general, subjects most sensitive to oxygen changes are also most sensitive to CO_2. A few subjects are quite insensitive to these chemical stimuli and allow large changes in arterial oxygen and CO_2 with little response in ventilation. The reflex ventilation increase of beginning exercise is usually followed 40–50 seconds later by a further sharp increase, apparently chemical in origin. When work stops, ventilation falls abruptly. This fall is small or absent in subjects sensitive to O_2 and CO_2. It may also be small in insensitive subjects. This suggests the presence of a factor other than arterial O_2, CO_2 tension, and the reflex effects of moving muscles.

Life Stress and Water Balance in Diabetes Mellitus. LAWRENCE E. HINKLE, JR., CLIFFORD J. EDWARDS and STEWART WOLF,* New York, N. Y.

Earlier studies on diabetic and non-diabetic subjects have established that a significant rise in blood ketones and major changes in blood glucose concentration may occur in association with serious conflicts in the life situation. The present study is concerned with the effect of such conflicts on water, glucose and electrolyte excretion.

Experiments were carried out on 17 diabetic and 14 non-diabetic subjects who had undergone detailed psy-

chological study. Measurements of urine volume, chlorides, glucose, and ketones, and of blood glucose and ketones, were made while the subjects were at rest, in a post-absorptive state, 24 hours after the last administration of insulin. After a suitable baseline of control observations a discussion and re-enactment of significant personal conflicts was abruptly undertaken for a period of about one hour. This was followed by a period of diversion and strong reassurance.

In 15 of 17 diabetic subjects, and 6 of 7 non-diabetic subjects, the rate of excretion of water, glucose, chlorides and ketones rose 200 to 500 per cent during the conflict period, and subsided after the stressful situation was removed. Increased glucose excretion was not dependant upon an increase in blood glucose concentration since the rate of glucose excretion bore no relation to changes in the blood glucose level. Under stress as much as 5.2 cc./min. of water, 18 mg./min. of chlorides, 500 mg./min. of glucose, and 0.25 mg./min. of ketones were excreted.

In 13 diabetic and 8 non-diabetic subjects during identical control observations without stress such increases were not found, but low and constant rates of excretion were maintained.

It is concluded that not only the ketonemia but also the dehydration of diabetic acidosis may be set in motion by stressful life experiences; and also that pronounced changes in fluid and electrolyte excretion may occur independently of concentration of either the blood glucose or ketone bodies.

Coproporphyrin Excretion in Experimental Liver Injury. F. W. HOFFBAUER,* Minneapolis, Minn.

An increase of urinary coproporphyrin excretion is frequently regarded as a sensitive index of liver functional impairment. Studies were made of the excretion of this pigment in the urine (UCP) and in the feces (FCP) of rats subjected to chemical and nutritional liver injury. The average values in normal rats, expressed as gamma per 48 hours, were for 25 males, UCP–49 (range 14 to 67), FCP–36 (range 5 to 91); for 22 females UCP–14 (range 6 to 48), FCP–40 (range 8 to 79). Approximately 90 per cent of the coproporphyrin was the type III isomer. The sex difference noted for the urine coproporphyrin is not understood. Acute lead poisoning in the rat produced a four to six fold increase in the UCP. In this respect, the rat is similar to other species. In the rat, liver damage did not result in striking increases in the UCP, however.

Rats fed choline deficient diets survived 103 to 219 days; they failed to show significant increases in the UCP though fatty cirrhosis was present in all. Rats maintained on normal diets were given 10 per cent alcohol in place of drinking water; they failed to show liver damage or elevated UCP values after 226 days. They were then placed on a choline deficient diet; after 155 days, the UCP values for the alcohol group were no higher than the control group that received water. Acute liver damage produced by carbon tetrachloride resulted in slight transitory elevations of the UCP; chronic liver damage due to feeding thioacetamide did not.

Since in human alcoholism and "alcoholic" cirrhosis, significant increases of UCP (type III isomer) are usual, it is believed that the present results are important from the standpoint of comparing the effects of alcohol and nutritional deficiency in man with those observed experimentally.

Two-Stage Measurement of the Anticephalin Activity of Normal and Abnormal Plasmas. RUTH R. HOLBURN and JOHN W. STOKER, (Introduced by L. M. Tocantins), Philadelphia, Pa.

Platelet-poor citrated plasma collected with special precautions is defibrinated and incubated in siliconized glassware, for a fixed interval of time, with a purified cephalin suspension. The plasma/cephalin mixture is diluted, recalcified and at 2 to 3 minute intervals, fibrinogen is added. The thrombin output per minute (prothrombin conversion rate) is estimated and compared with that of control normal plasma (of equivalent prothrombin, Ac-globulin content) unincubated with cephalin. The results are expressed in units, one unit representing the anticephalin activity in the plasma which will, after incubation with cephalin, bring about a reduction of 0.01 Iowa thrombin units per minute, in the rate of conversion of prothrombin. The values for plasmas of normal individuals and those with hemorrhagic and thrombotic disorders have been studied.

The Use of Intra-articular Temperature Measurement in the Evaluation of Anti-arthritic Agents. JOSEPH L. HOLLANDER, EMERY K. STONER and ERNEST M. BROWN, JR., Philadelphia, Pa., (Introduced by Francis D. W. Lukens).

In previous reports the methods of measuring the internal temperature of joints and the physiological factors altering joint temperature have been described. The procedure involves the introduction of a filamentous thermocouple into the joint space through an aspirating needle. Aside from the sedimentation rate and clinical evaluation there are no objective criteria for the changes in rheumatoid arthritis. Recently, we have found the joint temperature to be of value in following the response of arthritic patients to Cortisone or ACTH and in the assay of drugs proposed for the treatment of this disease.

Daily intra-articular temperature measurements of actively inflamed rheumatoid arthritic joints were made on 18 patients before, during, and after administration of ACTH or Cortisone. Variation of joint temperature from day to day during the control period never exceeded 0.3° C., *under standard conditions* of activity and room temperature. In every instance there was noted a prompt fall in the intra-articular temperature, amounting to at least 1.5° C. within the first 24 hours after the administration of 300 mgm. of Cortisone, and within 4 hours after the administration of 25 mgm. of ACTH. Continued administration of either hormone

produced further drop in joint temperatures to approximately normal levels, and following withdrawal of the hormones a rise in the temperature was seen. Administration of large doses of other supposedly active anti-arthritic steroids (Pregnenolone, Testosterone, etc.) for as long as several weeks failed to produce any measurable drop in intra-articular temperature in any case. The method is suggested as a critical screening test for rapid evaluation of new steroids for possible anti-arthritic activity.

Plasma Volume Changes Produced by Inhalation of CO_2. JOSEPH H. HOLMES, THOMAS M. PARRY, WILLIAM B. DRAPER and RICHARD W. WHITEHEAD, Denver, Colo., (Introduced by Harry Gordon).

Plasma volume changes were studied in a group of 13 human adult subjects (6 male, 7 female) during the inhalation of either 20 per cent, 25 per cent, or 30 per cent CO_2 in oxygen over a 15 minute period while under pentothal sodium anesthesia. The average blood pH was lowered to 7.06 by 20 per cent CO_2 and 6.94 by 25 per cent CO_2. Control observations under pentothal sodium alone did not alter significantly the serum concentrations of protein or dye (T-1824) or the hematocrit value except in one experiment where there was slight hemodilution. At the end of 15 minutes inhalation of CO_2 the serum concentrations of protein and dye (T-1824) and the hematocrit value had increased to approximately the same percentage of the control value. The average decrease in plasma volume was 10.2 per cent when calculated from the change in dye concentration, 10.5 per cent when calculated from the change in protein concentration and 10.4 per cent when calculated from the change in the hematocrit value. The reduction of plasma volume ranged from a minimum of 3 per cent to a maximum of 18 per cent. In this small series the hemoconcentration was not proportionate to the percentage of CO_2 inhaled. In 11 subjects measurements were also made of the change in serum concentration of NaSCN. The observed decrease in serum concentration would correspond to an average increase of 6 per cent in the fluid available for solution of thiocyanate.

Methylandrostenediol, A Non-Virilizing Steroid Hormone with Testosterone-like Effects. F. HOMBURGER, S. C. KASDON and W. H. FISHMAN, Boston, Mass., (Introduced by S. Proger).

17 β-Methyl-Δ^5-androstene-3(β), 17 α-diol was found in bioassays to have a potent renotropic effect upon the experimental hydronephrotic mouse kidney. Since this property equalled that of testosterone propionate, methylandrostenediol was given to women with cancer of the breast in lieu of testosterone. Remissions occurred resembling those sometimes obtained with testosterone. There was complete absence of virilization at high dosage levels. Metabolic studies showed effects much like those of testosterone. Some clinical effects of methylandrostenediol as a protein anabolic agent and in renal disease are being studied.

Direct Action of Vitamin B12 upon Human Bone Marrow; The Effect of Instillations of Vitamin B12 and Folic Acid into the Bone Marrow as Studied by Histochemical Techniques. DANIEL HORRIGAN and RICHARD W. VILTER,* Cincinnati, Ohio.

Chemical relationships of folic acid and vitamin B12 to nucleic acid metabolism have been shown by 1). studies on bacterial metabolism, 2). observations on persons with various types of megaloblastic anemia, and 3). observation of effects of vitamin B12 on ribonucleic acid of hepatic cells poisoned with carbon tetrachloride. Direct instillation of these substances into bone marrow and histochemical staining methods offer other techniques for investigating these relationships in vivo.

Vitamin B12, one microgram, or folic acid, one milligram, was injected into the iliac crest marrow cavities of five patients with megaloblastic anemia. Forty eight hours later, marrow was aspirated from the same site and also from the opposite iliac crest. Smears obtained were stained 1) with Wright-Giemsa stain for differential cell counts, 2) with methyl green-pyronin for demonstration of cytoplasmic basophilia (ribonucleic acid), and 3) by the Feulgen reaction for demonstration of nuclear desoxyribonucleic acid. Control smears were obtained from normal persons and from a patient with erythroid hyperplasia due to hemolytic anemia.

Local instillation of vitamin B12 resulted in maturation of erythroid cells at the injection site; marrow obtained from the opposite iliac crest was unchanged. Qualitative changes in ribonucleic acid also were observed when specimens of marrow from the injected side were compared with those from the opposite iliac crest and from normal persons; however, no alteration of desoxyribonucleic acid was noted. Instillation of folic acid did not influence maturation of bone marrow cells or the appearance of nucleic acid.

From this study, the authors conclude 1) that vitamin B12 can be utilized locally by bone marrow cells and corrects a qualitative abnormality in cellular ribonucleic acid of persons with pernicious anemia, 2) that folic acid cannot be utilized locally and probably must be converted to an active hematopoietic substance by enzymatic activity elsewhere in the body.

Experimental Studies of Intramyocardial Oxygen Tension: Increases Consequent on Breathing Pure Oxygen in Normal Hearts and at the Borders of Ischaemic Areas. ORVILLE HORWITZ, JOHN J. SAYEN, WARNER F. SHELDON and P. T. KUO, Philadelphia, Pa., (Introduced by Hugh Montgomery).

Platinum electrodes for estimating relative tissue oxygen tension were inserted into the exposed left ventricular muscle of twelve anesthetized dogs, using the technique described (for skin) by Montgomery and Horwitz.

Results: (1) Fairly constant readings at one-minute intervals were obtained in normal myocardium. Inhalation of 100 per cent oxygen regularly increased these values by 50 to 200 per cent within three minutes. Resumption of air breathing caused prompt return to initial levels. Inhalation of 10 per cent oxygen depressed the values 50 per cent or more. (2) At the center of areas made ischaemic by three- to eight-minute occlusion of the distal anterior descending coronary artery the electrode readings fell rapidly to small fractions of control levels, and returned within a few minutes after occlusion ceased. Electrodes in muscle remote from the ischaemic area were not significantly affected. (3) Inhalation of 100 per cent oxygen from the onset or in the course of coronary occlusion caused values to rise in muscle not deprived of blood supply, but failed to prevent, or raise, low values at the centers of ischaemic areas. However, values at the borders of ischaemic areas, having fallen initially with coronary occlusion to levels comparable with the centers, rose 25 to 200 per cent within three minutes of inhalation of 100 per cent oxygen while coronary occlusion was maintained.

Conclusions: (1) The platinum electrode is applicable to the study of simultaneous changes in local oxygen tension in different portions of the beating heart. (2) The method lends itself to studies of the effect of therapeutic agents on localized myocardial ischaemia produced by experimental interference with the coronary circulation. (3) The data suggest that inhaling high concentrations of oxygen may prevent necrosis of borderline muscle in human myocardial ischaemia.

The Serum Iron in Diseases of the Liver. Robert B. Howard, Minneapolis, Minn., (Introduced by J. T. Syverton).

The serum iron was measured in a group of patients with various types of hepatic disorders. These included "alcoholic cirrhosis," cirrhosis following infectious hepatitis, cirrhosis associated with ulcerative colitis, idiopathic cirrhosis, and hepatitis of both the epidemic and homologous serum types. Several of the patients in the group without an alcoholic background presented the picture of cholangiolitic cirrhosis.

The patients with "alcoholic cirrhosis" tended to have low levels of serum iron, the majority of them below the lowest value found in a group of 30 normal controls. The non-alcoholic group, on the other hand, showed serum iron values which were significantly higher than those of the control group, although there was much overlapping between these latter two groups. More important, however, was the fact that in the non-alcoholic group in a given instance of acute hepatic damage, or of an acute exacerbation of chronic disease, improvement was reflected by a progressive decrease in serum iron values; conversely, a rising serum iron value indicated progressive deterioration of hepatic function. It was also of particular interest that in the "alcoholic" group several patients with evidence of marked hepatic functional impairment maintained low serum iron values.

The height of the serum iron level was not a function of the serum bilirubin level. There was no relation between serum iron values and hemoglobin except in two instances where massive bleeding from esophageal varices resulted in marked anemia and low serum iron values.

Changes in Normal Renal Function Resulting from ACTH and Cortisone. S. H. Ingbar, A. S. Relman, B. A. Burrows, E. H. Kass, J. H. Sisson, and C. H. Burnett,* Boston, Mass.

Significant changes in renal function followed administration of ACTH or cortisone to four adult males with normal kidney function. Dosage schedules varied from 70 to 400 mgm. daily for several days with ACTH, and from 200 mgm. daily for seven days to 1.6 Gm. in two days with cortisone. Inulin clearance increased up to 40 per cent with ACTH in large doses, but was unchanged with ACTH in low doses or cortisone at any dose. Clearance of PAH increased with both agents, and more markedly when large doses were administered. Tubular secretion of PAH following load administration increased (up to 35 per cent) with cortisone. With ACTH no change in PAH secretion occurred, but blood levels were not as high after ACTH as during control periods.

Changes in creatinine clearance following ACTH in large doses varied between a 38 per cent fall in one subject to a 9 per cent rise in another; C_{Cr}/C_{In}, however, uniformly fell (as much as 56 per cent) regardless of the direction of changes in creatinine clearance. No consistent changes in creatinine clearance followed cortisone or ACTH in low doses. Uric acid clearance increased significantly following ACTH in large doses, a reflection of lowered plasma levels and increased urinary excretion. Cortisone and low doses of ACTH produced little effect on uric acid clearance.

Phosphate excretion and clearance increased with both agents in large doses, but especially with ACTH. During PAH loads in ACTH subjects the usual increases in phosphate clearance were accentuated, and C_{PO_4}/C_{In} exceeded 1.0 in one subject.

The only significant changes in excretion of sodium and potassium demonstrable were: (1) large doses of cortisone induced sodium retention; (2) the natruresis which followed sodium para-aminohippurate loads was diminished by ACTH and cortisone, while potassium excretion was greatly increased; (3) natruresis occurred with some lots of ACTH known to be heavily contaminated with posterior pituitary.

The Distribution of Blood in the Rabbit Kidney. William Insull, Jr., and Irving G. Tillotson, Cleveland, Ohio, (Introduced by J. M. Hayman, Jr.).

Trueta has postulated that the blood reaching the kidney has two potential routes through that organ and according to circumstances it may pass almost exclusively by one or the other. He recorded no measurements of blood flow and few of blood pressure.

Rabbits under sodium pentothal anaesthesia were eviscerated and prepared for measurement of renal blood flow

by a modified Brodie technic. Blood pressure was recorded from a carotid cannula attached to a mercury manometer. The glomeruli receiving blood were stained with Janus green injected into the stump of the superior mesenteric artery.

Under control conditions either all glomeruli were stained, or those unstained were scattered irregularly through the peripheral and mid zones of the cortex. In a certain number of experiments in which renal blood flow or systemic blood pressure or both were reduced following stimulation of the sciatic nerve or renal artery or by hemorrhage, only the juxtomedullary glomeruli were stained. In no experiment were the peripheral glomeruli stained and the juxtomedullary unstained.

Perfusion of the excised kidney with Berlin blue in 6 per cent acacia at 50 cm. water pressure injects all glomeruli. As the perfusion pressure is reduced the peripheral glomeruli are not injected. When the perfusion pressure is about 20 cm. water only the juxtomedullary glomeruli are injected.

These experiments lend no support to the conception that a normal renal blood flow can be diverted or shunted through cortical or medullary channels. When renal blood flow or blood pressure is reduced under certain conditions the juxtomedullary glomeruli are preferentially perfused. The lower resistance of these channels would appear to be one factor.

Metabolic Studies During Treatment of Severe Congestive Heart Failure with 50 mgm. Sodium Diet. LLOYD T. ISERI, ALBERT J. BOYLE, WILLIAM A. ROSOW, ROBERT GRIFFIN and FREDERICK ENGSTROM, Detroit, Mich., (Introduced by Gordon B. Myers).

A synthetic liquid diet adequate in caloric and protein content and containing 50 mgm. of sodium was used in six cases of severe cardiac decompensation. The diet was given for a period of ten to fourteen days in five of the cases. The sixth case did not tolerate the diet after three days.

All cases were refractory to the usual regimen of low salt diet and frequent mercurial injections. Evaluation of compensation was determined (1) by clinical means including degree of cyanosis, dyspnea, rales, and edema; and (2) by objective means including venous pressure, circulation time, plasma and blood volumes, vital capacity, roentgenogram of the chest, and body weight.

Balance studies for sodium, potassium, chloride, nitrogen and water were carried out during the synthetic 50 mgm. sodium diet in five cases. In four of the five cases balance studies were continued for longer periods on a 200 mgm. sodium diet. Insensible loss was determined in two cases.

Clinical and objective evaluations showed distinct improvement in all five cases. Metabolic studies showed that (1) weight loss was correlated with negative sodium and water balance; (2) the calculated extracellular sodium and water balance was approximately equal to the total balances; (3) small amounts of sodium were found to enter the cells; (4) there was a marked uptake of potassium; (5) compensation may occur with decrease in venous pressure and circulating blood volume without much change in extracellular volume; (6) plasma sodium and blood nonprotein nitrogen concentrations remained normal; (7) extracellular volume during decompensation was 30 per cent of the body weight; and (8) positive nitrogen balance was maintained.

It is concluded that (1) 50 mgm. sodium diet is effective in treating cardiac decompensation; (2) loss of weight during cardiac recompensation corresponds to extracellular fluid loss with little change in intracellular fluid; and (3) there is a marked uptake for potassium, suggesting true deficiency.

Studies on Hematopoietic Recovery from Radiation Injury. LEON O. JACOBSON,* ERIC L. SIMMONS and WILLIAM F. BETHARD, Chicago, Ill.

The surgically mobilized spleen or the appendix of young adult rabbits was lead-protected during whole body exposure to 800 r or 1000 r X-radiation. By histopathologic study the recovery of the irradiated hematopoietic tissues of these animals was compared to that of rabbits without lead protection of the spleen or appendix during irradiation. A more rapid recovery of the irradiated hematopoietic tissues (bone marrow, lymph nodes, and thymus) occurred in rabbits which had lead protection of the spleen or appendix during irradiation than in the rabbits without lead protection of the spleen or appendix during irradiation. This same phenomenon has been observed in mice and rats in which the spleens were lead-protected during irradiation. Ectopic blood formation is greatly intensified in the lead-protected spleens of mice and rats after whole body X-irradiation; whereas, in the lead-protected spleens of irradiated rabbits, ectopic blood formation is minimal and absent in the lead-protected appendices of irradiated rabbits. Several possibilities may be offered to explain these findings. The lead-protected lymphatic tissue may reduce radiation toxicity and allow more rapid regeneration of irradiated hematopoietic tissue or the lead-protected lymphatic tissue may provide cells for colonization of irradiated hematopoietic tissue from which repopulation proceeds. It seems more likely that lymphatic tissue or hematopoietic tissue exerts humoral control over hematopoiesis. The spleen body weight ratio in mice is approximately 1 : 100, in rats 1 : 250, rabbits 1 : 2000, and in man 1 : 500. Since the spleen body weight ratio of man lies between that of rats and rabbits, extrapolation to man is not unreasonable. The implications of these findings make attempts at isolation of the assumed factor or factors in hematopoietic tissue responsible for effective stimulation of irradiated hematopoietic tissue of importance from the standpoint of the treatment of radiation injury as well as refractory anemias.

Evidence of Simulated Adrenal Cortical Activity During Pregnancy in an Addisonian Patient. JOSEPH W. JAILER * and A. I. KNOWLTON, New York, N. Y.

A patient with Addison's Disease was studied during the course of two pregnancies. During the periods of gestation, treatment with DCA and salt was continued. The patient remained well and gained weight normally. Her blood pressure, blood sugar and serum sodium values taken at frequent intervals showed very little change. Gonadotropin, estrogen and pregnanediol excretions were characteristic of a normal pregnancy. The excretion of 17-ketosteroids which were 4.5 mg. in the fourth month of gestation gradually rose to a high of 9.9 mg./day immediately prior to delivery. In the last trimester of her second pregnancy the neutral reducing lipids (phosphomolybdic acid reduction method) reached levels as high as 5.0 mg./day. The values of both these steroids rose in a manner qualitatively similar to that observed in normal women. During the last trimester, administration of epinephrine on two occasions resulted in a 40 per cent decrease in circulating eosinophils as did a single injection of 25 mg. ACTH.

Within ten days after delivery, the values for both types of steroids fell to levels characteristic of Addison's Disease; 1.7 mg. 17-ketosteroids and 1.3 mg. reducing lipids. Eosinophil tests with both epinephrine and ACTH were repeated and at this time no significant fall in eosinophiles occurred.

Urine collected from the patient's male infant for the first three days of life revealed an average daily excretion of 0.6 mg. 17-ketosteroids and 0.3 mg. neutral reducing lipids. These are normal values for newborns. Fourteen days after delivery the patient received a five-day course of ACTH, 100 mg. daily. During this period no fall in eosinophiles or rise in the excretion of 17-ketosteroids or neutral reducing lipids was observed.

These findings suggest that steroids from the placenta may contribute significantly to the increased excretion of 17-ketosteroids and neutral reducing substances observed in pregnancy.

The Hypertensive Pattern in the Critically Damped Ballistocardiogram. R. J. JONES and N. E. GOULDER, Chicago, Ill., (Introduced by Wright Adams).

The low-frequency, critically damped ballistocardiograms of 25 normal young adults and 27 older, non-cardiac patients are compared with those of 20 hypertensive patients with regard to the time in the cardiac cycle and the relative amplitudes of the I, J, and K peaks. In all hypertensives, with one exception, the I peak or J peak occurred earlier in the cardiac cycle than in any of the young normals or in the majority of the older patient normals. The two oldest men in the patient group had short intervals well in the hypertensive range, but presented no hypertension. It is postulated that this early occurrence of the I and J waves is related to a change in the shape of the systolic volume ejection curve incident to the decreased elasticity of the great vessels due to arteriosclerosis or an elevated diastolic pressure.

It is further noted that the vertical HI amplitude, expressed as per cent of the IJ amplitude, was smaller in 15 of the hypertensives, while the JK amplitude was higher in 12 than in any of the young normals. The possible influence of the cardiac axis is investigated by comparing the cosine of the angle of inclination of the heart's long diameter with the HI and JK amplitudes. The correlation coefficients ($r = +0.886 \pm 0.030$ and -0.644 ± 0.080) in 51 cases, including the hypertensive patients, indicate a significant relationship. The deep K wave, seen often in patients with aortic valve lesions, is differentiated from that of the hypertensive pattern by its associated high normal HI amplitude and a normal or delayed I peak. Explanation of these findings in accord with present ballistic theory is given.

The Unique Function of Certain Components of Complement in the Hemolytic Reaction of Paroxysmal Cold Hemoglobinuria. WILLIAM S. JORDAN, JR., LOUIS PILLEMER and JOHN H. DINGLE,* Cleveland, Ohio.

Studies of two patients with paroxysmal cold hemoglobinuria have confirmed the need for human or guinea pig complement during both the cold and warm phases of the Donath-Landsteiner reaction. A reciprocal relationship was demonstrated between the amounts of complement required in these two phases. Moreover, a reciprocal relationship also existed between the amount of complement present and fixation of antibody as indicated by antiglobulin serum and the hemolysin titer. When tested with usual dilutions of guinea pig complement, no hemolysis occurred with sera heated at 56° C. for 30 minutes. Using 1–2 complement, however, hemolysins from both patients showed maximal activity even after heating at 62° C. for 30 minutes.

The data indicate that this system is not only unique in requiring complement for antibody fixation as well as for subsequent hemolysis, but it is also unique in not requiring all components of complement for hemolysis. Serum and cells were chilled, washed, and warmed in fractions of serum, each lacking one of the components of complement. Only cells chilled in that fraction lacking C'4 did not hemolyze when whole complement was added in the warm phase. With cells chilled in the presence of whole complement, only those warmed in that fraction lacking C'2 did not hemolyze.

It is suggested that the reported variations in the heat stability of the hemolysin may be attributed to inactivation of human complement and the failure fully to restore complement activity on the subsequent addition of guinea pig complement. Hemolysis occurs in the absence of C'1, the so-called combining component of complement, and of C'3, the enzyme-like component. Hemolysis does not occur in the absence of the closely related components, C'4 and C'2. C'4 is apparently required in the cold phase, C'2 in the warm phase.

The Hemodynamic and Renal Functional Effects of Venous Congestion of the Limbs in Patients with Diabetes Insipidus. WALTER E. JUDSON, FRANKLIN H. EPSTEIN, CLARENCE M. TINSLEY, BELTON A. BURROWS and ROBERT W. WILKINS,* Boston, Mass.

In experiments reported to the Society last year, it was found that venous congestion of the limbs of normotensive subjects and of hypertensive patients (before and after splanchnicectomy) usually caused a marked fall in urine flow associated with definite though lesser decreases in renal plasma flow, glomerular filtration rate, and sodium and chloride excretion. Ordinarily there was a moderate rise in pulse rate, but little or no change in arterial pressure, although occasionally the pressure decreased sharply (vaso-vagal collapse). During similar experiments patients with diabetes insipidus usually showed only slight decreases in urine flow, but the normal reduction in renal plasma flow, glomerular filtration rate and electrolyte excretion. This was true when there were negligible effects on arterial pressure. However, when vaso-vagal collapse occurred, either spontaneously or as a result of the venous congestion, patients with diabetes insipidus exhibited a marked antidiuresis, which was accompanied at first by equally marked decreases in renal plasma flow, glomerular filtration rate and electrolyte excretion, but which persisted (with increased inulin U/P ratio) for a half to one hour after the arterial pressure and the other renal functions had returned to control values.

These data suggested that at least three separate mechanisms, one controlling water excretion (posterior pituitary), one controlling sodium excretion (? adrenal cortex), and certain intrinsic renal adjustments may be involved in the antidiuretic responses to venous congestion of the limbs, and that the participation of the splanchnic sympathetic nervous system is not necessary. Further evidence in support of these concepts has been obtained recently in normotensive and splanchnicectomized hypertensive subjects under a large osmotic (mannitol) diuresis. In these experiments venous congestion of the limbs caused no appreciable change in urine flow, although it resulted in the normal decrease in sodium excretion.

Experiences with the Use of Cation Exchange Resins in the Treatment of Edema. STANLEY S. KAHN and KENDALL EMERSON, JR.,* Boston, Mass.

Two forms of synthetic cation exchange resins, a carboxyl and a sulfonate exchanger, have been tested for their ability to remove sodium and water in man. The resins were administered orally in doses of 20 to 100 grams daily. In five patients receiving diets containing less than 1 gram of sodium, approximately 0.3 of a milli-equivalent of sodium and 1.5 milli-equivalents of potassium were removed in the stool per gram of resin administered. The increase in total fecal calcium excretion varied from none to 3 milli-equivalents per day during resin administration as compared to the control values. In one patient after treatment for a period of fifty days with large doses (up to 100 grams daily) of the sulfonate resin, an abrupt fall in the serum level of calcium and potassium occurred with symptoms of tetany and potassium deficiency and the laboratory findings of hypokalemic alkalosis. By mixing equal parts of a carboxyl resin saturated with potassium and one saturated with ammonia it was found possible to prevent excessive deprivation of potassium without, at the same time, interfering with the removal of sodium. In all patients there was either a slow diuresis with gradual weight loss or a decrease in the previous rate of salt and water retention during resin administration.

Urinary ammonia excretion was measured in three patients before, during and after resin therapy. In two of these in whom renal function was normal, a marked increase in urinary ammonia occurred during resin administration. Urinary ammonia failed to rise in the third patient, in whom there was severe renal damage, and subclinical acidosis developed.

Thus severe renal damage would appear to contraindicate resin therapy. The only other untoward symptoms noted were occasional mild nausea, anorexia and constipation which usually disappeared with continued administration of the resin.

Observations on a New Oral Diuretic Compound (1 Ethyl · 3n Propyl · 4 Amino-Uracil). A. A. KATTUS and E. V. NEWMAN,* (Introduced by C. B. Thomas).

Oral administration of 1 ethyl · 3n propyl · 4 amino-uracil (synthesized by V. Papesch) to dogs caused marked diuresis. Administration of 50 mgm./kilo/day to six dogs for ten days produced no functional or histological evidence of damage to the peripheral blood, kidneys, liver or adrenals.

In twelve of thirteen normal human subjects, oral administration of 300 mgm. four times in one day produced striking diuresis. The average sodium excretion on the test day was 193 per cent of the mean excretion on three preceding control days, while the average urine volume was 168 per cent of the control volumes. When 10 of these patients were tested with a single subcutaneous injection of 2 cc. of Thiomerin the average sodium output for that day was 179 per cent of the control while the urine volume was 173 per cent of the control. Thus the diuretic potency of this orally administered compound is comparable to the effect of a parenterally administered mercurial.

Ten edematous cardiac patients have been treated with this drug in oral doses of 300 mgm. four times daily in courses of one to three days. In eight of the ten cases there was striking sodium and water diuresis with concomitant weight loss during administration of the drug. No evidence of renal toxicity or untoward side effects was detected.

The drug was tested in three patients with the nephrotic syndrome. One, a child, with renal insufficiency, failed to respond. An adult with adequate renal function responded dramatically with a loss of 30 lbs. of edema; the third, a diabetic nephrotic in uremia showed only a moderate response on a single day of drug therapy. In no case was there evidence of increased renal damage.

Determination of glomerular filtration rate and renal blood flow on the dog during intravenous administration

indicate that the drug acts by inhibiting the tubular reabsorption of sodium.

The Response of the Human Colon to Acetylcholine. FRED KERN, JR., THOMAS P. ALMY and NATALIE J. STOLK, New York, N. Y., (Introduced by David P. Barr).

Previous studies in our laboratory have shown that in human subjects given methacholine (acetyl-beta-methylcholine) subcutaneously, there is marked diminution of motility of the sigmoid colon and augmentation of cecal activity. These changes in colonic motility are those seen during diarrhea. In view of the poorly understood role of the autonomic nervous system in the mechanism of diarrhea, studies have been done on the effect of acetylcholine itself upon the colon.

Sigmoid motility has been recorded kymographically by means of an in-lying balloon passed through the proctoscope. Acetylcholine chloride (1 per cent) has been administered intravenously by continuous infusion for 10–15 minutes to each of 17 normal males, at the rate, 40–110 mgm. per minute, necessary to produce moderate physiological effects (flush, salivation, restricted respiration, alteration in blood pressure and pulse). In 13 subjects there was an abrupt disappearance of sigmoid waves; in two subjects there was an increase in motility of the sigmoid; and in two experiments there was no effect. Fluoroscopic observations indicate that acetylcholine also causes an increase of contractility of the cecum.

It is expected that evaluation of the sensitivity of the colon to acetylcholine may shed light upon the mechanisms of functional diarrhea and ulcerative colitis.

Studies on Amino Acid Excretion in Man; VII. Effect of Various Protein Supplements in a Normal Man, Two Patients with Benign Gastric Ulcer and Two Patients with Chronic Ulcerative Colitis. JOSEPH B. KIRSNER * and A. LEONARD SHEFFNER, Chicago, Ill.

Four types of protein foods: (1) normal whole protein: meat and eggs; (2) dehydrated whole protein: skimmed milk powder; (3) fluid whole protein: evaporated milk; and (4) hydrolyzed protein: an enzymatic digest of liver, were fed to a normal man, two patients with benign gastric ulcer, and two with chronic ulcerative colitis in consecutive six-day metabolic periods; the intakes of nitrogen and calories were maintained at constant levels. In addition to nitrogen balances, eight amino acids: leucine, isoleucine, valine, threonine, arginine, histidine, lysine, and methionine, were measured microbiologically in the food, plasma, and in six-day collections of urine and feces.

In the normal subject the nitrogen balances were positive only when meat and eggs or skimmed milk powder were fed. In the patients with gastric ulcer more nitrogen was retained during the ingestion of the two milk preparations. In the patients with ulcerative colitis the nitrogen balance was distinctly negative only when the hydrolysate was administered.

In general, significantly larger quantities of individual amino acids appeared in the urine during the hydrolysate regimen. The output of lysine increased also during the ingestion of evaporated milk. The excretion of nitrogen and amino acids in the feces was approximately normal in the patients with gastric ulcer and was significantly increased in those with ulcerative colitis.

The outputs of individual amino acids in the feces usually were highest during the oral ingestion of protein hydrolysate and smallest during the intake of whole protein; these differences were most pronounced in the patients with ulcerative colitis.

The individual free and total non-protein amino acids in plasma fluctuated without relationship to the type of protein food administered.

The Significance of the Plasma Tocopherol Concentration in Liver Disease, in the Fasting State and Following Single Test-Doses of Tocopherol. GERALD KLATSKIN and WILLARD A. KREHL, New Haven, Conn., (Introduced by Francis G. Blake).

The mean plasma tocopherol concentration of 43 subjects with liver disease (0.95 ± 0.31 mg. per cent) did not differ significantly from that of 51 randomly-selected, convalescent, hospital patients (1.00 ± 0.37 mg. per cent), nor that of 21 healthy adults reported by Lemley (1.09 ± 0.17 mg. per cent). The positive correlation with age and serum cholesterol concentration reported by others was not corroborated, nor was there any relationship between the plasma tocopherol level and the state of hepatic function.

The mean plasma tocopherol curve of 19 liver disease subjects, given 500 mg. dl, alpha-tocopheryl acetate orally, showed a significantly lower peak and a slower rate of fall than that of 21 controls. Four of the former failed to show any response. Similar results were obtained in 6 liver disease subjects given water-soluble, dl, alpha-tocopheryl phosphate orally. No significant correlation was demonstrated between the maximum rise in plasma tocopherol and the level of the fasting tocopherol concentration, the state of hepatic function, or the concentration of serum cholesterol.

No significant difference between the mean plasma tocopherol curves of liver disease and control subjects was observed following the intramuscular injection of dl, alpha-tocopherol in sesame oil, or of a finely dispersed, aqueous emulsion of dl, alpha-tocopheryl acetate, stabilized with a mixture of Tweens. These compounds were poorly and irregularly absorbed in both groups, possibly obscuring real differences in tocopherol utilization. An unexplained paradoxical fall in plasma tocopherol was observed after intramuscular injection of dl, alpha-tocopherol in oil.

Conclusions: (1) low plasma tocopherol levels, occasionally present in liver disease, may be related to associated malnutrition, or other factors, rather than to hepatic dysfunction, (2) the abnormal tocopherol tolerance curves in liver disease have not been explained, but are not necessarily indicative of significantly diminished absorp-

tion and tissue storage, nor are they necessarily directly related to hepatic damage.

The Use of a Cation Exchange Resin in Patients with Cardiac Edema. HENRY KRAUS, Boston, Mass., (Introduced by Lawrence B. Ellis).

An ammonium cation exchange resin (Win-3000) was administered for periods from one week to three months to 22 patients with cardiac edema.

In the intestinal tract, this resin exchanged ammonium ions for sodium and other cations. The ammonium ions were absorbed, producing effects similar to those of therapeutic amounts of ingested ammonium chloride. All patients had a progressive drop in the carbon dioxide combining power to 30–35 volumes per cent. None, however, developed an uncompensated metabolic acidosis.

The average patient treated with this resin had a definite diuresis and weight loss, usually first observed on the second or third day of treatment. The weight loss occurred gradually and the total amount lost varied with the severity of edema. Four patients who received the resin for as long as three months maintained their base weights within very narrow limits and remained symptom free. Two patients who were refractory to mercurials responded satisfactorily to the resin. No patient who responded to mercurials failed to lose edema fluid on the resin.

None of the patients developed hyponatremia as a result of the resin therapy. A progressive fall in serum potassium levels was observed in several patients, without definite symptoms of hypopotassemia. Four patients, who had been maintained on the same doses of digitalis for over one year, showed typical signs of digitalis toxicity when they developed hypopotassemia. Most of the patients showed a progressive lowering of their serum calcium levels, but none showed evidence of clinical hypocalcemia.

In this series of patients, resin therapy was effective in controlling edema. The affinity of this resin for other cations in addition to sodium complicated the management of these patients. For this reason, it is suggested that this particular resin is not suitable for the routine management of cardiac edema.

The Distribution and the Pathologic Effects of I^{131} in Man. GEORGE S. KURLAND, DAVID L. CHAMOVITZ and A. STONE FREEDBERG,* Boston, Mass.

Despite the wide clinical use of radioactive iodine, data on the distribution in man and, consequently, on the radiation delivered to the thyroid and other organs, are scanty. The distribution of I^{131} was studied in 13 patients. Seven euthyroid patients were given 300–800 microcuries of I^{131}, carrier-free, 4–168 hours before orchidectomy or oophorectomy. In the remaining 6 cases, 5 euthyroid and 1 hyperthyroid, 2–66 millicuries were administered 1–80 days before death. The per cent uptake of I^{131} was measured and the equivalent roentgens delivered were calculated. The thyroid gland was found to contain 100 to 2000 times more I^{131} per gram than the lung, which was next in radioactivity content. Kidney, liver, spleen and bone marrow were next in the order of concentration. Four pituitary glands contained 0.004, 0.025, 0.75, and 0.9 per cent per gram of tissue as compared to the thyroid; a fifth pituitary gland contained no measurable activity. In two of three instances, the bone marrow contained amounts of I^{131} equal to or greater than any organ except the thyroid. The radioactivity content was small in the gonads of four patients examined at necropsy and in the gonads obtained at orchidectomy or oophorectomy in seven additional cases. In the testis, the concentration was 0.001–0.02 per cent of the administered dose. In two of three ovaries from women 40–67 years of age, no measurable concentration of I^{131} was present; in the third, the ovary contained 0.0006 per cent of the administered dose.

The histologic findings in eight euthyroid patients given 17.5–66 millicuries I^{131}, 1–80 days before death, are consistent with these observations. Careful microscopic examination revealed no effects attributable to I^{131} in any organ except the thyroid. Clinical observations in 165 patients are in accordance with the above and will be discussed.

The Significance of Urinary Dehydroisoandrosterone. RICHARD L. LANDAU, KATHRYN KNOWLTON and KATHLEEN LUGIBIHL, Chicago, Ill., (Introduced by Allan T. Kenyon).

The enhanced excretion of urinary 17-ketosteroids induced by adrenocorticotrophin has aroused increased interest in the meaning of the 17-ketosteroids of adrenal origin. Their relationship to the C 21 corticoids is not clear, and it frequently has been suggested that they may be derived from an adrenal androgen.

A modification of the Pettenkofer reaction has been employed to follow the excretion of dehydroisoandrosterone during adrenal cortical and testicular stimulation and while administering testosterone and dehydroisoandrosterone. It has thus been possible to confirm the adrenal origin of this 17-ketosteroid and to show that it holds a key position in the metabolism of adrenal steroids.

Two normal men received chorionic gonadotrophin with resultant enhanced secretion of testicular androgen as manifested by the characteristic anabolic response. Though urinary 17-ketosteroids were significantly elevated, the excretion of dehydroisoandrosterone and related steroids was unaffected, and no elevation was noted during testosterone propionate administration. Accordingly it appears that dehydroisoandrosterone is neither liberated by the testis nor metabolically derived from testosterone.

The administration of adrenocorticotrophin to two normal young men induced a sharp rise of 17-ketosteroid excretion and a parallel increase in dehydroisoandrosterone. In the two studies 30 and 31 per cent of the elevation in 17-ketosteroids was accounted for by dehydroisoandrosterone, and a comparison of the altered steroid excretion pattern in one subject with that which

followed the administration of dehydroisoandrosterone acetate strongly supported the suggestion that dehydroisoandrosterone and its metabolic derivatives comprise most of the 17-ketosteroids of adrenal origin.

The correlation of its excretion with adrenal activity and its structure suggest that dehydroisoandrosterone may be an intermediate between cholesterol and C 21 corticoids or a by-product of this synthesis. It is also possible that it possesses as yet undemonstrated physiological properties or is related to the hypothetical adrenal androgen. It seems unlikely that dehydroisoandrosterone is derived from C 21 corticoids.

Salutary Action of ACTH in a Case of Periarteritis Nodosa: the Effective Dose as Measured by Nitrogen and Electrolyte Balances. MELVIN H. LEVIN, WILLIAM S. BECK, WILLIAM S. ADAMS and RALPH GOLDMAN, Los Angeles, Calif., (Introduced by Samuel H. Bassett).

Metabolic balances were conducted for 135 days in a patient with periarteritis nodosa receiving Armour's ACTH. Dramatic clinical improvement occurred with prompt relief of asthma, anorexia, asthenia, and improvement in well-being. Pulse and temperature decreased; blood pressure increased during treatment. A biopsy, originally positive, was negative on 3 subsequent occasions. The eosinophile count dropped from 1500/cumm. to 0, returning to 500 between courses of ACTH.

During the first 55 days, on a formula containing 2200 calories and 75 gms. protein, the patient received two 15 day courses of 40 mg. ACTH per day. During the remaining 80 days, on a diet of 3100 calories and 133 gms. protein, ACTH was administered continuously for five 10 day periods in doses of 10, 20, 40, 20 and 10 mg. per day respectively.

The metabolic data confirmed the effects reported in normal subjects: negative N, K, P, and Ca balance, Na and Cl retention, decreased glucose tolerance and increased urinary excretion of uric acid, creatine, and 11-oxy- and 17-ketosteroids. Following withdrawal, the changes temporarily reversed, suggesting transient hypoadrenocorticalism.

In addition, during the control period of the increased caloric and protein regimen, striking nitrogen storage occurred, indicating marked depletion of body protein. When ACTH was given on a stepwise dosage schedule, the positive N balance was completely negated at levels of 20 and 40 mg. per day. Other metabolic changes, including eosinophile response, occurred in stepwise increments with maximum effect at the dose of 40 mg. per day. *Successive decrements in dosage were not accompanied by proportional reverses in metabolic phenomena, indicating that the level of adrenal cortical activity, once established, could be maintained with smaller doses of ACTH.* On final withdrawal, marked positive N balance was again established, with continuing rapid repletion.

The Effects of Induced Hyperglycemia on Renal Oxygen Consumption and Blood Flow. BENJAMIN A. LEVITAN, Durham, N. C., (Introduced by Frank L. Engel).

Oxygen consumption by the kidney greatly exceeds osmotic work performed in urine formation. Several possible explanations exist for this high utilization of energy: (1) The kidney requires large amounts of energy to maintain the special structure and function necessary for urine formation. Little additional energy is necessary for the actual work. In a familiar analogy, it costs nearly as much to operate an empty ward as it does a full ward. (2) The total capacity of the kidney for work is limited and approaches maximum even at rest. Increased tubular transport of one matabolite is accomplished by decreased transport of other metabolites so that total work performed and oxygen consumption remain unchanged. (3) The kidney uses its large resting oxygen consumption for maintaining its own internal structure and function, but requires additional oxygen when tubular work is increased.

To study this problem, renal arteriovenous differences in oxygen and in hippurate contents and glomerular filtration rates were measured in five normal subjects before and during maximal glucose transport.

Renal arteriovenous oxygen differences increased in four subjects and decreased in one. PAH differences decreased in all. Values for renal blood flow calculated without renal vein catheterization are abnormally small. True blood flow increased by an average of 30 per cent, and average oxygen consumption increased by 66 per cent.

During maximal glucose transfer, the normal kidney increases its oxygen consumption by increasing both oxygen extraction and blood flow.

The kidney differs from muscle which, though requiring little energy to maintain resting functional organization, increases its metabolism many times when active. It is unlike the brain, which uses energy to maintain its resting functional organization and expends little additional energy in thinking. It resembles the liver which is continually active in the fasting state but can increase its utilization of energy in response to appropriate stimuli.

Characterization of the Anemia of Chronic Renal Insufficiency. J. PHILIP LOGE, ROBERT D. LANGE and CARL V. MOORE,* St. Louis, Mo.

A restudy of the anemia of chronic renal insufficiency has produced evidence to support the commonly held belief that erythropoiesis is depressed, and has also demonstrated that at times the anemia may be definitely hemolytic.

I. Evidence for depressed erythropoiesis.

Chronic renal insufficiency was commonly associated with a stable or slowly progressive anemia of moderate severity, no significant reticulocytosis, and a decreased utilization of intravenously administered radioactive iron. Under these circumstances, there was no evidence of increased hemolysis. Serum bilirubin

and fecal urobilinogen excretion were not elevated. Furthermore, normal red blood cells transfused into these patients survived normally as did the patients' red cells in healthy recipients. The osmotic and mechanical fragility determinations were within normal limits. Blood loss was not detected in those patients who served as subjects for this study.

II. Evidence that the anemia may at times become hemolytic.

In patients with chronic glomerulonephritis and marked azotemia, the anemia may become rapidly progressive. It is at this time that evidences of increased hemolysis have been detected. Normal red cells transfused into these patients survived considerably less than the expected 110 to 130 days, yet the patients' own cells survived normally in healthy recipients. The hemolytic component, therefore, seems to be an extracorpuscular defect. The anemia was accompanied by a moderate reticulocytosis, but no detectable increase in serum bilirubin or fecal urobilinogen excretion. The Coombs' anti-human globulin test was consistently negative. Osmotic and mechanical fragility determinations were moderately increased in some instances.

Serial serum iron and free erythrocyte protoporphyrin values have been determined in each patient. As yet, unlike the anemia of chronic infection, no consistent pattern has been demonstrated.

It is recognized that blood loss may be partly responsible for the anemia of chronic renal insufficiency, but the prominent mechanism is an invariable depression of erythropoiesis associated, at times, with an extracorpuscular hemolytic factor.

Entero-Hepatic Circulation of Bromsulphalein. STANLEY H. LORBER and HARRY SHAY, Philadelphia, Pa., (Introduced by Richard A. Kern).

Variations in the blood level of bromsulphalein obtained in some patients following the 5 mg./Kg. dose of the dye, when repeated at daily or weekly intervals, made it difficult to interpret minor degrees of dye retention. This difficulty did not occur after the 2 mg./Kg. dose. Since the duodenum may contain relatively high concentrations of bromsulphalein during the course of the test, an entero-hepatic circulation of the dye was considered as a possible explanation for these variations. This was investigated in 4 subjects, 3 of whom had no evidence of liver disease.

Three types of tests were performed on each subject, employing in each the 2 and the 5 mg./Kg. dose of bromsulphalein: (1) Determination of bromsulphalein blood levels 30 and 45 minutes after intravenous administration of the dye. (2) Dye determination in blood specimens at 5, 10, 15, 30 and 45 minutes after duodenal instillation of the dye. (3) Intravenous test with duodenal aspiration measuring blood levels and duodenal output of the dye.

Demonstrable blood levels of bromsulphalein were obtained after duodenal instillation of the 2 and the 5 mg./Kg. dose. Furthermore, removal of bile containing dye by duodenal aspiration during the intravenous test could reduce serum dye levels below those obtained when duodenal contents were not aspirated. Concentrations of dye in the aspirated duodenal juice were significantly higher after the 5 mg./Kg. dose.

The results indicate that brosulphalein may be absorbed from the upper intestinal tract and partake in an entero-hepatic circulation. Because lower concentrations of dye are present in the duodenum after the 2 mg./Kg. intravenous dose than after the 5 mg./Kg. dose, re-absorption of significant quantities of bromsulphalein are less likely to occur. These results suggest that the smaller dose is preferable for clinical use.

A Study of Porphyrin and Hemoglobin Metabolism with the Aid of Glycine Containing N^{15}, in a Case of Chronic (Mixed) Porphyria. PAUL LOWRY and VIOLET HAWKINSON, Minneapolis, Minn., (Introduced by C. J. Watson).

An unusual opportunity was recently available to study porphyrin and hemoglobin metabolism in an individual with chronic porphyria of the mixed type who was excreting large amounts of proto- and coproporphyrins type III in his feces. This man was given glycine tagged with N^{15}. Serial determinations of the N^{15} in crystalline hemoglobin protoporphyrin, stercobilin, and the fecal proto- and coproporpyhrins were then made over a five months' period. The N^{15} in the stercobilin and coproporphyrin rose to a high peak in the first eight days. The highest concentration in the fecal protoporphyrin occurred at 14 days while that in the hemoglobin protoporphyrin reached a relative plateau at 24 days. A prompt decline in the stercobilin and coproporphyrin N^{15} curves was noted well before the maximum content of N^{15} had been reached in the fecal and hemoglobin protoporphyrins. The N^{15} in the hemoglobin photoporphyrin followed a plateau-like curve with a slight progressive decrease in concentration. The N^{15} in the fecal protoporphyrin declined after the initial peak and did not rise at the time of hemoglobin breakdown which was manifested by a second elevation in the stercobilin N^{15} curve.

The N^{15} data indicate a slight but continuous random destruction of erythrocytes without other evidence of greater than normal hemolysis. A partial derivation of stercobilin from a source other than circulating hemoglobin was again noted. The present data indicate that the fecal protoporphyrin in this case is formed neither from the disintegration of hemoglobin nor by resynthesis from degradation products of the hemoglobin protoporphyrin. Evidence is presented that coproporphyrin III is formed in the main more rapidly than the hemoglobin protoporphyrin and independent of hemoglobin destruction. The findings are not inconsistent with the concept that coproporphyrin III is a precursor of hemoglobin protoporphyrin.

The Value of the Agglutination Test in Differentiating Chronic Active Brucellosis from Postinfectious Neurasthenia. ROBERT L. MAGOFFIN, DEAN S. FLEMING and WESLEY W. SPINK,* Minneapolis, Minn.

In each of 48 patients with culturally proved brucellosis, the serum agglutinins were measured early in the course of the illness and again one year or longer after the onset of symptoms. Thirty-one of the patients were males, 17 were females, and their ages ranged from 4 to 67 years. The duration of illness from onset to complete subjective recovery varied from 1 month to over 6 years; 13 patients recovered within 6 months, 24 within 1 year and 32 within 2 years. Eight patients who had illnesses of longer duration subsequently recovered, but 8 had not recovered 2 to 5 years after the onset of symptoms.

"Active disease" was defined as the presence of demonstrable fever, and/or bacteremia, and/or symptoms sufficiently severe to be incapacitating. Patients having only weakness, nervousness, easy fatigue, headaches or generalized aches with little or no incapacitation and having no demonstrable fever or bacteremia were considered to be in a convalescent phase of illness. Patients were classified as recovered only when subjectively well.

By these criteria, 24 patients had active illness for less than one year. In these patients, with few exceptions, titers were high (at least 1:160) during active illness, falling to low levels or zero upon recovery. Fifteen patients with active infection for 1 to 4 years maintained high titers throughout their protracted illness. In 9 patients with active infection for less than 12 months, chronic subjective symptoms persisted for 18 months or longer, yet the titers declined to low levels as the symptoms of active infection disappeared. It is suggested that the symptoms persisting in these 9 patients typify those of a postinfection syndrome occurring in individuals unable to meet the normal demands of convalescence.

The Effect of Positive Pressure Breathing on Air Flow Resistance of the Tracheobronchial Tree. J. V. MALONEY, JR., A. B. OTIS, W. O. FENN and J. L. WHITTENBERGER, Boston, Mass., and Rochester, N. Y., (Introduced by Cecil K. Drinker).

Positive pressure breathing is considered to be of benefit in the treatment of asthma and pulmonary edema because the positive endobronchial pressures dilate the bronchi and reduce resistance to air flow. Evidence has been obtained in normal subjects to demonstrate that positive pressure breathing and voluntary breathing at an increased thoracic mid-position produce the same effects on airway resistance. In both normal and positive pressure breathing, lung distention is accomplished by the production of a pressure gradient in which the intrapulmonary pressure is greater than the intrapleural pressure. A given pressure gradient, whether created by elevating intrapulmonary pressure or reducing intrapleural pressure, will produce the same lung distension and the same force acting to distend the bronchi.

The pressure drop between mouth and alveoli during flow of air into and out of the lungs results in a negative alveolar pressure on inspiration and a positive pressure on expiration. Otis and Proctor's modification of an earlier method permits the measurement of alveolar pressure and, therefore, of tracheobronchial resistance. Determinations were made on a group of normal subjects who breathed around different thoracic mid-positions. Observations were repeated over the same range of mid-positions with the addition of 7 cm. H_2O continuous positive pressure. On changing from a mid-position near maximum inspiration to one near maximum expiration, there was an average increase in tracheobronchial resistance of 179 per cent (range 33 to 480 per cent) at the normal peak flow rate. At any given thoracic volume, positive pressure breathing produced the same air flow resistance as normal breathing. In conclusion, pressure breathing reduces the resistance of the tracheobronchial tree insofar as it increases thoracic volume. Equivalent changes may be produced by voluntarily increasing lung volume while breathing at atmospheric pressure.

Abnormal Ballistocardiographic Patterns in Disease, as Recorded with the Low Frequency, Critically-Damped Ballistocardiograph. JAMES A. L. MATHERS, JOHN L. NICKERSON, MYRON C. PATTERSON and THOMAS C. FLEMING, New York, N. Y., (Introduced by Robert L. Levy).

Sixteen patients with cardiac failure of varied etiology have been studied at frequent intervals during the period of recompensation and on numerous subsequent occasions. Observations were made of hemodynamic changes, cardiac output and ballistic patterns by means of the low frequency, critically-damped ballistocardiograph.

Abnormal ballistic patterns which are associated with impaired cardiac function, regardless of etiology, revert toward normal with improvement in the functional capacity of the heart. With the return of cardiac failure there is reversion of the pattern to a more abnormal form. Slight deviations from normal, *e.g.* upward bowing of the J wave, have been found in fifteen per cent of youths without symptoms or signs of heart disease. The changing patterns afford objective evidence of alterations in cardiac function.

Time Relations Between the Metabolic Changes of Experimental Diabetic Acidosis and Adrenal Cortical Hyperfunction. JANET W. MCARTHUR, DONALD HARTING, GEORGE A. SMART and NATHAN B. TALBOT,* Boston, Mass.

The temporal relation between the evolution of the metabolic phenomena characteristic of diabetic acidosis and the onset of adrenal cortical hyperactivity, which accompanies this state, has been investigated in a series of descriptive experiments. Complete balance studies together with frequent blood counts and urinary 11-17-oxycorticosteroid measurements have been performed on depancreatized dogs rendered ketotic by insulin deprivation.

The general clinical course of all the animals studied was remarkably uniform. Following insulin withdrawal, polydipsia and polyuria became manifest within a few hours. Anorexia and rapidly progressive muscular weakness appeared within 48 hours, vomiting in 60 hours and death in 72 hours. The metabolic balances were similar in all respects to those established in human subjects except for the superior capacity of the dog to conserve sodium despite mounting acidosis.

There was no indication of adrenal hyperactivity during the initial phases of the stress provoked by insulin deprivation. Although glycosuria became extreme within 12 hours after insulin was withheld, the eosinophil count and corticosteroid excretion remained stationary. Terminally, when the dog was prostrated, the eosinophil count fell abruptly and the neutrophil count and corticosteroid excretion rose. In addition, the blood sugar which had changed little after the initial increase following insulin withdrawal rose sharply.

Nitrogen and potassium balances became increasingly negative as ketosis increased. These substances were excreted in protoplasmic proportion except during the period immediately following insulin withdrawal and during the terminal period. The initial loss of excess potassium was attributed to the loss of liver glycogen. The final loss occurred concomitantly with evidences of adrenal hyperactivity.

An intimate temporal relation between adrenal hyperactivity, loss of potassium in excess of nitrogen and increased hyperglycemia has thus been shown to exist during the evolution of experimental diabetic ketosis.

Association of High Ionized Serum Calcium with Renal Failure in Plasma Cell Myeloma. GORDON C. MEACHEM and ROBERT W. HEINLE,* Cleveland, Ohio.

Of 31 patients with plasma cell myeloma, 9 developed renal insufficiency. Of the 9, 7 had sufficient data to determine that the serum ionized calcium level was high. Another had a serum calcium level of 13.0 mg. per 100 ml. Six of the 9 had serum calcium levels above 11.0 mg. per 100 ml. In 5 of the 9, serum globulin was less than 3.0 gm. per 100 ml. and one had a serum globulin between 3.0 and 4.0 gm. per 100 ml. Only 7 of the 31 patients had demonstrable Bence-Jones proteinuria and 4 of the 7 had renal insufficiency.

Insofar as is known, there have been no published reports of a high ionized serum calcium level in patients with plasma cell myeloma who have kidney insufficiency. It is possible that the renal failure is due to nephrocalcinosis resulting from the high ionized calcium level. At autopsy, one of the 9 patients had calcium deposits in the renal tubules identical in appearance with the nephrocalcinotic kidney seen in hyperparathyroidism.

Another possibility is that the combination of high ionized calcium, only slightly increased serum globulin, and the presence of Bence-Jones protein predisposes to renal failure. Tubular obstruction by protein casts is commonly considered to be the cause of renal failure in plasma cell myeloma. The excess of ionized calcium may combine with an abnormal protein to form casts which are more obstructive than the common type of protein casts.

Chloramphenicol-Fastness: In Vivo and In Vitro. MANSON MEADS, Winston-Salem, N. C., (Introduced by George T. Harrell).

In vivo: The development by gram-negative bacteria of fastness to chloramphenicol was observed during treatment with this drug of chronic urinary tract infections in human beings. Nine of 33 strains isolated from the urine of 24 patients demonstrated a decrease in susceptibility to chloramphenicol of 4 to 80 fold as measured by a serial dilution method in agar. Repeated urine cultures taken after treatment showed that two of the nine strains had lost the property of fastness to this drug in 1 and 5 weeks respectively. The development of resistance by bacteria was considered the principal cause of failure of treatment in five patients. In most instances, this phenomenon developed by successive small steps each of which occurred at unpredictable periods during the first week of therapy. When the development of fastness was associated with a marked and persistent diminution in the number of organisms, continued treatment with chloramphenicol eliminated the resistant strain in spite of low concentrations of active drug in the urine. A comparison of the cultural characteristics, biochemical reactions, and growth rates of the resistant variants and their sensitive parent strains failed to reveal significant differences.

In vitro: Variants exhibiting low degrees of fastness to chloramphenicol (less than 25 micrograms per cc.) were demonstrated in a highly susceptible strain of *Klebsiella pneumoniae* by exposing it to concentrations of this drug in agar which varied between 1 and 1000 micrograms per cc. By the use of the Fluctuation Test of Luria and Delbrück, these variants were shown to have arisen by mutation before contact with the antibiotic. Variants with higher degrees of resistance did not appear when very large populations ($\pm 10^{10}$ organisms) were examined. The property of fastness to chloramphenicol was highly drug-specific and inheritable; it was not dependent on the ability of the variant to destroy or inactivate chloramphenicol.

The Effects of Protoveratrine, a Pure Veratrum Alkaloid, in Hypertensive Patients. EDWARD MEILMAN and OTTO KRAYER, Boston, Mass., (Introduced by Samuel L. Gargill).

Protoveratrine, a pure crystalline ester alkaloid from Veratrum album with marked hypotensive properties, has been studied in a group of patients with renal or essential hypertension. In these patients, regardless of the duration of the hypertension, a marked fall in blood pressure to normal or near-normal levels may be obtained at doses free of significant side effects. There were 226 intravenous injections in 43 patients, 153 intramuscular injections in 14 patients, 7 of whom received from 5 to 42 consecutive intramuscular injections. In two individuals large doses caused vomiting. An effective intra-

muscular dose may be estimated from the effective intravenous dose. Duration of hypotensive action of 6 to over 12 hours may be obtained with a single intramuscular injection.

Besides its obvious usefulness as a tool for the study of hemodynamic factors in hypertension, an indication of the potential therapeutic application of this or related alkaloids in acute situations is afforded by the following responses to intramuscular administration. (1) In a patient with severe hypertensive cerebral, cardiac and renal disease, there was dramatic clearing of the symptoms of hypertensive encephalopathy (near-coma, irrationality, restlessness, headache) as well as diminution in some of the symptoms and signs of congestive failure. (2) A hypertensive patient with severe congestive failure, chronic pyelonephritis and nitrogen-retention obtained a lowering of pressure, relief of headache and a general sense of well-being that had been absent for months. (3) In a young woman with severe preeclampsia, generalized edema, 4 plus albuminuria, oliguria, and hypertension, who developed headache and spots before the eyes coincident with the onset of labor, there was prompt fall in blood pressure and disappearance of both headache and scotomata.

The Effect of a Synthetic Fat-Free Dietary Regimen on Serum Cholesterol. SHERMAN M. MELLINKOFF, THOMAS E. MACHELLA* and JOHN G. REINHOLD, Philadelphia, Pa.

Fourteen patients with a variety of benign lesions of the gastrointestinal tract were placed on a dietary regimen consisting entirely of a solution of equal parts of a protein hydrolysate and dextrimaltose, supplemented with iron and the essential vitamins. Two thousand to four thousand calories were thus supplied daily for periods averaging 15 (5 to 53) days. All of the subjects gained or maintained weight. Serum cholesterol concentration was determined at frequent intervals before, during and after the period of special alimentation.

A rapid fall in serum cholesterol, averaging 85 (5 to 169) milligrams per cent, occurred during the period of subsistence on the synthetic diet. Return to original levels occurred rapidly on resumption of ordinary diet. The degree of fall was greater in those patients in whom the initial cholesterol levels were highest, but in no instance did the level fall below 87 milligrams per cent.

The Effect of Spinal Anesthesia and Arterial and Venous Occlusion on the Digital Circulation. MILTON MENDLOWITZ,* ARTHUR S. W. TOUROFF and HAROLD ABEL, New York, N. Y.

When blood flow is measured in the toe by means of a calorimeter spinal anesthesia does not produce flow which is significantly greater than that which results from the application of indirect heat supplemented by the intravenous administration of tetra-ethyl-ammonium chloride. Because of the discrepancy between the results obtained by plethysmography as opposed to calorimetry, the accuracy of both methods was tested. No major source of error could be detected in the calorimetric method. The latter therefore was used to measure the effect of arterial and venous obstruction upon digital circulation. Arterial obstruction for 2 minutes or more produced a maximum decrease in minute flow of from 50 to 93 per cent, whereas venous obstruction for the same length of time produced a decrease of only from 0 to 39 per cent. These results would appear to indicate incomplete trapping of arterial inflow attributable probably to deep venous reflux. Similar though less striking differences in flow were observed after arterial or venous obstruction lasting from 10 to 30 seconds. It also was demonstrated that the very act of producing venous obstruction was capable of inducing a vasoconstrictor reflex that easily could "break through" the vasodilatation produced by indirect heating and less easily through that produced by indirect heat supplemented by the intravenous administration of tetra-ethyl-ammonium chloride. These results cast some doubt on the validity of venous obstruction plethysmography as a quantitative method of measuring digital blood flow.

The Production of a Pressor Response in Patients with Refractory Hypotension by Use of the Artificial Kidney. JOHN P. MERRILL and STEPHEN SMITH, 3d, Boston, Mass., (Introduced by Henry A. Christian).

During the course of hemodialysis with the artificial kidney, a pressor response characterized by both elevation of the systolic and diastolic blood pressures has been noted. The nature of this response has been studied by measurement concomitantly of peripheral resistance by direct arterial cannulation and of the cardiac output, employing the Fick principle using a venous catheter in the pulmonary artery. Observations in five hypertensive and one normotensive patient indicate that the pressor response is usually a result of increased peripheral resistance and frequently of increased cardiac output.

In six instances hemodialysis in patients with prolonged, severe hypotension resulted in elevation of both systolic and diastolic levels of blood pressure with clinical improvement. Increase in systolic blood pressure of 20–140 mm. and in diastolic pressure of 18–60 mm. resulted. All patients had previously failed to respond to large quantities of blood and/or plasma. All had evidence of pulmonary congestion as manifested by basal rales and had been digitalized without effect on the blood pressure. All patients had jaundice with either acute or chronic hepatic disease, cyanosis, and hypotension without clinical evidence of peripheral vasoconstriction. Three patients had fever, and in one patient a temperature of 105 degrees returned to normal during dialysis and the concomitant pressor response. In all patients the first beneficial result was transient, blood pressures and clinical status deteriorating toward predialysis levels over a period of from 8–12 hours. In two patients, the previous effects were reproduced by a second dialysis, in one of these with eventual recovery.

The role of the addition of glucose from the bath fluid

or the removal by dialysis of an unknown diffusible substance responsible for the "hepato-renal syndrome" is discussed in relation to the observations made on cardiac output and peripheral resistance in the other group.

The Nephrotic Syndrome in Children: Response to Intravenous Sodium Loads. JACK METCOFF and WILLIAM M. WALLACE, Boston, Mass., (Introduced by Arthur J. Merrill).

Renal responses to successive intravenous sodium loads of different magnitudes infused during two–three consecutive 69–90-minute periods have been studied in normal children and in children with the nephrotic syndrome. Inulin and thiosulfate volumes of distribution, plasma volume, electrolyte excretion, renal clearances and saturation were simultaneouly determined. Electrolyte balance studies were carried out in the days preceding, during, and following the load periods. Renal disability and associated edema render physiologic validity of such measurements of lesser value in the nephrotic than in the normal. Interpretation of the data is contingent upon this reservation.

The normal kidney responded to Na load by rapid excretion of that ion. An initially elevated excretion of K was rapidly curtailed. Excretion of sodium was achieved without significant increment per unit volume distribution in body water. In contrast, the nephrotic kidney responded to Na load by exaggerated K loss, with minimal extension of Na excretion. In some instances the data indicate tubular excretion of K. Na excretion was associated with marked increases of unit volume body water Na content. The pattern of urine flow and base excretion in response to load indicated a relative osmotic diuresis in both groups.

The excretion of K by the nephrotic was much greater than could be accounted for on the basis of contraction of extracellular K mass. Na retention was considerably greater than could be accounted for by observed weight change. Electrolyte balance studies were carried out in several patients with static edema. The pre and post load balances indicated that fluctuation in weight was more closely associated with K than Na balance. These observations suggested an unusual lability of intracellular K in the nephrotic syndrome.

Electrolyte Exchange Between Body Fluid Compartments During Recovery from Congestive Heart Failure. GEORGE E. MILLER, Buffalo, N. Y., (Introduced by Byron D. Bowen).

Metabolic balance studies of sodium, potassium, chloride and nitrogen have been carried out in eight patients recovering from cardiac decompensation. Changes in the chloride space, as determined from chloride balance and serum chloride concentration, have been used as a measure of the change in extracellular fluid compartment size. From the changes in chloride space, and the serum concentration of sodium and potassium, it is possible to calculate the changes in the absolute quantity of these cations in the extracellular fluid. With this information, together with the metabolic balance data, it is possible to derive the movements of sodium and potassium across the cell membrane.

External potassium balance, after being corrected for nitrogen balance, was positive in seven cases. The retained potassium was, however, in excess of that which could be accounted for in the extracellular fluid. This excess potassium must have crossed the cell membrane, resulting in a positive internal potassium balance.

The external sodium balance was negative in every instance. This loss of sodium was, however, quantitatively less than the amount of sodium which disappeared from the extracellular fluid compartment during the relief of edema. Thus the sodium unaccounted for by the external balance must have moved into cells, producing a positive internal balance.

The movement of sodium and potassium into cells during recovery from heart failure suggests that during the development of cardiac edema these ions are lost from the intracellular space. It is difficult to explain such a loss if the edema of congestive heart failure is a manifestation of primary sodium retention. In this situation sodium moves into cells and displaces potassium. One explanation for this finding is that cardiac edema represents a primary water retention with a dilution of extracellular osmotically active base which is then replaced from the intracellular store.

The Role of Adrenal Cortex in Alanine Metabolism. MAX MILLER,* BEECHER W. SITTERSON, HIRAM WOODWARD and JACK OWENS, Cleveland, Ohio.

The exact role of the adrenal cortex in protein metabolism is as yet unsettled. In particular it is not known whether the adrenal hormone affects the reaction linking proteins and amino acids, or the conversion of amino acids to non-nitrogenous products. The studies to be reported concern the metabolism of alanine in normal man, and in patients with altered adrenal function.

Four normal subjects, 3 patients with untreated Addison's disease and 1 patient with Cushing's disease, under basal conditions, were given intravenously one gram of d-l alanine (10 per cent solution) per kilogram in 60 minutes. Venous blood drawn before and after the infusion at 15–30-minute intervals for a period of 3 hours was analyzed for pyruvic acid, citric acid, glucose, and alanine. The amount of alanine excreted in the urine in a 12-hour period was determined. One patient with Addison's disease was restudied after treatment with desoxycorticosterone and also with adrenal cortical extract.

In normal subjects, blood pyruvate increased 26–47 per cent while citrate fell 29–64 per cent, compared with control levels. The response of the Addisonian patients fell within the same range. Administration of DOCA or ACE did not alter the response. Blood glucose changes were not consistent. In the patient with Cushing's disease similar changes were observed. Balance studies showed that 76, 77, and 76 per cent of the injected alanine in normals, Addison's and Cushing's disease, respectively,

was utilized in the 12-hour period. In the patient with adrenal insufficiency DOCA and ACE did not alter the balance.

It is evident that the interconversion of alanine to pyruvate, its effect on blood citrate, and the rate of disappearance of exogenous alanine in man at various levels of adrenal cortical function is essentially the same.

The Effect of Adrenocorticotropic Hormone and Cortisone on Antibody Production in Human Beings. GEORGE S. MIRICK,* Baltimore, Md.

The capacity of human beings to produce antibody while under treatment with ACTH and cortisone was tested. Twelve patients with asthma, lupus, rheumatoid arthritis, or related diseases were vaccinated on or near the day treatment was started with 1 cc. of a solution containing 0.06 mg. each of six pneumococcal polysaccharides (Squibb's Combination A). Eight of these patients then received ACTH and 4 received cortisone throughout the period of study. Serum was obtained before vaccination and treatment and at intervals of several days thereafter for several weeks. As controls 16 other patients with chronic diseases were similarly vaccinated and bled. All the sera were tested for antibodies against Pneumococcus Type II by agglutination and mouse protection techniques.

The results indicated that antibody was produced as promptly and in as high titer in patients receiving ACTH or cortisone as in controls. However, the degree of induced skin sensitivity to pneumococcus polysaccharide (Francis Test) was depressed in some patients during treatment.

The gamma globulin fraction of all the sera was measured by the turbidity method of Kunkel. No consistent variation from the basal level was noted in the sera of the control patients. However there was a consistent drop in this serum fraction in thirteen of fourteen patients during ACTH or cortisone treatment even though specific antibody against the pneumococcus was increasing at the time. The drop varied from 1 to 60 Kunkel units with an average fall of 12 units and was noted during treatment even in patients whose original values were within normal limits by this test. Titers of anti-blood group substance, typhoid agglutinins and C-reactive protein showed only slight and irregular fluctuations.

Enzymatic Characteristics of the Hemolytic Principle of Mumps Virus. HERBERT R. MORGAN,* Ann Arbor, Mich.

Mumps virus possesses the ability to produce hemolysis of erythrocytes of man, monkey, guinea-pig and chicken. This hemolytic action is prevented by the serum of patients convalescent from mumps. It can be clearly differentiated from the capacity of mumps virus to agglutinate erythrocytes and to elute therefrom. By treating the virus with a variety of physical and chemical agents such as heat, formaldehyde or ultra-violet light under certain conditions, the infectivity and the hemolytic activity of the virus were destroyed while leaving the hemagglutinating capacity intact.

In its (1) action on various substrates, (2) destruction by heat, (3) reversible inactivation by changes in hydrogen ion concentration, (4) maximum range of activity as related to time, temperature and pH, and (5) inhibition by certain substances such as calcium, the hemolytic principle of mumps virus has many of the characteristics of a relatively labile enzyme.

Further experiments indicate that this enzymatic action of mumps virus damages cells other than erythrocytes.

Studies on the Mechanisms of Saline Diuresis. RICHARD J. F. MURPHY, Durham, N. C., (Introduced by Julian M. Ruffin).

Water excretion by the kidney is regulated to a great degree by the posterior pituitary gland. In normal subjects, intravenous pitressin in doses of 1 milliunit per kilo causes a striking inhibition of water diuresis, the urine flow falling from an average of 15 cc. to 1 cc. or less per minute. The effect lasts about 40 to 50 minutes. Doubling or tripling the dose causes no further reduction in urine flow. There are no consistent effects on renal blood flow or filtration rate, and in these doses patients show no symptoms or signs other than the antidiuresis. The excretion of sodium and chloride is not changed in a consistent manner.

Normal subjects receiving 20–30 cc. per kilo of .85 per cent NaCl intravenously in from 25–40 minutes, have a good initial diuresis which is comparable to that caused by water. During this period, the urine contains from 25 to 40 meq. of sodium. The body is therefore losing more water than salt. After a variable interval, the urine output declines sharply and becomes fixed at a lower rate. The urine sodium concentration rises so that absolute excretion is unchanged. Intravenous injection of 1 milliunit per kilo of pitressin now has little or no further antidiuretic effect and NaCl excretion is not appreciably changed. Urine output at this time is 2 to 4 times that of those subjects receiving water and pitressin.

The injection of .85 per cent NaCl induces a water diuresis which is cut off after a variable amount of water is lost from the body. It is suggested that the initial diuresis is related to dilution of circulating pitressin and related renal tubular effects and the succeeding antidiuresis is related to stimulation of the osmoreceptors of the posterior pituitary by the retained salt.

The excretion of salt is controlled independently of the excretion of water.

The Hepatic Blood Flow in Laennec's Cirrhosis, with an Estimate of the Relative Contributions from Portal Vein and Hepatic Artery. J. D. MYERS,* Durham, N. C.

The total hepatic blood flow (HBF) in 15 patients with Laennec's cirrhosis has been found either normal or moderately reduced using the bromsulphalein technic. In the individuals with enlarged livers, the hepatic arterial–

venous oxygen difference varied inversely with the flow to provide, under fasting and resting conditions, normal splanchnic oxygen consumption (Sp. O_2). In some patients, particularly those with small cirrhotic livers, the oxygen difference, although increased, does not compensate for markedly reduced HBF, thus resulting in subnormal Sp. O_2. The hepatic venous–arterial glucose difference in cirrhosis is subnormal. This, together with the decreased HBF in some subjects, provides a subnormal mean net splanchnic glucose production.

The significance and validity of the above data would be enhanced by a separation of total HBF into its portal venous and hepatic arterial components. This would allow, particularly, correction of Sp. O_2 and net splanchnic glucose production to true *hepatic* oxygen consumption and *hepatic* glucose output. The administration of sodium sulfathiazole orally to 3 subjects with large, accessible portal venous collaterals about the umbilicus resulted in a high concentration of drug in portal collateral blood, the hepatic venous concentration being intermediate between this and arterial blood. The proportion of this distribution allows calculation of the ratio of portal venous to hepatic arterial circulation. In two patients with small cirrhotic livers, the portal venous flow comprised 75% or more of the total flow, whereas in a subject with an enlarged cirrhotic liver, the hepatic artery contributed 75%. The oxygen difference between arterial and portal collateral blood ranged from 1.0 to 2.3 vols.%, meaning that ¾ or more of the estimated Sp. O_2 is true hepatic oxygen consumption. The fasting arterial–portal collateral glucose difference was in all instances 2 mg.% or less, indicating that the calculated net splanchnic glucose output approached closely the real hepatic glucose production.

A Rational Interpretation of the Dilution Curves Obtained by the Dye Injection Method of Stewart and Hamilton for Cardiac Output. E. V. NEWMAN,* M. MERRELL, C. MONGE, W. P. MCKEEVER, W. R. MILNOR and A. GENECIN, Baltimore, Md.

The purposes of our studies are (1) to derive a theory which expresses the concentration change in the outflow fluid of a flow system such as the human heart and lungs after a single instantaneous injection of a known amount of an indicator substance such as T–1824, (2) to test the theory by comparison of dilution curves obtained from mechanical models in which the flow and the volumes of the compartments are known with theoretical curves and (3) to apply the theory to the analysis of dilution curves obtained on human subjects.

An equation was derived which expresses the variation of concentration with time as a function of the amount of dye injected, the rate of flow through the system, and the volumes of three chambers in series. The right heart, the lungs and the left heart are theoretically considered as the three separate successive volumes in which the dye is mixed and diluted.

The dilution curves obtained from a mechanical model are nearly identical with the theoretically derived curves. The equation gives the outflow fluid concentration as the algebraic sum of three exponentials whose rate constants are made up of known constants consisting of the volumes in the system, the amount of dye injected and the flow through the system.

Comparison of the theoretically derived and mechanically produced dilution curves with human curves shows close similarity. The relationship of the constants derived from human curves to the volume of blood in the heart and lungs is discussed. Our mathematical and mechanical models provide a basis for the interpretation of human dye dilution curves in terms of rational functions.

A device for rapid accurate collection of serial samples from flow systems has been constructed.

Alterations in Sodium Excretion, Glomerular Filtration and Cardiac Output in Normal Subjects. B. B. OLIVER, SEYMOUR EISENBERG, TOM LOMBARDO and WILLIAM VIAR, Dallas Texas, (Introduced by T. R. Harrison).

The findings may be summarized as follows:

Sitting position as compared to recumbent: marked decline in sodium excretion, no consistent change in glomerular filtration (creatinine clearance), moderate decline in cardiac output (electrokymograph).

Compression of the neck of sitting subjects: increase in sodium excretion, no change in glomerular filtration, no change in cardiac output.

Small venesection in sitting position: decline in sodium output, no change in glomerular filtration or cardiac output.

Small bleeding in sitting position with neck compressed: increased sodium output, no change in cardiac output or glomerular filtration.

Large venesection in recumbent position: marked decline of long duration in sodium excretion, slight transient decline in glomerular filtration, no change in cardiac output.

Digitalis: no change in sodium output, no change or transient decrease in glomerular filtration, decline in cardiac output.

The findings suggest that in healthy persons alterations in distribution and volume of body fluids are more important than alterations in cardiac output in regulating sodium excretion. They also indicate the predominant importance of tubular activity as compared to glomerular filtration.

The Effect of Concentrated Salt-Poor Human Albumin on the Excretion of Water and Electrolytes in Normal Dogs. JACK ORLOFF and WILLIAM D. BLAKE, New Haven, Conn., (Introduced by C. N. H. Long).

The intravenous administration of concentrated salt-poor human albumin results in a decrease in the urinary excretion of salt and water in normal man and a diuresis in edematous patients with hypoalbuminemia. It was believed originally that these phenomena could be more extensively explored in dogs. In strikng contrast to the findings in man however, the administration of concen-

trated salt-poor human albumin to both hydrated and hydropenic unanesthetized normal dogs resulted in an enhanced excretion of salt and water. Changes in plasma volume and in the concentration of total proteins did not differ from those previously observed in normal man. The rate of glomerular filtration was not altered significantly. It would appear that some function of the administered albumin results in a decreased reabsorption of water. Although no satisfactory explanation for these results is available from the experimental data, the danger of relating animal to human studies is apparent.

The Role of the Spleen in the Regulation of the Peripheral Blood Leukocyte Level. J. G. PALMER and ILEEN KEMP, Salt Lake City, Utah, (Introduced by M. M. Wintrobe).

It has been observed that splenectomy results in a significant and persistent elevation in the number of circulating leukocytes in human subjects. Whether this is the consequence of a decreased rate of destruction or an increased rate of leukopoiesis is not known. Experiments have been designed to investigate this problem in the rat.

Following removal of the spleen, the leukocyte count rises within 7 days to levels 50 to 100 per cent higher than the pre-operative count, and remains elevated for 70 to 90 days, after which it gradually returns to normal levels. Following control operations (partial omentectomy or unilateral nephrectomy) a leukocytosis of smaller magnitude occurs and normal values are achieved within 14 days. The rise in leukocytes is due to an increase of both granular and non-granular leukocytes. Removal of as much as 75 per cent of the spleen produces leukocyte changes similar to those seen following control operations rather than those following total splenectomy.

If the spleen is removed from one partner of parabiotic rats, no rise occurs in the white cell count of either animal. If the spleen is then removed from the other partner, leukocytosis develops in both animals and follows a curve similar to that of single splenectomized animals.

Leukopoiesis was retarded in rats by producing a deficiency of pteroylglutamic acid. Splenectomy in these animals produced no change in the white cell count.

These findings are discussed with respect to the possible role of the spleen in controlling the leukocyte count. Although the results are not conclusive, it is believed that they are more compatible with the hypothesis that the spleen inhibits production or delivery of leukocytes rather than that it acts by affecting the rate of removal of white cells from the circulation.

Studies of Renal and Hepatic Function in Normal Man During Thiopental, Cyclopropane and High Spinal Anesthesia. E. M. PAPPER, D. V. HABIF and S. E. BRADLEY,* New York, N. Y.

The cardiovascular stresses imposed by anesthesia and surgery evoke widespread circulatory readjustments. The renal (RBF–PAH clearance) and/or hepatic (EHBF–BSP method) blood flows were estimated in normal males before and during thiopental, cyclopropane, or high spinal anesthesia and subsequent surgical procedures in order to assess the role of the kidneys and liver in this process. Glomerular filtration rate (GFR–mannitol or inulin clearance) and renal excretion of water, sodium, potassium and chloride were also measured.

Cyclopropane and thiopental appeared to be equally effective in reducing EHBF (4 subjects) and RBF (12 subjects), apparently by inducing local vasoconstriction. High spinal anesthesia (nupercaine) did not alter EHBF (4 subjects) or RBF (5 subjects) except as a result of incidental arterial hypotension. Under these circumstances, flow in both the splanchnic bed and the kidneys appeared to fall to about the same extent as the arterial pressure. Changes in BSP removal and extraction were attributable in large part to the decrement in EHBF and in BSP loading rather than to hepatocellular dysfunction. Regardless of cause, the reduction in RBF was always associated with a fall in GFR in association with an elevation in filtration fraction. With few exceptions water and electrolyte excretion fell more than GFR. The urinary concentrations of sodium and chloride decreased markedly whereas the potassium concentration was usually unaffected. Subsequent surgical manipulation produced little or no further change.

Metabolic Effects of ACTH in Acute Leukemia. OLOF H. PEARSON and LEONARD P. ELIEL, New York, N. Y., (Introduced by Rulon W. Rawson).

A twenty-nine-year-old male physician with acute granulocytic leukemia received ACTH, 100 milligrams daily, for twenty-four days, which resulted in a temporary, clinical and hematological remission. Within forty-eight hours after starting ACTH, abdominal and generalized aching pains ceased, purpura in the skin and mucous membranes disappeared, a sense of well-being developed, and appetite increased. During the first week of therapy, enlarged lymph nodes shrank in size. Hematologic improvement was characterized by an initial, rapid fall in white blood count from 92,000 to 2,000 followed by a gradual rise to normal levels; a progressive increase in the number of mature, circulating leucocytes; a rise in reticulocytes followed by an increase in hemoglobin and red cell count; an increase in platelets; a decrease in immature myeloid cells in the bone marrow from ninety-seven to less than twenty per cent; and an increase in marrow normoblasts from 0.4 to 37.5 per cent.

During the first twelve days of ACTH, there was a markedly negative nitrogen, phosphorus and potassium balance. Losses reached a peak on the fourth day, amounting to −30 grams of nitrogen, −3.2 grams of phosphorus, and −80 milliequivalents of potassium. During the first six days, the phosphorus loss was greater than would be expected from the nitrogen and calcium balance, suggesting that tissue high in phosphorus content was being destroyed.

Hematological relapse occurred about one month after ACTH was stopped. Readministration of ACTH failed

to induce a second remission. The metabolic response during the second course of ACTH was of much less magnitude than during the first course. The disproportionate loss of phosphorus seen during the first course of ACTH was not observed during the second period of therapy.

Cortisone in Hypertensive Vascular Disease. GEORGE A. PERERA,* THOMAS C. FLEMING, KERMIT L. PINES and MARGARET CRYMBLE, New York, N. Y.

Previous short-term observations have indicated that cortisone administration may be associated with a decline in blood pressure in uncomplicated hypertensive patients. It seemed desirable to record the effects of increased dosage given for a longer period of time.

Clinical and metabolic studies were therefore undertaken in a woman with uncomplicated hypertensive vascular disease who received 200 mgs. of cortisone acetate (Merck) daily in divided doses for one month. Observations were made after an adequate baseline and on a constant regimen.

Among the manifestations noted during steroid therapy were insomnia, increased appetite, increased scalp hair loss, menstrual changes and delayed healing of a superficial pyogenic abscess. In the dosage employed, cortisone administration induced negligible fluid, electrolyte and carbohydrate changes, a marked negative nitrogen balance, a fall in serum potassium and cholesterol concentrations, transitory tyrosinuria, some increase in 17-ketosteroid and "corticoid" excretion, a decrease in renal plasma flow and a small decrease in cardiac output.

Cessation of therapy was associated with the temporary appearance of the signs and symptoms of hypoadrenalism. These included slight salt and water diuresis without significant change in plasma volume, a fall in serum sodium concentration, hypoglycemic shock and a delayed but striking sustained depression of 17-ketosteroid excretion.

Following a preliminary rise, there was a small but definite decline in "resting" blood pressure while the patient was receiving the steroid. This persisted for several weeks after the cortisone had been discontinued.

Cardiac Catheterization Following Acute Myocardial Infarction. WALTER H. PRITCHARD and H. K. HELLERSTEIN, Cleveland, Ohio, (Introduced by J. T. Wearn).

Cardiac output after acute myocardial infarction has been determined by auricular catheterization technique in eleven patients. In four, determinations were repeated after three weeks.

All patients withstood atrial catheterization uneventfully. Electrocardiograms taken continuously during the introduction of the catheter and at frequent intervals thereafter, showed no changes in cardiac mechanism or additional evidence of coronary insufficiency. Coronary pain had subsided and did not recur during the catheterization. None was critically ill at the time of catheterization and all are still living from 2 to 8 months following the study. Cardiac failure was absent.

Six determinations were carried out within the first ten days after infarction, and the remaining nine after 2 to 4 weeks. Outputs were done in duplicate or triplicate at each catheterization. Outputs, A–V oxygen differences, oxygen consumption, pulse rates and blood pressures maintained the same constancy during duplicate determinations as normal controls. Pulse rates ranged from 60 to 91 and the average blood pressure at the time of first catheterization was 102/70.

Data obtained reveal that as a group the cardiac indices are in the lower range of normal. Six patients studied within the first ten days after their infarctions, however, all showed reduced indices which averaged 2 L./min./m^2. Values for outputs in the 3rd and 4th weeks were slightly higher, falling in the lower range of expected normal.

Oxygen consumption and calculated values for cardiac work were also somewhat reduced, the latter reductions being caused by both low blood pressure and low output.

In four patients on whom early and late catheterizations were performed, there was no change in cardiac output during recovery in three, but in one a definite rise of 30 per cent occurred, and this rise was attributed to a larger stroke volume. In only two patients were arterial saturation values below 90 per cent.

There was no apparent correlation between the size of infarct as judged by electrocardiogram and the level of blood flow at the time of catheterization.

The Effect of Sodium Intake on the Action of ACTH in Uncomplicated Essential Hypertension. WILLIAM RANSOHOFF, ALBERT A. BRUST, WILLIAM N. CHAMBERS, ALVIN P. SHAPIRO, MORTON F. REISER, SAMUEL D. LOUBE, I. ARTHUR MIRSKY* and EUGENE B. FERRIS,* Cincinnati, Ohio.

A study was designed to determine the effect of sodium intake on the action of ACTH in uncomplicated essential hypertension. The patient selected was studied in each of five periods: (1) 4.2 grams sodium diet—5 days; (2) 0.2 grams sodium diet—17 days; (3) 0.2 grams sodium diet plus ACTH (100 mg./day)—9 days; (4) 4.2 grams sodium diet plus ACTH—6 days; (5) 4.2 grams sodium diet—12 days.

In period 1, control values were obtained for water and electrolyte intake, weight, blood pressure, tetraethylammonium chloride (TEAC) blood pressure "floor," blood volume, ballistocardiogram, electrocardiogram, total blood leukocytes, eosinophils, serum sodium and potassium, glucose tolerance, and urinary output of water, 17-ketosteroids, sugar, sodium, potassium, uric acid, and creatinine.

In period 2 (low salt), the TEAC "floor" fell, but the other values remained unchanged.

ACTH during low sodium intake (period 3) caused a slight increase in urinary 17-ketosteroids and glucose. The TEAC "floor" rose above control values, but the blood pressure remained unchanged. The left ventricular strain pattern (previously present) disappeared; the Q–T

interval became shorter. Total leukocytes remained normal; eosinophils fell to zero.

When sodium was added (period 4), "moon-face" and acne appeared abruptly and water was retained. As compared to period 3, stroke volume rose strikingly and left ventricular strain pattern reappeared. Urinary output of 17-ketosteroids and glucose increased markedly and leukocytosis appeared (21,000). The TEAC "floor" became further elevated; the blood pressure rose slightly. (This response of the TEAC "floor" to ACTH has been observed in two additional cases.)

In period 5, withdrawal of ACTH resulted temporarily in a marked negative sodium balance during which the TEAC "floor" fell to "desalt" levels.

These data suggest that many metabolic and physiologic effects of ACTH may be strikingly influenced by sodium intake. The height of the TEAC "floor" closely parallels the metabolic responses to ACTH.

Antibody Response after Hemolytic Streptococcal Respiratory Infection in Childhood. LOWELL A. RANTZ,* MARGARET MARONEY and JOSEPH DI CAPRIO, San Francisco, Calif.

Serial serum antistreptolysin "O" titers were obtained for several months following Group A hemolytic streptococcal respiratory infections in 80 infants and children. Three well defined patterns of antibody response were observed. In Group A, the mean age of the patients was approximately 12 months; the range from 2 months to 5 years. Antistreptolysin production by these individuals was feeble, the maximum titer attained being 12 units per ml. Definite infection was established in nearly every case by the presence of otitis media or rhinitis.

The mean age of Group B was about 2 years; the range from 8 months to 7 years. A well-defined antibody response occurred in each of these cases; the peaks being from 50 to 500 units per ml. An exceedingly rapid decline followed so that very low levels (12 units per ml.) were reached in 4 months or less.

Group C was composed of children with a mean age of 5 years; the extremes being 1 and 7 years. The antistreptolysin response in these individuals was vigorous and well sustained. Titers fell slowly and were often in the range of 100 to 200 units per ml. 6 months or more after the initial infection. The variations in antibody mechanics were not related to the administration of penicillin to approximately one-half of the patients in each group.

Evidence obtained from the study of multiple reinfections by Group A hemolytic streptococci in a small number of infants suggests that the changing patterns of antibody response with advancing age are not the result of maturation of the antibody forming organs, but of their conditioning by repeated streptococcal infections. These observations are of particular interest because children who develop rheumatic fever after hemolytic streptococcal infection regularly display an antistreptolysin response similar to that observed in Group C.

Plasma Proteolytic Activity in Pneumonia. OSCAR D. RATNOFF, Baltimore, Md., (Introduced by Palmer H. Futcher).

Despite considerable current interest in the fibrinolytic activity of plasma, little has been reported concerning changes in disease. In patients with pneumonia, dramatic changes occur in the plasma fibrinogen concentration. For this reason, such patients were studied for possible changes in fibrinolytic activity. Bloods were drawn daily in 12 patients with pneumonia. The concentration of fibrinogen, and both plasmin and plasmin-inhibitory activity of plasma were measured on each specimen, as well as the clot lysis time, the sedimentation rate, and gamma globulin by the method of Kunkel. Uniformly, in patients with pneumococcal and atypical pneumonia, the plasma fibrinogen was elevated in the acute phase and fell during convalescence. There was no correlation between the sedimentation rate and the plasma fibrinogen. The gamma globulin level rose at the end of the first week of the patient's illness. Spontaneous fibrinolytic activity, measured as the fibrinolysis time of recalcified plasma, was unduly long in some but not all of the patients. There was no correlation with the plasma fibrinogen level. Available plasmin activity was measured after activation with purified streptokinase, and proteolysis assayed by measuring caseinolysis turbidimetrically. By this technique, the plasmin level was either normal or slightly elevated when the fibrinogen level was at its peak. Plasmin rose during early convalescence, reaching a peak 2 to 5 days after the fibrinogen reached its highest level. It has previously been reported that plasmin-inhibitory activity of plasma is elevated in some patients with pneumonia. In the current study, the inhibitory activity, measured against bovine plasmin, rose above normal early in convalescence in most patients. The data presented suggest that the rise in plasma fibrinogen during pneumonia is not due to depressed available fibrinolytic activity. During convalescence from the pneumonia, plasmin, and to a lesser extent, plasmin-inhibitory activity, rise.

Comprehensive Analysis of Ventilatory and Circulatory Factors in Relation to Gas Exchange. RICHARD L. RILEY * and ANDRÉ COURNAND, New York, N. Y.

Using pCO_2 and pO_2 as coordinates, one can plot the alveolar respiratory quotient as a straight line passing through the inspired air point and the blood R.Q. as a curve passing through the mixed venous blood point (an extension of the Fenn diagram). The partial pressures of the following six values all fall on the gas or blood R.Q. lines: inspired air, expired air, 'effective' alveolar air, 'effective' capillary blood, arterial blood and mixed venous blood. These values divide the inspired air–mixed venous blood pO_2 gradient into five component parts, each of which is related to a specific ventilatory or circulatory factor in gas exchange. At a given rate of oxygen intake, the inspired air–expired air pO_2 gradient is inversely proportional to the minute volume of

ventilation; the expired air–'effective' alveolar air gradient is related to the proportion of tidal air distributed to areas which are non-perfused (dead space) or poorly perfused with blood; the 'effective' alveolar–'effective' capillary gradient is related to the diffusion coefficient of the lung; the 'effective' capillary–arterial blood gradient is related to the proportion of blood flow distributed to poorly ventilated or non-ventilated areas; and the arteriovenous gradient is inversely related to the cardiac output. Technics for determining the respective gradients and defining the corresponding physiological factors require that the composition of inspired air, expired air, arterial blood and mixed venous blood be known at two different levels of oxygenation, brought about by breathing different concentrations of oxygen in the inspired air. Results of such analyses of pulmonary gas exchange are shown for patients with pneumonectomy, silicosis and emphysema, and the pathological implications are discussed.

The Effect of Poliomyelitis Virus upon Cells in Tissue Cultures. F. C. ROBBINS, J. F. ENDERS, and T. H. WELLER, Boston, Mass., (Introduced by Charles A. Janeway).

The murine adapted Lansing strain of poliomyelitis virus can be propagated in suspended cell cultures of various human embryonic tissues. Recently we reported the growth of the Brunhilde virus, a non-murine adapted strain, under similar conditions as well as cultivation of both strains in cultures of human foreskin. The Lansing strain has been maintained in cultures of human embryonic skin, muscle, brain, and intestine for 7½ months and in foreskin for 112 days.

The poliomyelitis viruses appear to injure the human embryonic tissues in which they are propagated. This effect is indicated by (1) histologic changes, (2) reduced metabolism, and (3) inhibition of ability of the cells to multiply or migrate.

Histologic changes consist of necrosis with no apparent selection as to cell type. They can be distinguished only by comparison of preparations from infected tissues with those from comparable control tissues.

The reduced metabolism of the infected tissue is indicated by its impaired capacity, as compared with non-infected tissue, to lower the reaction of the culture medium. This phenomenon becomes apparent only after 12 to 20 days of contact with the virus.

The inhibiting effect of virus upon growth of infected cells is demonstrated by explanting fragments of tissue into hanging drop preparations of clotted chicken plasma and chick embryo extract. In such preparations fragments of human embryonic skin and muscle uniformly show outgrowth of cells even after 20 days or more of cultivation in flasks. Outgrowth from infected fragments on the other hand is markedly impaired or fails to occur when the tissue has been maintained in flask cultures from 8 to 20 days.

Specific immune serum can check temporarily the cytopathogenic effect of the Lansing virus.

Application of these findings to further study of poliomyelitis is discussed.

Influence of ACTH on the Excretion of Histamine and Histidine in Patients with Allergic States or Rheumatoid Arthritis. BRAM ROSE,* J. A. P. PARE, K. PUMP, R. STANFORD and L. G. JOHNSON, Montreal, Can.

Histamine metabolism in the rat is related to Adrenal Cortical function, in that removal of the adrenal gland results in a marked increase in the tissue Histamine of this species. Studies were made therefore on the Histamine and Histidine excretion in urine on a series of fifteen cases of allergy, mainly asthma, and five cases of Rheumatoid Arthritis before, during and after the administration of ACTH.

In all of the cases but two an increase in Urine Histidine occurred within 24 hours of the administration of ACTH, the values reaching those observed during pregnancy. Withdrawal of ACTH was followed by a prompt return to normal values.

The changes in the amount of Histamine excreted in the urine were quite unusual in the cases of Asthma. In most a moderate to marked increase occurred following administration of ACTH, with a return to normal as symptoms subsided. From 4 to 7 mgms. per 24 hrs. were excreted during ACTH therapy as compared to 0.5 to 0.7 mgms. prior to treatment. In two cases, amounts equal to 200 mgms. were excreted during ACTH administration. There was little or no change in the Histamine excretion in the urine of four of the cases of Rheumatoid Arthritis. In a fifth a moderate rise was observed. The material in the urine was extracted and assayed on the isolated guinea pig ileum. It behaved pharmacologically like Histamine in all respects. Attempts are being made to isolate it as the dipicrate.

These studies are part of a detailed survey including steroid, electrolyte, and nitrogen and vitamin balance and will be discussed in relation to the Histamine content of human tissue in normal and allergic subjects.

The Dependence of Water Diuresis upon Electrolyte Excretion. JACK D. ROSENBAUM, WILLIAM P. NELSON, III and MAURICE B. STRAUSS,* Framingham, Mass.

When normal subjects are given 20 ml. of water per minute orally, diuresis commences within an hour and reaches a peak rate within the second hour. This peak rate exhibits wide variations. When the previous intake of sodium chloride has been low, it may not rise above 6 ml. per minute in spite of the fact that large water balances are accumulating in the body, manifested by decreases of as much as 10 per cent in hematocrit, serum protein and electrolyte concentrations. With a moderate sodium chloride intake preceding the experimental observations, peak diuretic rates twice as great are found. With excessive sodium chloride ingestion on the preceding day, peak rates of over 18 ml. per minute have been observed. In no case has the peak rate been maintained for more than a few hours except by measures which maintain electrolyte excretion.

Urinary excretion of electrolyte in normal man is suppressed during the night and rises sharply in the morning, then falling off slowly. This occurs regardless of whether the subject has been on a low, normal, or high salt intake previously. The mechanism of this diurnal variation is not apparent. If, however, excessive water ingestion is begun in the morning when sodium chloride excretion is high, larger peak rates obtain than if the experiments are begun later in the day when sodium chloride excretion is lower.

Contrary to reports of a dehydrating effect of continuously administered water, our observations indicate that large positive balances occur with resulting hypotonicity of body water.

These observations suggest that, under the given experimental conditions, the rate of water diuresis depends on the amount of electrolyte being excreted.

The Blood Volume in Congestive Heart Failure. JOSEPH F. ROSS,* WILLIAM H. BAKER and EDWARD D. FREIS, Boston, Mass.

Several theories of the pathogenesis of congestive heart failure are based on the assumption that the blood volume is greatly increased in this condition. Support has been given to this assumption by reports that the blood volume as measured by the dye dilution method is greatly increased in congestive heart failure. Serious objections may be brought against the validity of the dye dilution techniques in such patients.

We have performed blood volume determinations on patients with congestive heart failure and on controls using a radioactive phosphorus tagged red blood cell method as well as the T-1824 dye plasma volume method.

Our studies indicate that there is no significant increase in the circulating blood volume in patients with congestive heart failure over controls as determined with the tagged cell method.

These observations suggest that the pathogenesis of congestive heart failure is not dependent on an increase in circulating blood volume. The significance of these findings will be discussed.

The Practical Application of a Hemagglutination Reaction in Pulmonary Tuberculosis. SIDNEY ROTHBARD,* ALFRED S. DOONEIEF and K. EILEEN HITE, New York, N. Y.

To ascertain the value of the specific agglutination of sheep or homologous human erythrocytes sensitized with an extract of tubercle bacilli or old tuberculin (Lederle) in the diagnosis of tuberculosis, 580 samples of sera from 421 normal adults and patients were tested.

From 110 normal adults, the sera of 105 contained no antibodies for the agglutination of the sensitized erythrocytes; 3 had titres of 1–2; and 2 of 1–4. From 111 patients with bronchiectasis, lung abscess, bronchiogenic neoplasms, metastatic lung cancer, Hodgkin's disease, Boeck's sarcoid, silicosis, primary atypical pneumonia, syphilis, or pulmonary infarction, the sera of 107 contained no antibodies; sera from 3 patients with syphilis had titres of 1–2; and serum from one patient with primary atypical pneumonia had a titre of 1–4.

Of 309 serial samples of sera from 151 patients with active pulmonary tuberculosis, antibodies were found in 284 sera from 138 patients or in 92 per cent. The titres ranged between 1–8 and 1–512 with a mean of 1–32. Sera from patients with exudative, pneumonic infiltrates or hematogenous spreads contained the highest titres. In 10 patients hemagglutinating antibodies gradually disappeared with the subsidence of disease activity and absence of tubercle bacilli from sputa or gastric secretions.

Of the sera from 50 patients with apparently arrested disease, 25 showed no antibodies; whereas, in the remaining 25, antibodies were noted in titres of 1–8 or higher. From 12 of these latter 25 patients subsequent bacteriological studies revealed tubercle bacilli indicating active disease although the lesions on roentgenogram remained stable.

This hemagglutination reaction described by Middlebrook and Dubos appears to be highly specific for tuberculosis and reveals no significant heterologous reactions in sera from patients with other common pulmonary diseases. Unlike the tuberculin test, this technique apparently indicates the presence of active pulmonary tuberculosis.

Relation of Plasma Cell Growth to Abnormal Serum Protein Components and Bence Jones Proteinuria in Multiple Myeloma. R. W. RUNDLES, M. L. DILLON, EDITH S. DILLON and G. R. COOPER, Durham, N. C., (Introduced by D. T. Smith).

The relationship of plasma cell proliferation to the abnormal serum proteins and to Bence Jones proteinuria in multiple myeloma has been studied during urethane therapy. The administration of 90–300 gm. of urethane in 6–10 weeks reduces in most patients the percentage of abnormal plasma cells in the marrow and produces morphologic changes indicative of arrested or retarded growth.

Sixty electrophoretic analyses of the serum proteins were made in 11 patients followed 3–28 months. Six patients had tall, sharp peaks of gamma protein. Three had virtually normal patterns 2–4 months after therapy. Slight homogeneity remained in the gamma globulin. In a fourth patient gamma protein was reduced 50 per cent. In two there was no change in serum proteins or in plasma cells. One patient with a virtually normal serum protein pattern initially developed an "M" peak during an exacerbation of his disease 17 months later.

One patient with a large protein increment with mobility intermediate between gamma and beta globulin obtained a partial remission during the first treatment period but relapsed after 3 months. Urethane was then given continuously, 1275 gm. in 14 months, during which he relapsed. After urethane was discontinued Bence Jones protein in the urine declined from an average of 17–19 gm. per day to 0.25–0.4 gm., serum protein with

the mobility of the abnormal component fell from 2.35 gm. to 1.0 gm. per 100 cc., and the hemoglobin which had fallen below 6.0 gm. per 100 cc. was again maintained at normal levels.

As plasma cell growth is inhibited by urethane in multiple myeloma, abnormal serum protein components, even those generally found not to represent Bence Jones proteinemia, are reduced or may virtually disappear. This change parallels the reduction or disappearance of Bence Jones proteinuria. During prolonged continuous administration of urethane myeloma cells may become dependent on the chemical.

Antistreptolysin "O" in Urine and Serum of Patients with the Nephrotic Syndrome. DAVID A. RYTAND,* LOWELL A. RANTZ * and ELIZABETH RANDALL, San Francisco, Calif.

The titer of antistreptolysin "O" (AST) was determined on 29 occasions in the urine of 20 patients with the nephrotic syndrome (titration in a 10 per cent solution of urinary proteins in saline after dialysis and lyophilization). Rates of AST excretion varied from 27 to 11,500 units per 24 hours.

In all of the 10 patients whose rates of AST excretion were under 800 units per 24 hours, serum AST was only 12 units (or less) per ml. This group included 5 of the 6 children studied. In those excreting more than 800 units daily, serum AST levels ranged from less than 12 up to 166 units per ml. AST clearances varied between 2.7 and 790 ml. per 24 hours; in general, patients with greater clearances had higher spontaneous rates of proteinuria as well as more AST per gram of urinary protein, and were older but did not show high serum AST titers.

The results may be considered not only from the standpoint of pathological physiology of proteinuria, but also in relation to the typically very low serum AST titers of the nephrotic syndrome. In some patients, especially adults, AST excretion appears adequate to reduce serum titers. In others, particularly children, AST excretion seems too little to account for the low serum titers.

Management of Respiratory Center Failure in Bulbar Poliomyelitis with Electrophrenic Respiration. S. J. SARNOFF, J. L. WHITTENBERGER, J. V. MALONEY, JR., B. G. FERRIS, JR. and L. C. SARNOFF, Boston, Mass., (Introduced by Fredrick J. Stare).

The reflex central suppression of spontaneous breathing observed during electrophrenic respiration in normal man led to investigations aimed at finding whether the respiratory "fibrillation" of bulbar poliomyelitis could be similarly suppressed. Nine patients were studied who exhibited moderate to severe respiratory irregularities due to bulbar poliomyelitis. In all cases electrophrenic respiration promptly suppressed the chaotic respiratory movements and produced regular effective ventilation. In one patient a grossly irregular spontaneous breathing pattern was converted to a more regular pattern following one hour of electrophrenic respiration, thus facilitating the subsequent control of respiration by the tank respirator. Hypertension, whenever present in this group of patients, was promptly alleviated following the application of electrophrenic respiration. A striking sedative effect on restlessness was also observed when adequate ventilation was supplied by this method. Three instances of spontaneous hypoventilation (without respiratory irregularities) due to bulbar involvement will also be presented.

Involvement of the Left Ventricle is of Primary Importance in Constrictive Pericarditis. C. GLENN SAWYER, Boston, Mass., (Introduced by C. Sidney Burwell).

Six patients with constrictive pericarditis have been studied by means of the cardiac catheter. Previous studies showing low stroke and cardiac outputs in such patients have been confirmed. New observations concerning the relationships of the pulmonary "capillary" mean, the pulmonary artery diastolic, the right ventricular end diastolic, the right auricular mean, and the peripheral venous pressures have been made. These pressures have been not only elevated, but have also shown in any individual patient a strikingly similar degree of elevation.

These findings are interpreted as showing that the right ventricle is accomplishing little work, that the pulmonary congestion in constrictive pericarditis has been underestimated in the past and, most important, that involvement of the left ventricle by the constricting scar is the primary problem in this disorder.

The significance of these observations in regard to clinical diagnosis is discussed, and the importance of left ventricular decortication by the surgeon is emphasized.

Cerebral Metabolism in Pernicious Anemia. PERITZ SCHEINBERG, Durham, N. C., (Introduced by E. A. Stead, Jr.).

Mental dysfunction in pernicious anemia is not so commonly recognized clinically as are the signs of spinal cord and peripheral nerve involvement. Measurement of cerebral blood flow and metabolism by the nitrous oxide method in 27 observations on 15 patients with proven pernicious anemia indicate that defects in cerebral metabolism are much more pronounced than had been expected from clinical observations. Seven of the patients were restudied one to four times during specific therapy.

Despite the anemia, the mean cerebral blood flow was not significantly increased above normal, although the patient's with the most severe anemias showed the fastest flows. The arterial-cerebral venous oxygen and glucose differences were reduced 29 and 24 per cent respectively; cerebral oxygen and glucose consumption were reduced 37 and 34 per cent respectively. Cerebral venous oxygen tension was reduced 32 per cent. The mean cerebral vascular resistance was normal.

There was no correlation between the degree of anemia and the decrease in cerebral oxygen and glucose con-

sumption; three patients without anemia, but with mental status and neurological defects, showed very low values for cerebral oxygen and glucose consumption. There was a rough correlation between mental status and cerebral oxygen consumption. Of the seven patients restudied after therapy, five showed increases in cerebral oxygen consumption, but none approached normal.

Four patients with anemia due to relatively acute blood loss showed normal values for cerebral oxygen consumption, by virtue of striking increases in cerebral blood flow.

These data indicate that pernicious anemia produces alterations in cerebral metabolism which may not be completely reverted by treatment and hematological remission. By some unknown mechanism, cerebral oxygen consumption in this disease may be reduced to one-third its normal value and the patient maintain relatively normal activities. The mental dysfunction in pernicious anemia may be accounted for by the decreased cerebral metabolism.

Pherentasin: A Pressor Substance Present in Arterial Hypertension. HENRY A. SCHROEDER* and NORMAN S. OLSEN, St. Louis, Mo.

Further studies have defined the humoral pressor substance present in hypertensive arterial blood to include the type of case in which it exists, its concentration and its probable nature. It has been named "pherentasin" (Greek phero = hold up, entasis = pressure). Elevation of the blood pressure of rats with renal hypertension for 15 to 30 minutes or longer occurs after intravenous injection of about 0.2 γ; prolonged potentiation of the action of epinephrine on the vessels of the rat's mesoappendix occurs after intravenous injection of 0.02 γ or less. Pherentasin is a water, alcohol and chloroform soluble substance recoverable in concentrations of 10 to 20 γ per liter of blood; it is somewhat unstable, nonprotein, and amine-like. It differs from known pressor agents. Pherentasin has been detected in the blood of 31 of 33 patients with "nephrogenic" hypertension ("fixed" diastolic pressure, slight diminution of renal function; organic renal parenchymal disease). In "malignant" hypertension it was present in only 5 of 18 cases and was not found in nitrogen retention. Smaller amounts were found in neurogenic hypertension (fluctuating blood pressure, little or no evidence of renal damage, good response to vasodilatation procedures); the rat pressor assay was positive in only 11 of 47 samples although by the mesoappendix test it was detected in 12 of 15. Of 14 with "endocrine" hypertension (central obesity, menstrual disturbances, low sweat sodium levels) only one was positive. Two of 26 normotensive individuals had pressor or vasoactive substance; both suffered from infectious mononucleosis. Chemical fractionation showed excellent agreement with both biological assay methods, the material being readily purified. It is concluded that this highly active pressor substance appears in the blood in most types of hypertension, increases in amount as nephrosclerosis develops, often disappears in the malignant stage, and does not usually accompany one specially defined hypertensive syndrome.

Observations on Electrolyte Balance During Mercurial Diuresis in Congestive Heart Failure. WILLIAM B. SCHWARTZ and WILLIAM M. WALLACE, Boston, Mass., (Introduced by Samuel A. Levine).

Extended balance studies were carried out on six patients with congestive heart failure in an attempt to relate the changes of electrolyte concentration in extracellular fluid [ECF] to the extent of their removal during mercurial diuresis. In all but one patient ECF chloride concentration [Cl] was reduced, bicarbonate concentration [HCO_3] was increased, and sodium concentration [Na] remained essentially unchanged. Concurrently, Na and Cl were lost in the urine in a proportion that approached the reverse of that found in the ECF, that is, there was a greater negative balance of Cl than Na. K was often present in the urine in amounts larger than accounted for by the edema fluid removed, and cumulative deficit of K occasionally developed. Usually following two to three daily mercurial diureses the patients became hypochloremic, alkalotic and refractory to further administration of the drug. Often urinary loss of Cl adequately explained the fall of ECF [Cl]. In many cases, however, reduction of [Cl] was less than would be defined by balance measurements. If no Cl shift occurred, the data indicated a transfer of Na to the intracellular compartment. Concurrent negative balance of K presumably represented reciprocal loss of intracellular cation.

Administration of NH_4Cl to the chloride-depleted, refractory patient resulted in Cl retention, restoration of ECF [Cl] and reduction of [HCO_3]. If Na shift had previously occurred, Na returned to the ECF and there was simultaneous K retention. The earlier sequence of events was thus reversed and the patient again responded to the diuretic until hypochloremia and alkalosis reappeared.

These effects of mercurial diuretics did not occur invariably. In one patient balance data showed losses of electrolyte and water comparable with ECF composition. Prolonged administration produced a continued diuretic response without changes in ECF electrolyte concentrations and without the appearance of a refractory phase.

Interactions Between Gluco-Corticoid and Mineralo-Corticoid Hormones. HANS SELYE,* Montreal, Can.

Mineralo-corticoids such as desoxycorticosterone acetate (DCA) and Reichstein's compound "S" (desoxocortisone) cause hypertension, nephrosclerosis, myocarditis, periarteritis nodosa and other lesions characterized by hyalin degeneration of mesenchymal tissues ("diffuse collagen disease"). Essentially similar changes have been obtained by *lyophilized anterior-pituitary tissue* (LAP) or crude alkaline anterior-lobe extracts, which produce a predominantly "mineralo-corticotrophic" response.

The same corticoids and pituitary extracts also tend to aggravate the course of an experimental arthritis (produced by injection of formalin or mustard into the joint region) and of certain anaphylactoid reactions (e.g., that produced by intraperitoneal egg-white injection) in the rat.

On the other hand, a *gluco-corticoid* compound, cortisone, and the predominantly "gluco-corticotrophic" purified *ACTH*, tend to antagonize many of the above mentioned effects of mineralo-corticoids and LAP. Thus in the rat, cortisone prevents the development of mesenteric periarteritis nodosa by DCA; it even cures vessel lesions (despite concurrent DCA intoxication) after they have fully developed due to pretreatment with DCA. Furthermore, cortisone and purified ACTH inhibit the above-mentioned experimental arthritic and anaphylactoid responses. The increase in erythrocyte sedimentation rate produced by DCA is completely counteracted by cortisone in the rat.

Conversely, the renal damage caused by mineralo-corticoids is actually aggravated by cortisone. Combined treatment with the two hormones causes hyalinization of the glomerular capillaries and eventually acute glomerulo-nephritis. In large doses even cortisone alone induces similar changes especially in rats sensitized by unilateral nephrectomy and a high-Na diet.

While mineralo-corticoids cause hepatic and splenic enlargement with little or no thymico-lymphatic involution, glucocorticoids produce marked involution of the liver and of all lymphatic organs.

Adaptation can be acquired to cortisone.

The interactions between gluco- and mineralo-corticoids will be discussed in connection with the pathogenesis and causal therapy of the "diseases of adaptation".

Studies on the Mechanisms of Some Anemias with Biologically Tagged Erythrocytes. RAYMOND F. SHEETS and HENRY E. HAMILTON, Iowa City, Iowa, (Introduced by Elmer L. DeGowin).

Transfusion and differential agglutination provided information concerning physiologic mechanisms of anemias resulting wholly or in part from the shortened life span of erythrocytes. From the data these anemias may be classified as (1) those with cellular defects, either congenital or acquired, and (2) those due to extracellular mechanisms.

A rectilinear survival curve means that each cell has the same life span. The life span of normal erythrocytes is approximately 120 days. When the life span is shortened and the disappearance curve is rectilinear, it indicates that a cellular defect has uniformly shortened the survival. An exponential survival curve results when an extracellular destructive force removes the erythrocytes from the circulation at random irrespective of their ages.

Examples: *Cellular, normal.* The disappearance curve of normal cells in a normal recipient is rectilinear and the life span is about 120 days. *Cellular, congenital.* The survival curve of Cooley's trait cells in a normal recipient was rectilinear and the life span was 90 days. *Cellular, acquired.* The survival curve of erythrocytes from a patient with plumbism in a normal recipient was curvilinear and the life span was 85 days. The concept that a curvilinear disappearance curve may be associated with a cellular defect has not been previously recognized. *Extracellular.* An exponential survival curve was obtained when normal erythrocytes were transfused to a patient with an anemia associated with lymphatic leukemia. In a patient with hypersplenism a curvilinear survival curve with a life span of 85 days was found.

All studies were controlled by cross transfusion, by using erythrocytes for transfusion previously proved normal, and in the case of hypersplenism, by obtaining a normal curve after splenectomy.

These studies of the mechanisms of blood destruction cause question of the utility of the term "hemolytic anemia."

The Relation of Bone Marrow Metastases to the Anemia of Cancer Patients. SHU CHU SHEN and FREDDY HOMBURGER, Boston, Mass., (Introduced by Henry Jackson, Jr.).

Morphological studies of peripheral blood and bone marrow were made in 194 patients with advanced cancer. Sixty per cent were considered to be anemic because the hemoglobin was 80 per cent or below. In these 117 anemic patients, the hemoglobin was 70–80 per cent in 51, 55–69 per cent in 43, and 38–54 per cent in 33.

Of the 194 patients, 30.5 per cent had X-ray evidence of metastases to bone. Of those with metastases, 44 per cent were not anemic; 56 per cent were anemic, of whom only 6 per cent gave evidence of blood loss, none of hemolysis.

Cobaltous chloride, 120-240 mg. daily, was given orally to 7 anemic cancer patients with metastases to bone. Three of these patients had previously failed to respond to prolonged therapy with iron and crude liver extract. In all 7 patients following cobalt therapy, a significant increase in reticulocytes appeared between the fifth and tenth days. Thereafter, in 3 patients, the early types of red cells in the bone marrow increased and a gradual rise in hemoglobin to over 80 per cent together with a corresponding increase in erythrocyte levels took place. In 1 of the 7 patients, only a moderate, and in one other, no increase in hemoglobin took place. Two patients died too soon for elevation of the hemoglobin to have occurred.

Four additional anemic patients without metastases to bone showed definite reticulocyte responses, increases in red cells, hemoglobin, and hematocrit following cobalt therapy. In 3 of these patients, vigorous therapy with crude liver extract and iron had previously failed to elevate the blood values.

These results indicate that metastases to bone marrow do not often play an important role in the anemia of patients with cancer and that with or without metastases cobalt therapy may increase erythropoiesis.

The Enzymatic Degradation of Nucleic Acids in Purulent Exudates by Streptodornase. SOL SHERRY* and JOHN P. GOELLER, New York, N. Y.

It has been shown that the purulent exudates of patients contain large amounts of fibrous and viscous desoxyribosenucleoprotein (DNA protein) and that the local injection of streptococcal enzyme concentrates into the sites of purulent exudation produces a rapid depolymerization of the DNA protein in association with the rapid clinical improvement of patients.

In vitro studies of the rate and extent of the enzymatic degradation of purified DNA by extracellular streptococcal enzymes have been made. The results indicate the presence of a series of streptococcal desoxyribonucleases (Streptodornase) which first depolymerize and render the products acid soluble, then successively split the complex nucleotides to free purine bases (adenine and guanine) and pyrimidine nucleosides (cytidine and thymidine). A group of ribonucleases have also been identified which extensively degrade ribonucleic acid (RNA) beyond the mononucleotide stage. The end products of the RNA degradation have been found to differ qualitatively from those of DNA degradation. Hemolytic streptococci appear to produce a series of enzymes capable of action at different stages in the breakdown of DNA and RNA. These results are visually demonstrable by a new modification involving ultraviolet photography of paper chromatograms.

The localization of DNA substrate in purulent exudates of patients has been demonstrated as both extracellularly and intracellularly. The intracellular DNA protein appears in the nuclei of living and degenerating leukocytes. The extracellular DNA protein exists in an insoluble form in the sediment, and in a soluble form in the supernatant and is derived from the degeneration of the cellular elements. Studies have been made of the sites and extent of enzymatic degradation of DNA in purulent exudates in patients receiving local streptodornase injections.

Studies are in progress to define the sites of RNA localization in purulent exudates and their possible clinical significance.

Estimation of Plasmin Activity by Radioactive Measurement. N. RAPHAEL SHULMAN and H. J. TAGNON,* New York, N. Y.

The proteolytic enzyme, plasmin, is occasionally found in the plasma of patients with a variety of pathological conditions. Its presence is detected by observing the dissolution of the clot of fibrin (fibrinolysis) formed by coagulation of blood. Methods based on time of fibrinolysis are unsuitable for detecting quantities of plasmin insufficient to produce complete lysis of the clot, and there is reason to believe that plasmin as it appears in the blood clinically is frequently not detected because of this.

A more sensitive method was developed to permit quantitation of amounts of plasmin too small to completely dissolve a fibrin clot. The method consists essentially of using fibrin tagged with radioactive iodine as a substrate for plasmin and relating radioactivity in the non-clottable protein fraction to proteolytic activity. It was found that increasing amounts of plasmin produced increasing amounts of radioactivity in the supernate of the substrate. Using crystalline trypsin for comparison it was found possible to measure accurately plasmin activity in the order of 73×10^{-9} hemoglobin trypsin units.

An important factor in the sensitivity of the method is the use of radioactivity for measurement. The blank value depends only on the substrate, whereas, the blank of other methods (e.g. the tyrosine method) is so high when serum is used as a source of plasmin that changes due to small amounts of enzyme activity become comparatively insignificant. The determination of plasmin activity by this method is simple procedure that lends itself to routine use. The iodinated fibrinogen is easily prepared and is stable in the cold for over 6 weeks.

Normal human serum was shown to have no plasmin activity by this method. Results obtained with abnormal sera will be reported.

Asymptomatic Hyponatremia in Pulmonary Tuberculosis. E. A. H. SIMS, L. G. WELT, J. ORLOFF and J. W. NEEDHAM, New Haven, Conn., (Introduced by John P. Peters).

Ten patients with hyponatremia and pulmonary tuberculosis were studied. No frank evidence of renal or adrenal disease was demonstrated. These patients had advanced pulmonary disease, malnutrition and debility. They excreted 40 to 90 m.Eq. of sodium per day despite subnormal concentrations of sodium in the serum ranging from 123.7 to 130.7 m.Eq./L. Five patients excreted as little as 5 to 29 m.Eq. of sodium per day when the dietary salt was severely restricted. These patients did not present the clinical signs, symptoms, or other evidences of sodium depletion. There was no dehydration, peripheral circulatory failure, azotemia, or reduction of renal clearance. Calculations from data obtained during acute balance periods following the intravenous administration of salt supported the hypothesis that these patients did not have a contracted body water. The concentration of sodium in the serum remained in the subnormal or low normal range despite high daily intakes of salt. With clinical improvement this syndrome was reversed in two patients. Desoxycorticosterone produced a retention of sodium in four patients. Adrenal cortical extract did not promote retention of salt. Six patients had an essentially normal eosinopenic response to epinephrine. The six patients who were autopsied had normal adrenal glands.

The Levy-Power-Kepler test for adrenal insufficiency was invariably positive for part I and was positive in one instance for part II. A normal eosinopenic response to epinephrine and the excretion of an almost sodium-free urine with rigid salt restriction aid in differentiating this syndrome from Addison's disease.

It is suggested that a primary reduction in cellular osmolarity may be the initiating factor in the develop-

ment of this syndrome. The increased excretion of sodium at subnormal concentrations of this ion in the serum might represent an attempt to reduce extracellular tonicity to conform with a reduced cellular osmolarity.

Study of Human Serum Based on Analysis of Fractions Obtained in the Quantity Ultracentrifuge. J. R. SNAVELY, W. H. GOLDWATER, M. L. RANDOLPH, C. C. SPRAGUE and W. G. UNGLAUB, New Orleans, La., (Introduced by R. H. Turner).

Undiluted normal human serum which had been centrifuged at 800 revolutions per second for 4 hours was sampled for chemical analysis at 10 tube levels.

Outstanding features of the results of analyses for total protein and lipids are as follows: Total protein concentration (microkjeldahl) increased progressively from top to bottom. Albumin also increased toward the bottom but tended to level off in the deepest strata where globulin increment was maximal. Neutral fat, and with it a small but rather constant proportion of free and ester cholesterol and lipid phosphorus, was concentrated at the very top, and in a zone about half way down a large accumulation of cholesterol and lipid phosphorus was consistently observed.

Ultramicroscopy of top samples showed them rich in lipomicrons, and electrophoresis of the mid zone rich in cholesterol and lipid phosphorus showed the presence of albumin and beta globulin. In the lower part of the tube the ratio of concentrations of total cholesterol to lipid phosphorus was significantly lower than it was in the regions where lipid concentrations were high.

These and similar data suggested that this technic effected distribution of serum particles into three categories: (1) the heavy proteins, which moved only downward, (2) lipomicrons, which moved only upward, and (3) particles of intermediate density, which moved downward in the low density medium produced by sedimentation of heavy proteins, and upward in the high density medium near the bottom.

The Relation of the Cerebral O_2 Consumption to the Total Body Metabolism in Hyperthyroidism. LOUIS SOKOLOFF, RICHARD L. WECHSLER, KENT BALLS and SEYMOUR KETY,* Philadelphia, Pa.

It is generally accepted, though without adequate in vivo evidence, that the metabolism of all tissues is increased in hyperthyroidism. Studies of cerebral O_2 consumption by means of the nitrous oxide method were, therefore, made upon 9 hyperthyroid patients, to determine whether cerebral O_2 consumption increased in proportion to total body O_2 consumption in this disease. The diagnosis of hyperthyroidism was established on the basis of clinical manifestations, B.M.R., the up-take of radio-active iodine by the thyroid gland, and the level of protein bound iodine in the serum. The B.M.R. was determined for each patient following the cerebral study; these varied from + 30 per cent to + 88 per cent.

The mean values obtained for cerebral blood flow (65 cc./100 gms./min.), cerebral vascular resistance (1.8 mm. Hg/cc./100 gms./min.), and cerebral O_2 consumption (3.4 cc./100 gms./min.) did not differ significantly on statistical analysis from the mean values (54 cc./100 gms./min., 1.6 mm. Hg/cc./100 gms./min., and 3.3 cc./100 gms./min., respectively) obtained previously by Kety and Schmidt on 14 normal subjects. Furthermore, there was no significant correlation between the total O_2 consumption and the cerebral O_2 consumption ($r = -0.027$).

These results show quite definitely that the brain does not participate in the increased metabolic activity of the body in hyperthyroidism. It is possible that other organs may also behave in similar fashion to the brain.

The Relationship Between Serum Quinidine Concentrations and the Prevention and Treatment of Cardiac Arrhythmias. MAURICE SOKOLOW and ARCHIE L. EDGAR, San Francisco, Calif., (Introduced by Stacy R. Mettier).

The relationship between the serum concentration of quinidine and the prevention and treatment of the cardiac arrythmias has been studied in approximately 100 patients. The photofluorometric method was used for serum and urine. The drug was usually given orally, occasionally intramuscularly or intravenously. When the drug was given intravenously to dogs, the maximum blood level occurred in 15 seconds, with rapid decrease within 30 to 60 seconds.

Successful conversion to sinus rhythm resulted in approximately 80 per cent of 51 attempts in patients with chronic auricular fibrillation or flutter. Sinus rhythm was reestablished in some patients despite cardiac failure, preceding emboli, marked cardiac enlargement and well-marked mitral stenosis. Quinidine was usually given every two hours for five doses on each day, occasionally every four hours day and night. The individual dose varied from 0.2 to 1.2 Gm., usually 0.4 to 0.6 Gm. The average blood level required for conversion was 5.6 mg./l., with a range of 1.3 to 15.6; 80 per cent of conversions occurred between 4 to 8 mg./l. In 10 patients in whom levels exceeding 9 mg./l. were attained, successful conversion occurred in only 3.

Auricular flutter was found frequently at the height of quinidine effect. Further administration of quinidine often resulted in sinus rhythm. Auricular fibrillation was occasionally noted to progress through auricular flutter to auricular tachycardia; when quinidine was stopped, the rhythm returned to auricular fibrillation in the reverse order.

In several patients with recurrent paroxysmal auricular tachycardia, auricular fibrillation and ventricular tachycardia, critical blood levels of 4 to 5 mg./l. were necessary to prevent recurrent attacks. This level was obtained with maintenance doses varying from 0.4 Gm. t.i.d. to 0.6 Gm. six times a day. Frequent premature beats were suppressed at widely varying levels, occasionally persisting despite levels of 7 to 8 mg./l. The often recommended dose of quinidine of 0.2 Gm. t.i.d. was generally inadequate.

The Inhibitory Effect of Saturating Doses of Para-aminohippurate on Renal Tubular Reabsorption of Sodium in Man. J. STAMLER, W. HWANG and E. N. SILBER, Chicago, Ill., (Introduced by L. N. Katz).

Saturation of a renal tubular secretory or reabsorptive system is known to affect the handling of other organic substances by the tubules. We undertook to determine whether demonstrable interrelationships may exist between tubular transport mechanisms for strong electrolytes (Na and K) and organic compounds. Sodium and potassium excretion was studied by clearance methods in five adult human subjects before and after saturation of the renal tubular secretory mechanism for para-aminohippurate (PAH). The effect of PAH on electrolyte excretion was analyzed with and without the imposition of an intravenous sodium load. In all cases the sodium excretory rate showed a significant increase during renal tubular saturation with PAH. A 4–12 fold rise in urinary m.eq./min. output of Na supervened. This represented a 5–12 fold increase in per cent excretion of sodium filtered at the glomerulus. This increased Na excretion occurred without a rise in glomerular filtration rate or urine flow. Hence, the natruretic effect of PAH can be attributed only to an inhibition of tubular sodium reabsorption. No consistent changes in potassium excretion were concomitantly noted. Possible mechanisms and therapeutic implications of these phenomena will be discussed.

A Rapid Bedside Method for the Determination of Urinary Sodium Content. HIRSH SULKOWITCH, Boston, Mass., (Introduced by James L. Gamble).

Increasing knowledge of the role of sodium excretion in pathological states and in patients receiving therapy which alters the sodium excretion have created a need for a simple bedside procedure for the determination of urinary sodium content. A colorimetric method has been developed. Measurement is based on the finding that when a small quantity of violuric acid reagent is added to a buffered acid solution the presence of potassium ions produce a yellow color resembling that of urine with an absorption maximum at 3,665 A, while sodium ions produce a reddish violet color with an absorption maximum at 5,440 A. According to the experimental evidence the colors are due to a physical effect of the sodium and potassium on the reagent rather than a chemical combination of the metal and the organic compound. Phosphotungstic acid may be added to partially remove the potassium and ammonium ions so that they are non-reactive and thereby decrease the effect of these ions on the violuric acid reagent. However, it is possible to measure as little as 10 meq./L. of sodium in the presence of 200 meq./L. of potassium in urine.

Details of the procedure and data illustrating the accuracy of results obtained will be presented.

Effects of Injections of Hypertonic Glucose on Metabolism of Electrolytes in Edematous Patients. ROBERT TARAIL, DONALD W. SELDIN and ALLAN GOODYER, New Haven, Conn., (Introduced by Paul Lavietes).

Six to twelve hundred cc. of 25 per cent glucose were injected rapidly into seven patients with edema due to heart failure or hepatic cirrhosis.

The increase in effective osmotic pressure of the extracellular fluid produced by extreme hyperglycemia following the infusions withdrew water from cells, thereby expanding extracellular and blood volumes and diminishing the concentration of serum sodium. This movement of water out of cells was often accompanied by a transfer of potassium into cells, whereas in dehydration and starvation water leaves cells in association with potassium. As hyperglycemia and massive glycosuria developed urine flow increased markedly, but sodium excretion was only minimally augmented. In two cirrhotics with normal glomerular filtration rates, when glucose excretion reached a maximum of 29 and 37 grams per hour, urine flows were 720 and 790 cc. per hour, but the excretion rates of sodium were only 2 and 1 meq./hr., respectively. The renal tubular reabsorption of sodium remained almost complete despite marked glycosuria. Therefore, the augmented sodium excretion which accompanies a glucose diuresis in normal subjects cannot be ascribed solely to an intrinsic limitation of the capacity of the renal tubules to perform osmotic work or to reabsorb sodium against a concentration gradient.

As carbohydrate utilization accelerated, the concentration of serum potassium fell markedly because of the transfer of this ion into cells. The excretion of potassium increased more than was observed during glucose diuresis in normal subjects, the potassium being eliminated as potassium chloride.

The sudden expansion of extracellular and plasma volumes in the patients with heart failure did not affect their dyspnea. Two hydropenic patients developed severe muscular cramps 2 hours after the infusions which could not be ascribed to changes in the serum concentrations of calcium or sodium.

The Role of Antibody in "Allergic" Encephalomyelitis. LEWIS THOMAS,* P. Y. PATERSON and ELIZABETH SMITHWICK, New Orleans, La.

It has been suggested that an antibody directed against homologous brain tissue is responsible for the demyelinating disease which follows "immunization" with brain extracts plus adjuvants. An alternative explanation for the disease is that a toxic component of the injected brain tissue is released, in the presence of adjuvants, and causes demyelination.

In dogs, "allergic" encephalomyelitis has been produced with homologous brain extracts in approximately 60 per cent of the animals. Repeated injections for periods of six months or longer are usually required, but a significant number have become paralyzed following one injection. Paralysis usually occurs 7–10 days after injection, irrespective of the total number of inoculations. Such a short incubation period, especially following single injec-

tions, raises some question as to the direct role of an antibody as cause of the disease.

An antibody which produces complement fixation and flocculation reactions with alcohol extracts of homologous or heterologous brain is demonstrable in the serum of dogs 3–4 weeks after the injection of brain extracts plus adjuvants. The presence of the antibody cannot be directly correlated with the occurrence of paralysis. Some animals without detectable antibody have become paralyzed; others with high titers have remained healthy.

The antigen which reacts with antibody *in vitro* is present in brain, cord, and peripheral nerve, but not in other organs. It is contained in the acetone-soluble, unsaponifiable fraction of white matter lipids. This fraction, in combination with adjuvants, has produced typical encephalomyelitis in guinea pigs.

These results suggest that the antibody under study, while not itself responsible for demyelination, may be directed against a component of brain tissue which is necessary for the experimental disease. Further studies on the nature of the antigen, and the possible protective role of the antibody, are in progress.

The Relation of Influenza Epidemics in Ohio to Primary Pneumococcic Pneumonia at the Cincinnati General Hospital, 1936–1949. ROBERT T. THOMPSON and MORTON HAMBURGER,* Cincinnati, Ohio.

From July 1, 1936, to June 30, 1949, there were seven influenza epidemics in Ohio. During that time 3,105 cases of primary pneumonia due to typed pneumococcus in patients above 13 years of age were admitted to the Cincinnati General Hospital. In each of the seven influenza years there was an eccentric peak in the monthly occurrence of primary pneumococcic pneumonia which corresponded with the influenza epidemic; but in the six non-influenza years the monthly occurrence of pneumonia revealed plateau curves without peaks. Usually twice as many cases of pneumonia occurred during the first month of each influenza epidemic as occurred in the month prior to the epidemic. Nevertheless, the number of pneumonia cases per year (July 1 through June 30) decreased irregularly from 375 in 1939–40 to 122 in 1948–49.

Although pneumonia morbidity was increased, pneumonia mortality was not consistently changed, and the clinical manifestations of pneumonia were not notably altered during influenza epidemics. Pneumonia mortality was less than the preceding year in each of four influenza years (1938–39, 1939–40, 1945–46, and 1946–47), and greater than the preceding year in each of two influenza years (1940–41 and 1943–44). With improvement in therapy, the yearly pneumonia mortality decreased irregularly from 36.7 per cent in 1936–37 to 5.7 per cent in 1948–49.

Type 1 was the most frequent pneumococcus in five of the seven influenza years, and type 7 in two years. In the six non-influenza years type 1 was most frequent two years, types 1 and 7 were equally frequent one year, and types 2. 3, and 7 were each most frequent one year.

Hypertension Following Bilateral Nephrectomy. LOUIS TOBIAN, JR., Dallas, Texas, (Introduced by Gladys Fashena).

Sixty per cent of rats (16 out of 27) exhibited a significant elevation of blood pressure 3 days after bilateral nephrectomy, providing their diet before and after nephrectomy contained sodium salts. This elevation of blood pressure was not produced by increases in body water. Massive subcutaneous doses of DCA during the brief period following bilateral nephrectomy do not produce a further elevation of blood pressure.

The elevation of blood pressure following bilateral nephrectomy is completely prevented if the adrenals are excised at the time of the nephrectomy (13 rats).

Furthermore, the elevation of blood pressure following bilateral nephrectomy can be strikingly diminished (only 1 hypertensive out of 51 rats) if sodium is withheld from the diet.

Thus, dietary sodium and intact adrenals are necessary for the elevation of blood pressure after bilateral nephrectomy. This experiment illustrates a type of renal deficiency hypertension that can not possibly involve a renal pressor substance. Other types of renal hypertension may very well have a similar mechanism.

Effects of ACTH on Tuberculosis in Humans. RALPH TOMPSETT, CHARLES LEMAISTRE, CARL MUSCHENHEIM and WALSH MCDERMOTT,* New York, N. Y.

An investigation has been made of the effects of ACTH in patients with advanced tuberculosis, with particular reference to the acute manifestations of the illness and the evolution of visible tuberculous lesions (laryngeal).

In four subjects studied thus far, the administration of ACTH (100 mg. daily) has been followed within six to eight hours by amelioration and subsequent rapid disappearance of the systemic manifestations of acute illness. Complete defervescence has been accompanied by marked improvement in strength, appetite, and phonation, and by loss of previous cutaneous hypersensitivity to tuberculin. The onset of visible changes in the laryngeal lesions occurred within 24 hours and were increasingly evident thereafter. Laryngeal edema receded, granulations became less elevated and were covered with epidermis.

Sudden withdrawal of ACTH after a short period of administration was followed by the abrupt return of all previous signs of acute illness without return of the laryngeal ulcerations. Study of more prolonged ACTH administration in additional patients is in progress. Whether the ultimate effect of ACTH on the extensive pulmonary lesions of these subjects will be beneficial or adverse, is as yet unclear.

Regardless of ultimate outcome, it has clearly been possible to abolish the evidences of tuberculous illness by the administration of a substance which presumably acts solely on the host. Thus the present results with ACTH in a protracted destructive infection are comparable to Finland's previous observations in acute non-tuberculous pneumonias.

The usual clinical and roentgenographic studies have been accompanied by: direct observation and photography of the lesions; bacteriologic studies of the bacilli using recently introduced technics; immunologic studies (erythrocyte agglutinations, gamma globulin, tuberculin); and the effects of the introduction of such variables as antimicrobics and antihistaminics. Similar observations with Cortisone are also in progress.

HLZP—a New Zinc Protein in Human Leucocytes. BERT L. VALLEE and FREDERIC L. HOCH, Boston, Mass., (Introduced by H. Stanley Bennett).

The occurrence of zinc in human leucocytes has been reported; leucemic leucocytes have 10 per cent of the normal zinc content. In erythrocytes, zinc is present as an integral constituent of the carbonic anhydrase molecule, but the function of zinc in leucocytes and plasma is not understood. The present study on the relationship of zinc to the cellular proteins of leucocytes was undertaken to elucidate the role of zinc in these cells, and the significance of its diminution in the leucemic process. A diphenylthiocarbazone-trichloracetic acid technique was used which allowed simultaneous measurement of zinc and protein; zinc was extracted from all reagents before use.

1300 ml. of leucocytes were obtained from a large number of human bleedings, and the cells were frozen, thawed, and extracted repeatedly with 3 volumes of phosphate buffer at pH = 7.0, ionic strength = 0.01, T = 4° C., until no more soluble zinc-containing protein was eluted. The existence of a zinc-protein was demonstrated by its zonal flocculation upon fractional $(NH_4)_2SO_4$ precipitation at 0.5–0.6 saturation.

Carbonic anhydrase, present in small amounts from contaminating erythrocytes, could be clearly differentiated by its precipitation at 0.81–0.86 saturation, and by activity measurements. Further purification of the zinc-protein was effected by continued $(NH_4)_2SO_4$ fractionation of zinc-enriched precipitates. The firmness of zinc-binding was indicated by the constant zinc–protein ratio after prolonged dialysis, and by the increasing zinc–protein ratio after repeated precipitation during purification. A fraction containing 0.2 per cent zinc per gram of dried protein has been obtained. Further purification and biochemical and physical chemical procedures for characterization are in progress. The working designation HLZP (human leucocyte zinc-protein) has been applied to this protein. It is hoped that studies of the physiology of this protein will elucidate its role in normal and abnormal leucocyte function.

The Effect of ACTH on Blood Complement, Gamma Globulins, and Fibrinogen. J. H. VAUGHAN, T. B. BAYLES and C. B. FAVOUR, Boston, Mass., (Introduced by F. J. Ingelfinger).

Ten patients with rheumatoid arthritis, four with scleroderma, and five with lupus erythematosus disseminatus were studied. Within these three groups it was noted that the rheumatoid and scleroderma patients were alike with respect to the quantities studied, while the lupus patients stood apart.

In all three groups the gamma globulins and fibrinogen were characteristically reduced by the ACTH from initially elevated values to or towards normal. Upon cessation of the drug a relapse towards the pretreatment state was usually noted. Whereas the changes in the fibrinogen were rapid and nicely reflected the sedimentation rate the gamma globulin changes were slow to develop, usually lagging five to seven days after initiation or conclusion of therapy.

Titers of complement activity in the rheumatoid and scleroderma patients were normal or high during the control periods of study. During treatment with ACTH, which usually lasted three weeks, the complement titer tended to fall. Upon conclusion of therapy a rebound to pretreatment levels was often seen. Among the lupus patients the complement titer tended to be subnormal initially, and the rebound which characterized the immediate post-treatment period in these patients was marked by an uprise to levels of complement activity far higher than those which had characterized the pretreatment period. The elevated complement titers thus attained were noted to relapse to their former low values some time after the conclusion of therapy, at a time when the gamma globulins were again elevated.

It is felt that the effect of ACTH upon gamma globulins is probably mediated through the depressant effect of this drug upon the lymphoid tissues of the body. The changes in the fibrinogen are to be directly related only to the degree of disease activity. The mild depressant effect of ACTH upon serum complement is modified in lupus erythematosus by the fact that this is a disease apparently associated with some other specific mechanism for reducing complement activity. It would appear that the ACTH also depresses this mechanism (possibly associated with the gamma globulins), allowing the complement sometimes to rise during ACTH therapy and typically to rise at the conclusion of therapy when the peculiar depressant effect of ACTH itself on complement activity is removed.

Induced Variations in Pulmonary Arterial and Pulmonary Capillary Pressures in Man. JAMES V. WARREN,* JOSEPH S. WILSON and JOSEPH T. DOYLE, Atlanta, Ga.

In the course of a study of the mechanisms producing pulmonary congestion and edema, it has been found that striking changes in pulmonary arterial and pulmonary capillary pressure can readily be induced in the normal human subject. Pulmonary arterial pressure was measured in 14 subjects receiving one liter of physiologic saline solution intravenously in 10 minutes. In every case it rose by 50 to 260 per cent above the control level, with both systolic and diastolic pressures participating. The pulmonary capillary pressure, observed in four patients, responded by a similar increase. The pulse rate remained constant. In some cases there was an increase in cardiac output, but this could not be correlated with the magnitude of rise in pulmonary arterial pressure.

Although there was evidence of an increased total blood volume, the "pulmonary blood volume" determined by the dye method showed no consistent change in eight cases.

Opposite changes of a less striking degree have been produced in this laboratory by the pooling of blood with venous occluding tourniquets about the extremities.

The parallel changes in pulmonary arterial and pulmonary capillary pressures are interpreted as evidence against altered pulmonary vascular resistance. The induced changes, therefore, appear to be the result of a "back pressure" effect. No evidence is found of a correlation of pulmonary blood volume with the observed pressure change. It is quite possible, however, that an alteration in pulmonary blood volume too small to be measured by the present technique could cause significant pressure change in the relatively indistensible pulmonary veins and left atrium. The striking rise seen in normal subjects suggests the possibility that even greater changes may occur in patients with cardiac disease, and that these changes may be an important factor in the genesis of pulmonary edema.

Nitrogen Exchange and Caloric Expenditure in Patients with Malignant Neoplasms. CHRISTINE WATERHOUSE, LEONARD D. FENNINGER, ALBERT CRAIG and E. HENRY KEUTMANN, Rochester, N. Y., (Introduced by William S. McCann).

Animal experimentation has demonstrated that anorexia causes a malignant tumor to derive its nitrogen from normal body tissues. It has also shown that stores of body fat are depleted more rapidly than those of pair fed controls. Balance studies of nitrogen, calcium, phosphorus, potassium, sodium and chloride in two patients with Hodgkin's Disease, two with acute leukemia and four with widespread metastatic carcinoma give evidence that these principles apply to man.

The overall nitrogen balance was positive in all patients given a dietary intake considered adequate for individuals of similar size and activity. In one observation of low caloric but adequate protein intake, negative nitrogen balance was seen. Yet, low protein diets with 2000 or more calories produced only a slight negative balance. In contrast to previous reports indicating abnormal protein expenditure, these patients apparently retain nitrogen more rigidly than other protein depleted individuals if the caloric intake is maintained.

Caloric expenditure, calculated by the method of Newburgh, was such that six patients with actively growing tumors lost considerable body fat on caloric intakes ranging from 2000–2600 calories. In two of these patients fat storage occurred on the same dietary intake after effective therapy. Another patient with an actively growing tumor was in positive caloric balance on 3300 calories. Fat storage was observed in the eighth patient, an emaciated woman on an intake of only 2000 calories.

Because of recent interest in ACTH, detailed balance studies will be presented of a patient with acute myelogenous leukemia. Marked retention of nitrogen phosphorus and potassium occurred during this therapy.

In summary, the balance data obtained indicate that nitrogen storage occurs readily in patients with malignant neoplasms unless the caloric intake is drastically reduced; yet caloric expenditure in general seems to be high. Exception to the latter may be found in emaciated subjects.

Nitrogen and Electrolyte Balance in Hypertensive Patients on the Rice Diet. DONALD M. WATKINS, New York, N. Y., (Introduced by Alexander B. Gutman).

Balance studies were conducted for 32 one-week periods on 13 hospitalized hypertensive patients maintained on a diet of rice, fruit and sugar. On analysis this diet of 2,200 calories contained 4.9 grams nitrogen, 5.7 meq. sodium, 80.2 meq. potassium, 7.1 meq. chloride, 11.9 meq. calcium, and 14.4 mM phosphorus. Nitrogen balances were calculated in all periods; sodium, potassium, chloride, calcium, and phosphorus balances, in nine periods.

Markedly negative nitrogen balance and weight loss characterized the first two weeks of the diet. Output, largely urinary, exceeded intake by three to eight grams daily. Of 30 periods studied after the first two diet weeks, 17 showed a mean negative nitrogen balance of 0.72 gram and 13 showed a mean positive balance of 0.61 gram. The mean daily output of urinary and fecal nitrogen for these 30 periods was 3.17 and 1.75 grams respectively. Weight was constant or increasing. Although individual variation was marked, there was a trend toward positive balance as the time interval from onset of the diet lengthened. The data suggest that negative balances occurring after the first two diet weeks are of inconsequential proportions and that most patients on the rice diet will eventually reach essential nitrogen equilibrium. The minimum daily protein requirement for adult males maintained on this diet was estimated to be approximately 28 grams.

After the initial two weeks, the balance of sodium, potassium, and chloride was in general slightly negative, while balance was maintained for calcium and phosphorus.

Additional studies were conducted on five patients for a total of nine periods during which 400 ml. of sodium-free whole milk were added to the basic diet. This small supplement enhanced the digestibility and biological value of the rice protein and induced a strikingly positive balance of nitrogen and electrolytes.

The Effect of Auricular Fibrillation on Cardiac Output, Coronary Flow and Arterial Blood Pressure. RENÉ WÉGRIA,* CHARLES W. FRANK, GEORGE A. MISRAHY, ROBERT S. SIOUSSAT, LEONARD S. SOMMER and GEORGE H. MCCORMACK, JR., New York, N. Y.

The effect of auricular fibrillation on the cardiac output, coronary blood flow, and mean arterial blood pressure was studied in dogs anesthetized with pentobarbital. The cardiac output of the left ventricle and the blood

flow in the left descending anterior coronary artery were recorded continuously and simultaneously with two rotameters. The mean arterial blood pressure was recorded continuously with an optical manometer. Thirty-three bouts of electrically induced auricular fibrillation lasting from one-half to five minutes were studied in nine dogs. At the onset of fibrillation, there is an abrupt fall in cardiac output, blood pressure and coronary flow. After a few seconds, there is some rise in all three toward control. At the termination of fibrillation, there is a sudden increase in all three to levels greater than control. Following some of the shorter bouts of fibrillation, cardiac output, coronary flow and arterial blood pressure return to control simultaneously. In most bouts of fibrillation, the coronary flow is still increased above control level when both cardiac output and blood pressure have returned to control values. The significance of the phenomena observed will be discussed.

The Sternal Marrow in Diffuse Pulmonary Disease. AUSTIN S. WEISBERGER, Cleveland, Ohio, (Introduced by Alto E. Feller).

The roentgenographic appearance of diffuse pulmonary infiltration characterized by streaky or mottled shadows of increased density frequently presents a difficult diagnostic problem. In the absence of definitive bacteriologic, mycologic or immunologic findings, the differential diagnosis of tuberculosis, fungus disease of the lung, sarcoid, pneumoconiosis or interstitial fibrosis must be considered.

Sternal marrow needle aspiration biopsy with histologic examination of the marrow particles was performed on 12 unselected patients with undiagnosed diffuse chronic pulmonary disease. In 7 of the 12 patients, definite abnormal histologic findings were present in the marrow. Five of the seven had miliary granulomas consistent with sarcoid, tuberculosis, histoplasmosis or brucellosis. One had a typical caseous miliary tubercle and one had diffuse amyloidosis of the marrow. In two of the patients, miliary granulomas were also present in biopsy specimens of the lung and liver, and liver, respectively. The presence of amyloidosis was confirmed by a lymph node biopsy and the presence of tuberculosis was confirmed by culture of tubercle bacilli from gastric washings.

Two of the five patients with normal marrows were proven to have diffuse pulmonary fibrosis associated with bronchiectasis, one by lung biopsy and the other at autopsy. One was found to have sarcoid of the skin and tonsils. The remaining two patients had undiagnosed chronic pulmonary disease with no evidence of systemic involvement.

It is concluded that the roentgenographic appearance of diffuse discrete miliary opacities is frequently associated with widespread systemic disease and that sternal marrow aspiration with histologic examination of marrow particles may be of diagnostic value.

The Effect of Mercurial Diuretics on Urinary Ammonia and Titratable Acidity Excretion During Acidosis in Man. R. E. WESTON and J. GROSSMAN, New York, N. Y., (Introduced by L. Leiter).

Organic mercurial diuretics have been demonstrated to depress certain proximal renal tubular functions in man. To determine whether specific distal tubular functions are similarly affected, the effects of Mercuzanthin and Thiomerin, a xanthine-free mercurial, on urinary ammonia and titratable acidity production of fasting, resting subjects were studied. Eight cardiac and four non-cardiac patients were given 9-12 grams of NH_4Cl daily 3-4 days to stimulate the distal tubular base conserving mechanisms. Then, following three or more 15 to 20 minute control periods, during which urine was collected under oil from a vesical catheter, 2 cc. of the mercurial (=80 mgm. Hg) were injected intravenously and urine collections continued until after maximal diuresis of electrolyte and water had been attained. Bladder emptying was enhanced by abdominal pressure without injection of water or air.

The data indicate that ammonia production is not significantly decreased during mercurial diuresis. Immediately following the injection, at times, there was a slight transient decrease in all renal functions, including ammonia excretion, with a prompt return to control levels. Occasionally, small decreases in urinary ammonia excretion were observed after prolonged diuresis.

During maximal mercurial diuresis urinary titratable acidity excretion generally increased two- to threefold. Since there was a linear relationship between titratable acidity and phosphate excretion, this increased titratable acidity production presumably reflects depression of proximal tubular reabsorption of phosphate, making available more phosphate for hydrogen ion exchange in the distal tubule, which does not appear to be affected by the mercurial.

It is concluded that distal tubular production of titratable acidity and ammonia is not depressed by mercurial diuretics.

Observations on the Emotional and Symptomological Effects of Telling Adults That They Might Have Heart Disease. EDWIN O. WHEELER, CHARLES R. WILLIAMSON and MANDEL E. COHEN,* Boston, Mass.

During a community X-ray tuberculosis survey, observations were also made of X-ray heart shadows. Adults whose heart shadows were thought to be abnormal were requested to appear for heart examinations; they were told something might be wrong with their hearts.

One hundred seventeen of these (55 per cent definitely cardiac) were studied before this heart examination to determine possible emotional reactions following such news. Also, questions were asked to learn whether they developed cardiac symptoms following the suggestion that they might have heart disease.

Forty-three and six-tenths per cent of the group (i.e., 23.0 per cent of the men and 49.5 per cent of the women

—significance ratio 2.4) reported being upset and/or apparently were scared following the news of the possibility of having heart disease. In 20 individuals, this appeared as insomnia, anorexia, crying or worry.

However, development of cardiac symptoms was inconspicuous. In 10 individuals, symptoms appeared or worsened. Of these, 3 previously well (2.6 per cent) developed symptoms, 2 manifesting awareness of heartbeat alone and the other the symptoms of neurocirculatory asthenia (anxiety neurosis, neurasthenia, effort syndrome). The other 7 individuals had exacerbations of long-standing disorders—6, of neurocirculatory asthenia, and 1, of angina pectoris.

Forty-eight individuals were questioned about their theoretical knowledge of cardiac symptoms. They averaged knowledge of 1.2 cardiac symptoms per person. Twenty-five per cent did not know a single cardiac symptom.

It was concluded that telling an adult that he might have heart disease may be upsetting, but does not of itself immediately lead to cardiac symptoms. These observations may not apply to individuals who, through hospitalization or visits to physicians, may have had the opportunity to learn thoroughly the symptoms of heart disease.

Fecal Fatty Acids and other Lipids: A Study of Two Normal Human Adults Taking (1) A Diet Free of Lipid and (2) A Diet Containing Triolein as the Only Lipid. ERIC E. WOLLAEGER, WALTER O. LUNDBERG, JACQUES R. CHIPAULT and HAROLD L. MASON, Rochester, Minn., and Austin, Minn., (Introduced by Hugh R. Butt).

The fecal lipids of 2 normal men were measured during four successive dietary periods: (1) general mixed diet; (2) lipid-free diet; (3) same composition as period 2 except that 100 grams of triolein per day was substituted isocalorically for some of the carbohydrate in the lipid-free diet, and (4) general mixed diet. Feces were analyzed for total dry matter, total lipids, total fatty acids, saturated and mono-ethenoic, di-ethenoic, triethenoic and tetra-ethenoic fatty acids and cholesterol. Melting point, neutralization equivalent and iodine number of the total fatty acid fraction were determined. Postabsorptive analyses of plasma for fatty-acid composition, cholesterol, cholesterol esters and phospholipids were carried out at intervals.

When the lipid-free diet was substituted for the mixed diet containing fat, the excretion of total lipids dropped from an average of 7.7 gm. per day to 1.5 gm. per day, and the excretion of total fatty acids dropped from 4.3 to 0.45 gm. per day. There also was evidence of a difference in the composition of the mixture of fatty acids excreted while the men were on the two dietary regimens. These findings, together with others which will be reported, are at variance with some previous reports of lipid excretion in animals taking lipid-free diets. The present study does not support the conception that fecal lipid in the human being is largely endogenous and not greatly influenced by the amount and character of the lipid in the food.

During the triolein period, excessive amounts of fatty acid were excreted which were not all mono-ethenoic. Blood studies revealed subnormal levels of cholesterol during the lipid-free and triolein periods, but no consistent change in phospholipid or total fatty acids. The composition of the plasma fatty acids did not resemble that of the fecal fatty acids.

Studies of Alternating Sinusoidal Currents Introduced into the Heart in Life and Death. H. F. ZINSSER, JR., A. J. NEUMANN, C. F. KAY,* E. L. FOLTZ, D. D. TALLEY and J. H. HAFKENSCHIEL, JR., Philadelphia, Pa.

Experiments were initiated (1) To develop techniques for measurement of the distribution of electrical forces of known form and magnitude introduced into the heart and (2) To determine postmorten effects, with respect to time, on these measurements. Techniques were designed for application to electrocardiographic problems, particularly to suitability of cadavers as models.

Sinusoidal twenty cps electromotive forces were introduced into anesthetized dogs through dipoles placed by catheterization of the right ventricle and coronary sinus. These dipoles were shown to lie approximately at right angles to each other in serial anteroposterior and lateral chest X-rays. Potential differences between various positions on the body were measured electrocardiographically. The following factors were observed to influence measurements: (1) Input current and voltage, (2) Dipole location, (3) Prone versus supine position, (4) Unilateral and bilateral pneumothorax, and (5) Time postmortem.

An input of approximately one volt was sufficient to induce ventricular fibrillation and death. Potential differences between peripheral points increased linearly with input current in any series of measurements taken in rapid succession. A gross correlation existed between dipole orientation and magnitude of measurements from peripheral leads. Immediate postmortem changes in output were greater in the supine than prone position. Pneumothorax caused pronounced changes in output measurements. Death caused wide variation in right ventricular dipole impedance through nine hours, whereas coronary sinus dipole impedance changed less. Relation of input to output measurements changed after death, but the reasons for this have not yet been defined.

Chief obstacles to data analysis relate to: (1) Mechanical changes in heart and dipole positions, (2) Inability to maintain the postmortem lungs in a state comparable to that during life, (3) Difficulty in controlling certain postmortem changes not primarily cellular, but which affect body conductivity (e.g. effect of blood coagulation on input impedance), and (4) Inadequacy of commercial electrocardiographs as recording instruments at frequency and voltage used.