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MEDICINE—ITS MENTAL CLIMATE

By J. S. L. BROWNE

Mental climate is a phrase used by J. W. N. Sullivan to describe the ambience within which grow and develop the philosophy, the science, the art of an era or time. I trust you will forgive my vagaries in tracing those trends in medicine of our era which may reveal its mental climate since I believe that clinical investigation as a part of medicine grows and develops under the influence of this mental climate. We tend to spend too much of our time in air-conditioned rooms and fail to look at the weather outside.

What is a trend? It is the way or direction in which a process or subject is changing or progressing. It is not possible for a single observation to determine the trend; our day to day observations of the facts as they are will not reveal it clearly. Only by drawing a graph can we detect in which way the process is going. It is easier to see a trend in the past than in the present or the future and this is so of medicine as of other subjects. We have spoken so far objectively, as if we stood outside and were observing the trend in medicine. We, however, form part of that process throughout our lives. We recapitulate in our medical education, in part at least, the evolution of that living being which is medicine.

Growth and development is a property of life. Plants, animals and man each possess certain attributes in common. In the plant world the tree springs from the seed, grows, develops a trunk, branches, twigs, leaves, flowers—these are fertilized—then again the seed, and this process is repeated. In the animal world the individual starts as the fertilized ovum, develops, matures, procreates, ages and dies—continuing in its progeny. Man continues to exist not only by his physical continuance in his children, but by the transmission of his emotions and thoughts. He not only procreates, he creates.

All living beings are under the influence of their heredity and environment. Man is conditioned not only by his physical environment but by being taught to call things by certain symbols or words, which change their meaning in different lands and at different times. He is influenced by the religious, scientific, philosophical and social aspects of his day and all of these are conveyed to him through words written or spoken. However much he changes, there are certain fundamental emotions, ways of thought and concepts which keep recurring in each generation—the spirit of human nature—which the great philosophers, artists, and perhaps statesmen of each era interpret for their time. One of his fundamental urges is the desire for certainty which he never attains.

Let us see how medicine as a living being exhibits the attributes considered above, remembering that medical men themselves are the expression in their time of the development of the subject and recapitulate within their growth the growth of medicine itself. A botanical allegory of medicine may be drawn: Development begins in the seed of a fundamental science. Let us take the development of morphological pathology and gross anatomy; in the last century it grew into a huge tree, it specialized into many branches, it sheltered and shaded medical men from the sun of uncertainty. It flowered and continues to flower in its application to medical practice—cross fertilized, it formed part of the development of the newer trees of physiology, biochemistry and biophysics. Those seeds which fell close under the thick shade of its leaves failed to develop or were stunted because of the very protection which it offered from the sun of uncertainty. I have used morphological pathology as an example because its great development occurred in the immediate past of medicine and its influence on medical thought is still great. The same occurs in all sciences which are applied to medicine. Bacteriology, physiology, biochemistry and biophysics are forming part of the growth and differentiation of medicine of the present day.

What are the effects of this growing process on medical education and thought? The medical man, like other men, demands certainty, for which he constantly looks to the science of medicine. He also has a certain continuous medical spirit which must be satisfied, the personal relation to the patient. He seeks to satisfy this by practicing the art of medicine. This art is the practical expression of his application of the science of medicine as he knows it guided by the spirit which is within him. The medical teachers of 40 years ago had had their training in the science of medicine almost entirely in morphological pathology and bacteriology. There had been established a correlation between certain signs and symptoms in the living patient and the appearance of organs at autopsy. These correlations had been given labels, had been placed in pigeon holes and the teacher could only be certain that he had put the right label on by examination of the patient at autopsy or possibly at surgical operation. The teacher also possessed a clinical acumen derived from observation by means of his own senses. In addition in many instances as a successful family physician he considered his patient, whom he often looked after for many years, as a person. On the other hand in teaching he sometimes overemphasized the science of medicine and

came to regard a public ward case as increasingly interesting as the inverse square of the distance of that patient from the autopsy table. The students were taught on the wards, the outdoor was regarded as a means of discovering interesting cases for the wards and the student had no opportunity to see the art of medicine guided by its spirit as practiced in the teacher's office and when he visited the home.

To the next generation of teachers brought up in this tradition there came the increasing capacity to extend the facts gained by their own senses, by means of instruments and tests revealing the physiological and biochemical aspects of the processes going on in the patient. The number of facts available in any one patient increased and is increasing immensely. The growing trees of the various medical sciences and of medicine itself (as a sort of banyan tree which includes the others) developed more and more branches and twigs of specialization. On the one hand this growth lead to a greater likelihood of attaining intellectual certainty within the patient's lifetime, to a better recognition of disease as a physiological process and, through the development of special therapeutic agents, to a greater capacity for prevention, amelioration or even cure of these disease processes. This increased the interest in the physio-pathology of disease, the facts attainable during life increased the interest in the patient apart from his proximity to the autopsy table and the tendency to therapeutic nihilism was overcome. On the other hand the interest in intellectual certainty led physicians in the teaching wards to the collection of more and more facts by more and more laboratory investigations. Twenty tests were regarded as equal to one autopsy for the attainment of certainty. The brilliant flowers of laboratory facts were admired without realizing that they only flowered because of their connection with the previous development of medicine and because they remained in truth connected to the history and the physical examination. Plucked from the parent stem they tended to wither. The spiritual continuum of medicine, the recognition of the person in the patient, the sap which begins in the roots, flows through the trunk, leaves and flowers of medicine and connects and gives life to the whole structure was not clearly presented to the medical student.

In this era, which extends to the present, the older clinician feels that the newer one is not a doctor because he relies too much on the laboratory. It seems to me that there is no essential difference between the facts obtained by the senses and those obtained by the extension of these senses. What remains essential is the capacity of the doctor from his experience of man and of medicine to obtain the facts regarding the abnormal processes occurring in the person, beginning with history, followed by physical examination and then, by use of his experience and acumen to observe what further extension of his senses are most useful—what laboratory tests are needed.

As mentioned before, one great difficulty in hospital practice is the knowing of the person, his emotional and social environment. This combined with the desire for certainty, as we have said, led to a tendency to the fac-

tualization and scattering of the patient all over the lot of specialism. A reaction against this is occurring among the public and, I think, among younger medical men and students. This again is reflected in the growth of new trees in medicine—psychiatry and social medicine. These subjects will provide new ways of obtaining facts about the patient and about his person, through the senses of the doctor, by history taking either by himself or by some other person. It should be remembered, however, that these facts that approach the person most closely need all the more to be integrated into the whole in the spirit of medicine, by the doctor be he specialist or family physician. The patient may be as badly factualized or scattered by these new disciplines as by the older ones and they are just as subject to the error of regarding the label or pigeon hole as the truth itself and not only a convenient arrangement of the truth.

I spoke some time ago about the importance of symbols and words to man and how the meaning of these words changes with time. The establishment of pigeon holes or labels, that is, the naming of disease entities, is done by men who observe, by the methods available to them in their day, the correlation between signs and symptoms in the patient and some reference standard either morphological at autopsy; or biochemical or physiological, which is a constant feature accompanying these signs and symptoms and regarded as being in some way casually connected with them.

There is sometimes confusion as to what constitutes a disease entity. For example the word amenorrhoea obviously describes a symptom and the nature of the physio-pathological process underlying this symptom may be varied. In amenorrhoea one may recognize a quantitative aspect, an individual may be just not menstruating and any form of therapy will be effective, or may be ovariectomized when these same methods of therapy may be ineffective. It is perhaps less generally recognized that diabetes mellitus is also the name of a symptom as it was originally labelled. The concepts as to its physio-pathological basis have varied and each succeeding generation of doctors has used this same label for different things, all of them desiring certainty and saying: only if the signs and symptoms can be fitted into the particular pigeon hole which I have established on the basis of my interpretation of the science of medicine may they be tagged with this originally purely symptomatic label. In the case of rheumatic fever, this disease entity has been under the morphological sanction of the occurrence of the Aschoff body, which means strictly that unless the patient dies rheumatic fever cannot be proven. However, prolonged clinical experience has established the probability that if the patient has a certain number of signs and symptoms the correlation is good enough to justify the label. On the other hand the capacity to say this is NOT rheumatic fever is more limited. There are many cases which are almost-not-quite rheumatic fever which may easily be less marked examples of the same physio-pathological process. To establish a pigeon hole and say that this fits and this does not fit is satisfying for certainty and enables the doctor to move thereafter in an

easy manner along the well worn grooves of recognized prognosis and therapy. However, if a new sanction or index of the physio-pathological process is found, capable of indicating the quantitative aspect of this process, its acceptance will be difficult because it will be said that it occurs in cases which are not rheumatic fever and the false conclusion drawn that, because the signs and symptoms do not fit exactly into the pigeon hole, they have no relation to the physio-pathological process underlying the pigeon hole or label. Let us consider the meaning of the word functional. When I was a student it referred to a type of disturbance not accompanied by detectable morphological change, or to the physiological and biochemical disturbances resulting from an organic lesion. It now is used as being equivalent to psychogenic and this in turn to inexplicable and to mean that no physiological or biochemical changes are detectable to account for the symptoms. You will see that this change does keep the meaning in the same relative position in the tree of medical growth. In the days of morphological sanctions it meant that no cause could be found; in the days when physiological and biochemical sanctions have been added it still means this. This changing use of words causes great confusion between medical men trained at different stages of the growth of medicine even in the same generation. It also leads to great difficulty in clinical investigation since the investigator's thinking is conditioned by the concepts of disease entities and of words, which he has learnt during his medical training.

The trend of medicine is not often seen by those taking part in it. The medical man himself grows, branches, puts out leaves, flowers and goes to seed—some grow and flower for a longer, some for a shorter period. He does this within the growth of medicine itself which continues in other aspects beyond him. He has learned at a particular stage of medicine, that of his undergraduate and post-graduate days, and it becomes increasingly

difficult for him really to build into his thinking concepts which develop years later.

Each generation of medical men applies in its time the science of medicine as known at the time of its training to the practice of medicine and in turn advances the growth of the subject.

There is thus the science of medicine—the methods of obtaining facts and knowledge of the meaning of those facts; the art of medicine, the application of these facts to actual practice and the spirit of medicine—that deep sense of relationship to a person, demanding sensitivity, fine perception, true sympathy and wisdom. It should be recognized that the art of medicine changes. The doctors of yesterday were not good doctors only because they used the methods available in their time. The mere use of modern methods of laboratory diagnosis does not make a doctor a good or a poor one. It is the failure to integrate the facts obtained by any method and the failure to remain conscious of the spirit of medicine which makes a poor doctor be he general practitioner, internist, surgeon or psychiatrist.

The problem of medicine today is how can the reintegration of the patient as a person be achieved in the welter of facts developed through the science of medicine, and in view of the fact that no one man can know any but a small fraction of them. Each doctor can remain conscious of the spirit of medicine, even though he be a specialist and each family physician can do his best in relation to the stage of his own growth in the art of medicine.

In these ramblings I have tried to indicate something of the mental climate in which medical men and therefore medicine have grown and developed. Part of this climate has been the same for thousands of years, part of it has only recently developed but all of it has its impact on the growing medical man and on medicine itself.

ABSTRACTS

A Prothrombin Activator in Serum, and its Significance in Certain Hemorrhagic Diseases. BENJAMIN ALEXANDER, (by invitation) ANDRE DE VRIES, and (by invitation) ROBERT GOLDSTEIN, Boston, Massachusetts.

Normal serum contains a substance which can accelerate conversion of prothrombin to thrombin by thromboplastin plus calcium. This fact, reported by Ware *et al.* and confirmed by us, is demonstrable by the enhanced prothrombin activity of plasma-serum mixtures. A study of this serum activator in certain hemorrhagic disorders revealed that:

(a) Hemophilic blood consumes abnormally small amounts of prothrombin during coagulation. Hemophilic serum is devoid of activator. Adding normal plasma to hemophilic blood *in vitro* or *in vivo* accelerates its coagulation but fails to induce normal prothrombin consumption or serum activator evolution.

(b) In idiopathic thrombocytopenic purpura, the serum is similarly rich in unconsumed prothrombin and low in activator despite normal clotting time of the shed blood.

(c) Sera from dicumarolized subjects with hypoprothrombinemia are also low in serum activator.

Evolution of activator during coagulation is accordingly closely related to prothrombin consumption. It is proposed that this prothrombin activator furthers hemostasis by accelerating conversion to thrombin of additional prothrombin in the surrounding blood. Thus, *in vitro* and *in vivo*, clotting is hastened and the clot is propagated. Failure to evolve normal amounts of activator in the above disorders may explain their hemorrhagic phenomena despite relatively normal clotting time. Low serum activator may also explain the effectiveness of dicumarol in preventing thromboembolism.

Significance of Blood Carbonic Anhydrase Activity in Anemia. M. D. ALTSCHULE and (by invitation) H. D. LEWIS, Boston, Massachusetts.

A new method for estimation of blood carbonic anhydrase activity at body temperature has made possible the more accurate evaluation of the role of this enzyme in the symptomatology of anemia. The studies show that patients with anemia due to hemorrhage, febrile states, uremia, acute hemolysis, and, in most instances, leukemia, exhibit decreases in blood carbonic anhydrase activity parallel with diminution in hemoglobin and hematocrit levels. Patients with pernicious, "refractory," and, in some instances, nutritional anemias show much higher levels of blood carbonic anhydrase activity than would be anticipated from the erythrocyte count and hemoglobin and hematocrit levels. In view of the importance of the enzyme in carbon dioxide transport, especially under conditions of acceleration of the circulation, it is concluded that the observations are significant in relation

to variations in the degree of dyspnea, commonly associated with types of anemia.

A Type Specific Protein from Pneumococcus. ROBERT AUSTRIAN (Introduced by Colin M. MacLeod), New York, N. Y.

The capsular polysaccharide has long been recognized as the principal determinant of pneumococcal type specificity. The presence also of a hitherto undescribed type specific protein has now been demonstrated. By injecting rabbits with vaccines prepared from rough variants of pneumococcus types I, II, III and VIII, antisera have been obtained which react specifically with a protein extracted from pneumococci of the homologous type. The type specific protein can be extracted from both smooth and rough variants by heating the organisms in dilute acid.

The type specific proteins of pneumococci share certain chemical properties with M proteins of Group A hemolytic streptococci, but no cross reactions have been observed among the four pneumococcal proteins studied and those of twenty-nine types of Group A streptococci. Antisera against pneumococcal type specific proteins give negligible protection against homologous encapsulated pneumococci in mice. When a rough variant of pneumococcus type II is transformed *in vitro* to capsular types I or III, it retains the specific protein of type II, demonstrating thereby the independent variability of these two type specific characters. If transformation occurs in nature, its detection should be possible by studying a sufficiently large number of pneumococcal strains.

Does One Pituitary Hormone Stimulate All Three Functions of the Adrenal Cortex? FREDERIC C. BARTTER (Introduced by Fuller Albright), Boston, Massachusetts.

The adrenal cortex produces three functional types of hormones: (1) the "Na" hormones (desoxycorticosterone-like) which promote the retention of sodium and chloride and the excretion of potassium, (2) the "S" hormones ("11-oxycorticosteroids") which maintain the blood sugar in the fasting state by means of glyconeogenesis, and (3) the "N" hormones ("17-ketosteroids") which promote anabolism of protoplasm and, in the female, control the production of axillary and pubic hair.

Before adrenocorticotrophic hormone (ACTH) became available, the evidence indicated that the "Na" hormones were produced independently, the "S" hormones through stimulation by ACTH, and the "N" hormones through stimulation by some second pituitary tropic hormone (possibly the luteinizing hormone) which is not released before puberty. Thus, the rat is capable of retaining sodium and chloride in the absence of the pituitary; the pre-

pubertal child produces adequate "S" hormones but no "N" hormones.

With the use of purified ACTH the problem has been reexamined in human subjects.

The metabolic changes following ACTH include: (1) retention of sodium and chloride, with loss of potassium; (2) loss of nitrogen, phosphorus and calcium, with increased excretion of "11-oxysteroids"; and (3) increased excretion of 17-ketosteroids.

This evidence reopens the question as to whether ACTH stimulates all functions of the adrenal cortex.

Influence of Tobacco Smoking upon the Effectiveness of Antacid Therapy and Management of the Peptic Ulcer Patient. ROBERT C. BATTERMAN and (by invitation) IRVING EHRENFELD, New York, New York.

The influence of tobacco smoking upon the management of the peptic ulcer patient was studied in 108 ambulatory patients. In terms of the ability of the patient to respond to antacid therapy, the fifty-six patients who continued to smoke presented a satisfactory clinical response in only 46.8 per cent of the trials. On the other hand, the thirty-nine patients who never smoked presented satisfactory improvement in 85 per cent of the trials. The incidences of acute exacerbations during the period of antacid therapy reveals very strikingly the influence of smoking upon the cause of the peptic ulcer syndrome. The patients who smoked presented an acute exacerbation in 34, or 53 per cent of the trials in contrast to the non-smokers who had exacerbations in 17.5 per cent of the trials. In every case of the group of 26 patients who stopped smoking of their own accord before seeking treatment, there was a satisfactory clinical response to antacid therapy. The incidence of exacerbations was 11.5 per cent. Thirteen patients resumed smoking after clinical improvement occurred. Eleven showed an immediate regression of their disease with increased symptoms of acute exacerbations.

Effects of Proteinuria on the Kidney. JAMES H. BAXTER and GEORGE C. COTZIAS (Introduced by Homer F. Swift), New York, N. Y.

To determine effects on the kidney of prolonged, continuous proteinuria, comparable groups of young rats were given, for periods up to 6 weeks, twice daily intraperitoneal injections (1 cc./10 gm. body wt.) of 3 per cent solutions of *gelatin*, *human albumin*, *bovine γ -globulin*, *casein hydrolysate*, 1 per cent *urea*; the controls received the solvent solution (0.45 per cent *NaCl*). Animals were given no additional fluids.

Gelatin and *albumin* produced increased proteinuria; renal enlargement by about 40 per cent developed within 24 hrs. Particularly, *gelatin* caused paleness of kidneys and droplets in proximal convoluted tubule cells (*cf.* Oliver); a large content of injected protein in cortical tissue was demonstrated. Fat appeared normal. *Globulin* apparently was best retained; sustained serum pro-

tein elevation and hemodilution, and the least marked proteinuria and renal enlargement resulted.

Casein hydrolysate and *urea* induced little or no enlargement; this suggested that enlargement was caused by tubular reabsorption of protein, rather than by protein metabolites.

Illness occasionally observed was not attributed to renal damage. A few dilated, protein-filled nephrons were seen. Proteinuria and renal enlargement rapidly receded after termination of protein injections, and subsequent blood urea, serum protein, and renal histological studies were normal.

These results seem compatible with the concept that the large, pale kidney of nephrosis is a secondary manifestation caused in part by proteinuria of glomerular origin. No evidence was obtained that proteinuria itself induces chronic or progressive renal damage, except possibly that due to tubular obstruction.

Temperature-Elevating Effect of a Substance Obtained from Polymorphonuclear Leucocytes. PAUL B. BEESON, Atlanta, Georgia.

Fever occurs in many different types of disease, including such diverse entities as infections, neoplastic diseases, hemolytic crises, vascular accidents and mechanical injuries. The way in which these various processes affect temperature regulation is unknown, but the suggestion has been made that some agent, liberated from injured cells, acts on the cerebral thermoregulatory centers and disturbs their function.

The present work was done in an attempt to find in cells of the rabbit a substance which, on intravenous injection into normal rabbits, would cause a rise in body temperature. Four cell types were tested: erythrocytes, lymphocytes, large mononuclear cells (macrophages), and polymorphonuclear leucocytes. Only one of these—the polymorphonuclear leucocyte—caused fever. These cells were obtained from sterile peritoneal exudates, caused by injection of large volumes of physiologic salt solution. Aseptic technique and pyrogen-free materials were used in separating them from the fluid exudate. Elevations of 2-3° F. resulted from intravenous injection of approximately the number of cells normally present in the circulating blood. The rise begins in 10 to 15 minutes and reaches its peak within an hour.

When a suspension of polymorphonuclear leucocytes is subjected to mechanical lysis (by shaking with glass beads) and then centrifuged, the supernatant fluid is fully active in causing fever, whereas the cell residue has no effect. The fever-producing property disappears after heating to 75-80° C. for 30 minutes. The active substance does not dialyze through a cellophane membrane. Further studies on the nature of this substance are under way.

It seems possible that the liberation of material such as that present in the polymorphonuclear leucocyte of the rabbit plays a role in the pathogenesis of fever in certain diseases of man.

The Effectiveness of Bismuthoxy-p-N-Glycolylarsanilate (Win-1011) in the Treatment of Intestinal Amoebiasis.

D. A. BERBERIAN (Introduced by T. G. Klumpp), Rensselaer, New York.

Win-1011 is the bismuth salt of an arsenical, containing 15.7 per cent arsenic and 37 per cent bismuth, characterized by low oral toxicity. It was supplied by Winthrop-Stearns, Inc., for studies at the American University of Beirut, as 0.25 gm. tablets.

Sixty-eight cases of chronic and subacute intestinal amoebiasis were treated with *Win-1011* orally. Certain cases also received Chiniofon and/or bismuth subgallate; 32 control cases were treated with Chiniofon.

Endamoeba histolytica was demonstrated in stools of all patients prior to treatment. Each adult received 2 tablets (0.5 gm.) of *Win-1011* after each meal for 7 days (total 10.5 gm.); children received proportionately smaller doses. Chiniofon was given as 0.25 gm. tablets; a total of 11.25 gm. was given in 7 days. Medication was followed by periodic laboratory examinations (av. 9.4) over an average period of 108 days.

Win-1011 alone cleared without relapse 24/25 cases; Chiniofon alone cleared 5/11 cases. *Win-1011* combined or alternated with Chiniofon cleared 33/38 cases; *Win-1011* and bismuth subgallate alternately cleared 5/5 cases; Chiniofon with bismuth alternately cleared 10/21 cases. All patients were cleared temporarily. No side-effects of any kind occurred in patients receiving *Win-1011* alone; therapeutic response was prompt.

The Mechanism of Flattening of the Erythrocytes in Diseases of the Liver and Bile Ducts. LIONEL BERK (Introduced by Henry Jackson, Jr.), Boston, Mass.

Erythrocyte "flattening," shown by increased resistance to osmotic hemolysis and by calculations based on volume and diameter measurements, was demonstrated in the blood of patients with cirrhosis of the liver, and within a few days of the onset of obstructive jaundice and acute hepatitis. During recovery from the latter, flattening disappeared in about a week. Because the changes occurred so rapidly while the osmotic fragility curves remained symmetrical and no reticulocytosis was seen, the changes apparently occurred in circulating red cells.

Attempts to reproduce this phenomenon *in vitro* failed when normal red cells were incubated at 37.5° C. for as long as 48 hours in plasma from patients with flattened erythrocytes. However, flattening of normal red cells transfused into such patients was apparent when the "hump" on the abnormal fragility curve initially produced by their presence showed progressive diminution within 1 to 2 days and disappeared within 3 to 5 days thereafter, despite the demonstrated persistence of the normal transfused erythrocytes in the circulation.

Since the flat red cells usually showed no change in volume, an increase in the area of the cell envelope must exist. The failure to reproduce flattening *in vitro* suggests that the tissues contribute factors responsible for this change. No correlation could be established be-

tween increased osmotic resistance and bilirubin, cholesterol or bile salts retained in the plasma.

The Renal Tubular Secretion of Potassium. ROBERT W. BERLINER and THOMAS J. KENNEDY, JR. (Introduced by A. B. Gutman), New York, N. Y.

The potassium excreted in the urine ordinarily is considerably less than the amount contained in the glomerular filtrate, indicating a tubular mechanism for potassium reabsorption. We have obtained evidence that a tubular secretory mechanism for potassium is also present in the normal dog. This was first suggested by the constancy of potassium excretion after the administration of salyrgan. Following the injection of salyrgan, potassium excretion may either increase or decrease but rapidly attains a fairly constant level at which it remains despite appreciable variations in filtered load associated with changes in filtration rate (creatinine clearance). This finding could be explained by the complete reabsorption of potassium in the proximal tubule and the secretion of potassium at a constant rate in the distal tubule.

More direct evidence of tubular secretion was obtained by the intravenous infusion of potassium in dogs whose tolerance had been increased by oral administration of potassium. It has been possible to attain potassium excretion rates 45 per cent greater than the simultaneous glomerular filtration of potassium (plasma potassium uncorrected for Donnan equilibrium multiplied by creatinine or inulin clearance).

Experiments in progress indicate that a similar mechanism for tubular secretion of potassium exists in man.

Catheterization of the Coronary Veins and the Measurement of Coronary Blood Flow in Man. R. J. BING, W. T. GOODALE, J. E. ECKENHOFF, J. C. HANDELSMAN, J. A. CAMPBELL, H. E. GRISWOLD, L. D. VANDAM, M. HARMEL, J. H. HAFKENSCHIEL, M. LUBIN, and S. S. KETY (Introduced by Alfred Blalock), Baltimore, Maryland.

The coronary blood flow of the dog has been determined using the nitrous oxide method of Kety and Schmidt. This report deals with the catheterization of the coronary sinus and the middle cardiac vein and with the determination of the coronary blood flow in man.

The procedures were carried out largely on patients with congenital heart disease and on a small group of individuals with peripheral vascular disorders without cardiac involvement. A special catheter designed by one of us (W. G.) was used in the majority of cases, since sampling of coronary blood through the standard Courmand catheter was difficult. Position of the catheter in the coronary veins was established by fluoroscopic visualization, blood oxygen contents, and by pressure measurements.

Coronary veins were intubated in nineteen individuals. The arteriovenous oxygen differences ranged from 8 to 18 vol. per cent. In five patients the coronary blood flow could be measured. In two of these the flow was 60 and 80 cc./min./100 gms. of heart tissue respectively.

In three others where admixture with auricular blood was suspected, lower flows were observed.

The introduction of the catheter into the coronary veins and the sampling of coronary vein blood proved to be the greatest difficulties in measuring flow. Electrocardiograms before and following the procedure were normal, and the patients experienced no discomfort.

Studies of Carbohydrate Metabolism in Normal and Diabetic Patients by the Liver Catheterization Technic.

PHILIP K. BONDY (Introduced by James P. O'Hare), Atlanta, Ga.

The technics of hepatic venous catheterization and estimation of hepatic blood flow have been used to study the carbohydrate metabolism of normal and diabetic patients.

The difference in concentration of glucose, urea and other metabolites in the arterial and hepatic venous blood has been multiplied by the hepatic blood flow to estimate absolute hepatic balances.

In the normal, fasting human, the hepatic circulation contributes 3.4 ± 0.5 mg. of glucose/kg./min. to the peripheral circulation. At the same time, $0.2 \pm .04$ mg./kg./min. of urea are formed, a urea/glucose ratio of .059.

After the intravenous injection of 0.5 gm. of glucose per kilo in 15 minutes, glucose is retained by the splanchnic system (presumably the liver), the mean retention at the termination of the clysis being 7.1 ± 2.3 mg./kg./min. The liver begins to release glucose to the circulation when the arterial glucose level falls to about 170 mg./100 ml. This suggests that the stimulus for glucose release may be the rate of fall rather than the actual glucose level.

In ketonuric diabetics who had not taken insulin for at least 72 hours, the hepatic glucose output varied from 3.8 to 17.2 mg./kg./min. (mean = 7.8), i.e., about twice the output of glucose in the normal fasting individual. The urea output was .88 to 2.7 (mean = 1.3) mg./kg./min., a urea/glucose ratio of .17. The increased urea/glucose ratio suggests the enhanced importance of gluconeogenesis in supplying carbohydrate under these conditions.

After the administration of insulin to decompensated diabetic patients, an immediate fall of arterial and hepatic venous glucose levels occurred, but the liver continued to contribute glucose to the circulation in diminishing quantities until at least one hour after the beginning of intensive treatment. Direct glycogen estimations by liver biopsy also showed a latent period in the deposition of glycogen under these circumstances.

Renal Osmotic Work During Forced Diuresis in Dehydration in Man. The Effect of Glucose and Urea Loading. (By invitation) WILLIAM A. BRODSKY, and S. RAPOPORT, Cincinnati, Ohio.

Large doses of glucose and urea were administered to diabetic and non-diabetic subjects, previously dehydrated by food and water deprivation for 16 hours, who had reached minimum urine flows of 0.25–0.35 cc. per min., and maximal solute concentrations of 1000–1100 m. osm./L.

Loading with glucose increased the urine flow to about twenty times the control rate. During the diuresis, the urinary concentration of solutes decreased to about 700 m. osm./L. Urea had a smaller effect. The urine flow increased only four times with less decrease of osmolarity.

During glucose diuresis, urinary sodium and chloride losses per minute increased fourfold, whereas the potassium excretion was not affected. Urea loading produced little change in the electrolyte excretion.

The renal osmotic work was calculated according to the equation of J. D. Newburgh, $E = RT (X_i \text{ in } X_i/C_i + C_i - X_i)$, with the following results:

(1) The kidneys during the control period were at a relatively resting state with respect to osmotic work.

(2) During forced diuresis by glucose, the renal osmotic work per minute increased tenfold, while the work per cc. of urine elaborated decreased to one-half.

(3) During urea diuresis, a fourfold increase in osmotic work per minute was observed, while the work per cc. of urine formed remained constant or even increased.

X_i = concentration of given solute in urine (milli-osmols per liter).

C_i = concentration of given solute in blood (milli-osmols per liter).

The Diagnostic Significance of the Respiratory Variation in the Ballistocardiograph. HERBERT R. BROWN, JR., and VINCENT DE LALLA, JR. (Introduced by William S. McCann), Rochester, New York.

It has been demonstrated that the variation of cardiac output with respiration is such that right heart output increases with inspiration and decreases with expiration, whereas the left heart output is the reverse. The cardiac output as measured by the ballistocardiograph increases with inspiration, and decreases with expiration, thus paralleling the right heart variation, although it also includes the left heart changes. It may be concluded that the right heart respiratory variation is greater than the left.

Using Starr's formula the respiratory variation of minute volume was calculated on 48 normal adults from ballistocardiograms. The smaller expiratory output was subtracted from the larger inspiratory output, and the difference divided by the body surface area in sq. meters. The normal range of this ballistocardiographic "Respiratory Variation Index" is from 20 to 400 cc. per sq. meter body surface area, with 85 per cent of the total number below 300 cc.

It was found that in certain abnormal states, such as hypertension and coronary insufficiency, this variation is increased. Study of 20 cases where a diagnosis of coronary insufficiency was considered, ballistocardiographic tracings revealed a "Respiratory Variation Index" of 350 to 900 cc. per sq. meter body surface area, with 85 per cent of the cases above 400 cc. It is felt that this observation offers another aid in the diagnosis of coronary insufficiency in those cases where it is suspect, and where other diagnostic procedures are not helpful.

An increase in the ballistocardiographic "Respiratory Variation Index" was produced in normal subjects by introducing a resistance to breathing, and also by exposing normal subjects to cold.

It is possible that the mechanisms causing the increased ballistocardiographic respiratory variation in coronary insufficiency may be either one or both of the following: (1) increased pulmonary resistance causing a diminished venous return to the right heart on expiration, or (2) inadequate venous return to the right heart caused by pooling of blood in the venous system, with further diminution during expiration.

Should either of these theories prove tenable it follows that, in certain cases, coronary insufficiency is caused by inadequate left ventricular output.

Patterns of Cardio-Respiratory Functions in Exertional Dyspnea. ROBERT A. BRUCE, FRANK W. LOVEJOY, JR., GEORGE B. BROTHERS, and RAYMOND PEARSON (Introduced by Nolan L. Kaltreider), Rochester, New York.

Exertional dyspnea is reproduced by walking patients on a motor-driven treadmill at a standard rate of 2.6 M.P.H., or a slower rate of 1.7 M.P.H. Continuous measurements of cardio-respiratory functions and chest electrocardiograms are made for 10 minute periods of rest, walking, and recovery.

Normal subjects are asymptomatic and show no functional impairment. Uniform zones of response are obtained with 10 per cent coefficient of variability between men of 30 to 60 years of age (average 44 years). During the exercise and recovery the heart rates show high correlations with oxygen consumption.

Patients with exertional dyspnea show variable degrees of hyperventilation. Those with pulmonary emphysema, fibrosis, or beryllium granulomatosis show high ventilation equivalents. In contrast to normals there is little change in oxygen and carbon dioxide concentrations in either expired or alveolar air with exercise. Patients with heart disease exhibit tachycardia with exercise, and diminished tolerance to exertion. Since oxygen debts are large, and recovery prolonged, failure to maintain oxygen consumption proportional to tachycardia and metabolic demands is suggested. Variable ST segment and T wave changes are observed. Paradoxical changes in oxygen and carbon dioxide concentrations with exercise aid the differentiation of Tetralogy of Fallot from Eisenmenger's complex.

Evaluation of Neurogenic and Humoral Factors in Blood Pressure Maintenance in Normal and Toxemic Pregnancy Using Tetraethyl Ammonium Chloride. (By invitation) ALBERT A. BRUST, (by invitation) N. S. ASSALI and EUGENE B. FERRIS, Cincinnati, Ohio.

Previous studies in hypertension suggest that failure to obtain a fall in arterial blood pressure following autonomic blockade with tetraethyl ammonium chloride (TEAC) is due to the action of circulating pressor agents (humoral factor). When neurogenic tone is

abolished the blood pressure remains responsive to humoral agents and thus must be maintained by humoral mechanisms together with intrinsic vascular tone. Accordingly an assay of TEAC responses in normal and toxemic pregnancy was undertaken in an effort to throw light on the relative importance of humoral and neurogenic factors in these conditions.

Ten patients at term of normal pregnancy were tested prepartum and postpartum following intravenous administration of 400 mgm. TEAC. The lowest blood pressure level recorded following this procedure has been termed the TEAC floor. In every instance the prepartum response to autonomic block was a marked fall in blood pressure to mean levels of 50-60 mm. Hg even though clinical evidence of shock was not encountered. Studies conducted 24-48 hours after delivery showed a marked rise in TEAC floors, the immediate postpartum responses corresponding to those of 10 normal non-pregnant controls.

Similar prepartum and postpartum tests were performed on 18 patients with the clinical diagnosis of preeclampsia and 3 with eclampsia. Although some fall in blood pressure was noted in the studies preceding delivery, the lowest prepartum TEAC floor in toxemia was 20 mm. Hg above the highest prepartum TEAC floor in normal pregnancy, and differences up to 70 mm. Hg were observed. These striking differences were seen in both the systolic and diastolic blood pressure floors. Twenty of the 21 patients in the toxemia group showed a fall in TEAC floor following delivery while all 10 of the normal pregnant group showed a marked rise of the TEAC floor postpartum.

The low prepartum TEAC floors in the normal pregnancies followed by a rise to normal response after delivery suggest that a major portion of blood pressure maintenance at term is under neurogenic control and that humoral influences are at a minimum. Conversely, the failure of prepartum TEAC floors in toxemia to fall to levels comparable to those of the normal pregnancies supports the concept that humoral factors play a major role in sustaining the blood pressure at elevated levels in preeclampsia and eclampsia. Further evidence for this may be seen in the postpartum lowering of the TEAC floors in the toxemia group.

These studies further suggest that clinical assay with TEAC may be a helpful aid in the diagnosis of toxemia of pregnancy. Clues as to the course and severity of this condition may likewise be obtained by its use.

Kidney Function in Osteomalacia Resulting from Renal Acidosis. CHARLES H. BURNETT, (by invitation) BELTON A. BURROWS, and (by invitation) ROBERT R. COMMONS, Boston, Massachusetts.

Clearance measurements in five patients with osteomalacia and renal acidosis due to the syndrome previously designated as "tubular-insufficiency-without-glomerular-insufficiency" showed decreased $C_{Mannitol}$ and C_{PAH} and elevated filtration fraction. Tm_{PAH} was low and $C_{Mannitol}/Tm_{PAH}$ high in three of four patients studied. One pa-

tient with osteomalacia and the Fanconi syndrome had decreased C_{INULIN} , and C_{PAH} with a high filtration fraction.

Renal tubular bicarbonate reabsorption was measured once in each syndrome. Starting at acidotic levels heavy loads of sodium intravenously resulted in increased urine alkalinity, and bicarbonate excretion up to 0.4 milliequivalent per 100 cubic centimeters of glomerular filtrate while plasma bicarbonate was well under 25 milliequivalents per liter. In agreement with Pitts observations, two normal subjects began bicarbonate excretion only after plasma bicarbonate exceeded this level. Simultaneous bicarbonate and sodium excretion, measured only in the Fanconi syndrome, showed that most of the sodium being wasted was in combination with bicarbonate.

The clearance measurements suggest generalized renal impairment, but greater relative tubular than glomerular dysfunction in both syndromes. In each group the acidosis could be partially explained by the inability of the kidneys completely to reabsorb all bicarbonate filtered at low plasma levels of this anion.

The Oxygen Consumption of the Human Kidney.

WALTER H. CARGILL and JOHN B. HICKAM (Introduced by W. M. Nicholson), Durham, North Carolina.

Samples of renal venous blood were obtained by the catheterization technique and compared with simultaneous samples from the femoral artery for oxygen and sodium p-aminohippurate (PAH) content. Intravenous infusions of inulin and PAH were given and urine collected according to the usual clearance methods. Renal blood flow was calculated from the rate of PAH excretion, the arterial-renal venous PAH difference, and the hematocrit reading. The oxygen consumption of the kidney was estimated from the arterial-renal venous oxygen difference (renal oxygen extraction) and the renal blood flow. The glomerular filtration rate was measured at the same time by the inulin clearance. All subjects were studied under basal conditions.

A total of 35 subjects have been studied. For the sake of comparison, these have been divided into three groups: (1) ten patients without hypertension or clinically apparent renal disease, (2) seventeen patients with chronic pyelonephritis or essential hypertension, and (3) eight patients with subacute glomerulonephritis. In the normal subjects the mean renal oxygen extraction was found to be 1.4 vols. per cent, and the mean renal oxygen consumption 16.0 cc./min., standard deviation 2.8. The patients with chronic nephritis and hypertension demonstrated a normal oxygen extraction (1.5 vols. per cent) but a moderate to marked reduction in renal blood flow, so that the renal oxygen consumption for the group as a whole was below normal limits (mean 9.0 cc./min.), the decrease in oxygen consumption for each individual being a function of the decrease in blood flow. In this group of subjects a direct relation between renal blood flow and oxygen consumption was apparent. In contrast, the patients with subacute glomerulonephritis showed a reduction in oxygen consumption (mean 7.0 cc./min.) due almost entirely to a decreased oxygen extraction (mean 0.7

vol. per cent), since the renal blood flow of most of these patients was within normal limits.

In the entire group of 35 patients studied a positive correlation between glomerular filtration rate and renal oxygen consumption was apparent. No correlation was evident between the oxygen consumption and the degree of tubular reabsorption of water as measured by the inulin U/P ratio.

It is hoped that these findings will constitute a physiological basis for the clinical differentiation of patients with kidney disease into two groups: (1) those with a disturbance of renal metabolism secondary to occlusive vascular disease (chronic pyelonephritis and essential hypertension), and (2) those with an alteration in renal metabolism with a normal renal blood flow (subacute glomerulonephritis). Whether the decreased renal oxygen consumption in the second group is due to impaired glomerular filtration or primary tubular dysfunction is yet to be determined.

The Use of Radioactive Phosphorus in Measuring Plasma Phospholipide Formation in Patients with Cirrhosis of the Liver. The effects of Treatment with Methionine. DAVID CAYER and W. EUGENE CORNATZER (Introduced by David T. Smith), Winston-Salem, N. C.

In animals on deficient diets choline and methionine prevent fatty infiltration of the liver. They also stimulate the formation of liver phospholipides which are the main source of plasma phospholipides. Clinically, methionine is useful in the treatment of human beings with chronic hepatitis—an early stage of cirrhosis—as well as those with more advanced disease and ascites. To determine if the benefit is due to an effect on phospholipide formation, hospitalized patients with cirrhosis and normal individuals were given intramuscular injections of radioactive phosphate. At various time intervals after injection, radioactivity and total phosphorus content were determined in the lipide and in the inorganic fractions of plasma. On the basis of the specific activity—time curves obtained on the phospholipides of normal individuals, the 24 hour level was selected for comparison with that found in patients with cirrhosis. The specific activities (even when adjusted in relation to the specific activity of the inorganic phosphate in plasma) show considerable variations both in the control group and in patients with cirrhosis. No significant difference was found between the two groups. The possible effect of methionine on phospholipide turnover was investigated by reinjecting radiophosphorus after 30 days of treatment with methionine (3 gm. per day).

The Incidence, Character and Course of Liver Disease in Chronic Alcoholics as Determined by Needle Biopsy. THOMAS C. CHALMERS, T. LYNCH MURPHY and EDGAR B. TAFT (Introduced by Clark W. Heath), Cambridge, Massachusetts.

Liver biopsies were obtained within a few days of admission to the hospital from 24 patients manifesting incipient or active delirium tremens. Physical and lab-

oratory signs of liver disease were minimal or absent, but histologically all of the 24 livers were abnormal. In seven biopsied a second time there was improvement after treatment with a regular hospital diet.

These patients could be classified according to the Bowman-Jellinek scheme as either steady or intermittent drinkers. The two groups were equal in number and similar in respect to age and duration of alcoholism. The steady drinkers ate at least one good meal a day, were regularly employed and usually entered the hospital because of an infection. The intermittent drinkers neither ate nor worked while drinking and usually entered the hospital with uncomplicated delirium tremens. As shown in the table, the extent and character of the liver injury seemed to depend on the alcoholic habits of the patient. It is concluded that the liver is abnormal in chronic alcoholics after a bout severe enough to terminate in delirium tremens and that the steady drinker is more likely to show the histological picture of alcoholic cirrhosis.

	Intermittent drinkers	Steady drinkers
Total	12	12
Fatty metamorphosis	12	4
Fatty infiltration	0	8
Fibrosis—definite	3	7
Fibrosis—slight	1	3
Necrosis	1	6
"Alcoholic" hyaline	0	7
Unidentified pigment—moderate or more	8	1

The Effect on Respirations and Blood Pressure of Electrical Stimulation of the Orbital Surface of the Frontal Lobe and of Frontal Lobotomy in Man. WILLIAM P. CHAPMAN, (by invitation) ROBERT B. LIVINGSTON, and (by invitation) KENNETH E. LIVINGSTON, Boston, Massachusetts.

During light pentothal anesthesia transcortical electrical stimulation of the orbital surface of the frontal lobe produced arrest of respirations in the expiratory phase in six out of eight patients and elevation of blood pressure in five out of eight patients. Respiratory and blood pressure responses had consistent latency and recovery periods and were obtained independently or together depending on the area stimulated. The magnitude of blood pressure elevation was from ten to twenty mm. of mercury, these changes being from two to four times as great as the maximal variation during the control period. Blood pressure was recorded by a Hamilton manometer and respirations by a pneumatic cuff.

A significant lowering of elevated blood pressure in eleven mental patients, extensively studied, was maintained not longer than five months after frontal lobotomy.

These studies establish for the first time in man that stimulation of the orbital surface of the frontal lobe arrests respirations and elevates blood pressure. Frontal lobotomy apparently does not result in permanent lowering of blood pressure. The nature of this mechanism, the anatomical pathways involved, and the importance of

these observations relative to the role of emotions in modifying respirations and blood pressure are not understood.

The Electrolyte Content of Thermal Sweat as an Index of Adrenal Cortical Function. JEROME W. CONN and (by invitation) LAWRENCE H. LOUIS, MARGARET W. JOHNSTON, and (by invitation) BETTY J. JOHNSON, Ann Arbor, Michigan.

Several years ago we reported metabolic evidence indicating that the process by which normal men acclimatize to heat is associated with a sharp increase in adrenal cortical activity. In the course of this study it became clear that the electrolyte composition of the sweat was reflecting changes in adrenal cortical function.

The present study indicates (1) a consistent relationship between the electrolyte composition of sweat and the degree of activity of those corticosteroids which effect salt and water metabolism (S W corticosteroids), (2) that reabsorption of electrolytes by the tubules of the sweat glands and kidneys is affected in a similar way by the action of S W hormones but that the sweat does not "rebound" toward normal under continued activity of these steroids as does the urine, (3) that A C T H is capable of stimulating simultaneously increased production and release of all three types of corticosteroids (N, S, and S W), and (4) that in various clinical states involving increased or decreased function of the adrenal cortices, the electrolyte composition of the sweat affords clear evidence of the disturbance.

Results.

(1) *D C A* in normal humans produces a sharp fall in the concentrations of both Na and Cl of sweat and a rise in the concentration of K. Increased reabsorption of Na is more intense than that for Cl. This effect persists for as long as *D C A* is given and does not "rebound" on continued administration of *D C A*. Upon cessation of *D C A* an intense rebound occurs.

(2) *A C T H* in normal humans produces precisely the same effects upon the electrolyte concentrations of sweat and urine as those produced by *D C A*. Under continued administration of 120 mg. per day for 8 days, the rebound of the electrolyte concentration of urine had occurred by the third or fourth day of injection while that of the sweat did not rebound until two to three days after the last injection (the 17-ketosteroids had already returned to baseline).

In parallel but different in time relations, there occurred negative nitrogen balance, great loss of carbohydrate tolerance, overall retention of Na and Cl, and loss of K, typical hematological changes, initial increase in uric acid excretion, and a four to fivefold increase 17-ketosteroid excretion. No change was observed in the gamma globulin fraction of the serum proteins by electrophoresis nor in immune titers.

(3) *Sweat tests in patients with adrenal cortical dysfunction (14 cases).*

(a) Normal range of Cl conc. in m.eq. per liter	17.5 to	58.0
(b) Adrenal cortical carcinoma with Cushing's syndrome	1.7 and	2.7
(c) Adrenal cortical carcinoma with adrenogenital syndrome	5.7 and	9.1
(d) Cushing's syndrome without carcinoma (2 cases)	5.9 to	13.5
(e) Pan-hypopituitarism (3 cases)	68.0 to	75.0
(f) Addison's disease (7 cases)		
Untreated	105.0 to	122.0
Treated	25.0 to	63.0

Na concentrations show similar degrees of difference between normals and patients. K changes are smaller in degree but significant.

Improvement in Pulmonary Function after Anticholinergic Agents in Spontaneous and Methacholine-induced Asthma. JOHN J. CURRY, JOB E. FUCHS and SAMUEL E. LEARD (Introduced by William L. Fleming), Boston, Massachusetts.

Sporadic attention has been focused on the role of the parasympathetic nervous system in bronchial asthma. We have confirmed the abnormal responsiveness of the tracheobronchial tree to cholinergic substances using agents such as pilocarpine, neostigmine, furfuryl trimethylammonium iodide, methacholine and acetylcholine itself. The order of this surprising sensitivity and the resemblance of induced attacks to spontaneous asthma suggested that a survey of anticholinergic agents might furnish information useful in the treatment of bronchial asthma. The method of study has been outlined in part by previous communications. In brief it involves a sharp reduction in pulmonary function tests, induced by either spontaneous asthma or the injection of methacholine. In the former cases the improvement in pulmonary function following the administration of anticholinergic agents was recorded, whereas in the latter the degree of protection afforded by them against subsequent repeated doses of methacholine was measured. In the majority of tests a 9 liter Benedict-Roth type metabolism apparatus was used.

Results indicate that contrary to popular opinion the belladonna alkaloids, atropine, 1-hyoscyamine, hyoscyne and Bellafoleline afforded notable relief in spontaneous asthma and were very effective in protecting against methacholine-induced asthma.

Synthetic anticholinergic agents such as Trasentin and Syntropan with the exception of merperidine hydrochloride were not very effective. Sympathomimetic amines, such as ephedrine and Orthoxine, and also aminophylline were usually effective. Benadryl varied from no effect to slight effectiveness.

Cancellation of Fluoride Antiglycolytic Activity by Calcium and Magnesium Ions. T. S. DANOWSKI, Pittsburgh, Pennsylvania.

Release of glycolysis from fluoride inhibition by calcium and magnesium salts was studied in defibrinated

blood. CaCl_2 and MgCl_2 (20 to 80 milliequivalents per liter) in blood which contained 20 milliequivalents per liter of NaF completely or almost completely abolished the antiglycolytic effect of fluoride. In the lower concentrations, CaCl_2 proved more effective than MgCl_2 ; the reverse was true at 80 milliequivalent per liter levels. This release is related to calcium and magnesium ions, since other chlorides (KCl , NaCl , NH_4Cl) were ineffective. Furthermore, known accelerators of glycolysis in blood (PO_4^{3-} , SO_4^{2-} , and HCO_3^-) failed to cancel the fluoride effect. However, it was possible to show in fluoride-treated blood the characteristic acceleration which follows added SO_4^{2-} , by introducing magnesium in excess of the fluoride present.

It seems probable that the cancellation of fluoride activity by Mg^{++} and Ca^{++} is related to the high insolubility of the fluoride salts of these cations, and possibly to the replacement of deficits of Mg^{++} and Ca^{++} . The former is supported by the comparable efficacy in this respect of Ba^{++} which also forms an insoluble fluoride, and by the failure of CaF_2 and MgF_2 to suppress glycolysis in blood.

A Study of the Physiologic Function and Histopathology of Thyroid Adenomas Using Radioactive Iodine and Radioautography. BROWN M. DOBYNS and BEATRICE LENNON (Introduced by J. H. Means), Boston, Massachusetts.

The function of thyroid adenomas was demonstrated by radioautographs made from histologic preparations of nodules removed from 90 patients who had received radioactive iodine preoperatively. Localization of function was correlated with the histologic features of the tissue including cellular pattern, cell height, colloid formation, and nuclear and cytoplasmic details. These were compared with clinical aspects.

The degree of function of the adenomas runs parallel to the degree of cellular differentiation. Single or multiple hyperfunctioning adenomas, with a distinct histologic pattern, occurred in patients having thyrotoxicosis; however, appreciable numbers were found associated with normal or subnormal basal metabolic rates. In the latter group the total hyperfunctioning cell mass was insufficient to cause elevation in basal metabolic rates (these were thought to be related to some borderline clinical features of hyperthyroidism). A depression of the cell height of the uninvolved tissue was observed in instances of hyperthyroidism arising from hyperfunctioning adenomas. Here the uninvolved tissue was practically functionless. Some non-functioning hyperplastic adenomas presented a picture of irregular but increased cell height in contrast to a uniform increase in cell height found in hyperfunctioning adenomas. From histologic aspects the non-functioning hyperplastic adenomas graded into the papillary forms of malignancy without function.

The Paradoxically Retarded Bactericidal Activity of Penicillin at High Concentrations in Vitro and in Vivo.

HARRY EAGLE, Bethesda, Maryland.

The bactericidal activity of penicillin against a particular organism may be defined in terms of three concentrations: (1) that which serves only to reduce the rate of multiplication, (2) that which causes a slow bactericidal action, and (3) a somewhat higher concentration at which the organisms are killed at a maximal rate.

With some organisms this maximal rate is unaffected by even a 20,000-fold further increase in concentration of the drug. With other organisms, however (*e.g.*, all of 4 strains of Lancefield group B β -hemolytic streptococci, 2 of 4 strains of group G streptococci, 5 of 7 strains of *Streptococci fecalis*, 2 of 4 strains of other α -hemolytic organisms, and 4 of 9 strains of *Staphylococcus aureus* and *albus*), when the concentration of penicillin was increased beyond the maximally effective level, there was a progressive and in some instances striking decrease in the rate of bactericidal action.

A similar phenomenon was sometimes observed *in vivo*. In such cases the high concentrations of penicillin afforded by the frequent administration of large doses were significantly less effective than the lower concentrations afforded by smaller doses. In the treatment of infections with these zone-sensitive organisms, the most effective method of treatment may well be repeated small doses, or a continuous infusion at a rate designed to maintain the optimally effective concentration at the focus of infection.

Evidence for the Concept that Total Lung Rest is Provided by the Equalizing Pressure Chamber. CHESMORE EASTLAKE, JR. and JOHN E. GARY (Introduced by Alvan L. Barach), New York, N. Y.

Patients with pulmonary tuberculosis exposed to an alternating pressure of 55 mm. Hg 25 times a minute reveal absence of all discernible chest motion when the resistance in the respiratory passageway is counterbalanced by a differential pressure of 4 to 8 mm. Hg. X-ray studies have been made with superimposed lead crosses that demonstrate the degree of chest motion during normal breathing and the absence of motion during exposure to equalizing alternating pressure. A motion picture (4 minutes) reveals, through animation, the variations in air density and chest pressures, which explain the mechanism of the chamber and, by means of photography of patients, the degree of total lung rest obtained.

The Pulmonary Blood Volume by a Dye Injection Method and its Relation to Pulmonary Hypertension in Certain Cardiac Lesions. RICHARD V. EBERT and (by invitation) CRAIG BORDEN, (by invitation) HERBERT S. WELLS and (by invitation) RUSSELL H. WILSON, Minneapolis, Minnesota.

In 10 normal subjects and a group of patients with heart disease, the pulmonary artery was catheterized. Evans Blue Dye was injected rapidly into the pulmonary

artery and multiple blood samples were collected from the femoral artery. The serum concentration of dye plotted against time gives a curve which, in normal individuals, is symmetrical and reaches or approaches zero before recirculation begins. The mean circulation time (CTm) is read from the curve at the mid point of its area. The volume of blood in pulmonary vessels, left heart and larger systemic arteries (PBV) is equal to the cardiac output (L/Min.) $\times \frac{\text{CTm (Sec.)}}{60}$.

In patients with mitral stenosis and exertional dyspnea of long standing but without hepatomegaly or peripheral edema, the pulmonary arterial pressure is markedly increased but the PBV is normal. In left ventricular failure due to hypertension or aortic valve lesions, the PBV is considerably increased but the pulmonary arterial pressure is less strikingly elevated than in mitral stenosis. These findings suggest that the increased pressure in mitral stenosis is not due entirely to increased pressure in the left auricle but is due in part to pathological changes in the pulmonary vessels.

Improvement of Active Liver Cirrhosis in Patients Maintained with Amino Acids Intravenously as the Source of Protein and Lipotropic Substances. (By invitation) R. D. ECKHARDT, (by invitation) W. W. FALLOON, and C. S. DAVIDSON, Boston, Massachusetts.

Three patients with active cirrhosis of the liver were treated for 11, 18, and 20 days with a purified diet devoid of protein. The diet contained no source of the vitamin B-complex except choline in small amounts (30 to 100 mgm. daily). A capsule containing vitamins A, C, D, B₁, B₂, niacin, B₆, and pantothenic acid was given daily.

Protein was supplied intravenously as an amino acid mixture (Merck) prepared by the acid hydrolysis of casein, devoid of peptides, glutamic and aspartic acids, and supplemented with dl-tryptophane and glycine. The days' protein (50 to 100 Gm. of amino acids containing from 2.0 to 4.2 Gm. of methionine) was administered in one rapid intravenous injection each morning.

All three patients maintained a positive nitrogen balance with an average retention of 3 Gm. of nitrogen daily in spite of a loss in the urine of from 3 to 14 per cent of the amino nitrogen administered. The urinary excretion pattern of the "10 essential" amino acids was similar to that for normals after the same infusion (microbiological assay).

The amino acid mixture was well tolerated clinically. Hyperaminoacidemia and azotemia were not observed, nor was there a progressive increase in the urinary excretion of amino nitrogen. Improvement in liver disease was observed in all three by a progressive decline in the serum bilirubin and by improvement in clinical condition. A slight weight gain occurred.

It is concluded that not only are intravenous amino acids well tolerated by patients with active liver disease, but also that clinical improvement may occur when amino acids are the sole source both of nitrogen and of lipotropic substances except for small amounts of choline.

A Study of the Changes in Plasma Volume, Renal Function, and Water and Salt Balance Induced by Repeated Administration of Human Plasma Albumin to Patients with the Nephrotic Syndrome. HOWARD A. EDER, FRANCIS P. CHINARD, ROGER L. GREIF, GEORGE C. COTZIAS, ALMA HILLER, D. D. VAN SLYKE, and HENRY D. LAUSON (Introduced by Oswald T. Avery), New York, N. Y.

Salt-poor human plasma albumin was administered to patients with the nephrotic syndrome to obtain quantitative information regarding the mechanism of albumin-induced diuresis.

Albumin was administered daily for 1 to 3 months in doses ranging from 0.5 to 1.5 grams per kilogram. One month control periods preceded and followed albumin administration. At weekly intervals changes in the clearances of endogenous creatinine, urea, chloride, and protein were measured continuously during a 24 hour period in which each voided urine comprised a clearance period. On these days plasma volume and protein concentration were determined at frequent intervals. Para-aminohippurate clearances were measured every 2 to 4 weeks. Day to day changes were followed by determination of the total 24 hour clearance of endogenous creatinine and the excretion of urea, chloride, and protein.

Administration of albumin was followed by acute increases in plasma albumin concentration, plasma volume, and total circulating albumin. The renal blood flow and glomerular filtration rate increased during this same period; concomitantly the excretion of water, chloride, and protein increased.

The data may help to clarify the relationship of water and salt excretion to the processes of glomerular filtration and tubular reabsorption, which are ultimately responsible for the accumulation and elimination of edema fluid.

Studies on the Role of the Adrenal Cortex in Protein Metabolism. FRANK L. ENGEL and (by invitation) SARA SCHILLER, (by invitation) E. I. PENTZ, and (by invitation) PHILIP K. BONDY, Durham, N. C.

Based on the relatively constant accumulation rate of urea N following nephrectomy in the rat, a method has been devised capable of detecting changes in nitrogen metabolism of the order of 1.0 mg. N/100 gms. body weight for periods as brief as one hour. The relation of adrenal cortical extract (A.C.E.) to protein metabolism was studied by this technique with the following results: (a) An increase in protein catabolism begins two to three hours after A.C.E., characterized by approximately equal increments in urea N each hour for the next three hours; (b) An intravenous injection of an amino acid mixture (Merck's VuJ) results in a prompt increase in urea during the subsequent hour, less in the second hour, and none in the third; (c) A.C.E. plus VuJ yields no more urea N than either alone, 70 per cent of the urea appearing in the first hour, i.e., the response is as if VuJ alone were given. Liver glycogen levels are significantly increased after VuJ and VuJ plus

A.C.E.; (d) Intravenous glucose two hours after A.C.E. inhibits the usual increase in urea N but does not prevent that after VuJ. Liver glycogen values are increased after glucose and glucose plus A.C.E.; (e) The rate of urea formation from injected amino acids is identical in control and adrenalectomized rats after nephrectomy. Since the increase in nitrogen metabolism after A.C.E. can be inhibited by amino acids (VuJ) or glucose, while that after VuJ cannot be prevented by glucose, and since deamination and urea formation are unaffected by adrenalectomy, it is suggested that the changes in protein metabolism after A.C.E. may not be a primary effect of the hormone, but may be secondary to the alterations in carbohydrate metabolism.

A Study of the Circulation in Pulmonary Vascular Disease. EUGENE C. EPPINGER, (by invitation) JAMES W. DOW, (by invitation) JAMES L. WHITTENBERGER, (by invitation) HENRY BREAN, Boston, Massachusetts.

Measurements of the circulation by the venous catheter technique were made in four patients with pulmonary vascular diseases of varying etiology. Each complained of dyspnea on slight exertion despite a normal vital capacity; three of "dizzy spells," and two of these three of syncopal episodes.

Pulmonary artery pressures, pulmonary capillary pressures, and cardiac outputs were measured at rest; in two patients pulmonary artery pressures and cardiac outputs were measured during exercise.

The findings at rest were as follows:

1. Elevated pulmonary artery pressures.
2. Normal pulmonary capillary pressures.
3. Normal cardiac outputs.
4. Widened arterio-venous oxygen difference.
5. Arterial oxygen unsaturation.
6. Moderate elevation of the ventilatory volume.

Two patients exhibited the following responses to mild exercise:

1. Further rise in pulmonary artery pressures.
2. Marked widening of the arterio-venous oxygen difference, in direct proportion to increased oxygen consumption.
3. Unchanged cardiac output.
4. Increased arterial oxygen unsaturation.
5. Markedly increased ventilatory volume.

It is concluded that these patients have a high resistance to blood flow, localized in the region of the pulmonary arterioles, and that their disabilities arise, in part, from the inability to increase the cardiac output to meet the demands of exercise.

The Jarisch-Herxheimer-Reaction in Early Syphilis Treated with Crystalline Penicillin G. THOMAS W. FARMER (Introduced by J. E. Moore), Baltimore, Maryland.

1. Febrile Herxheimer reactions were observed in 41 per cent of 939 patients with early infectious syphilis

treated with crystalline penicillin G. These reactions occurred with equal frequency and severity in seronegative primary, seropositive primary and secondary syphilis.

2. In a group of 56 patients with relapsing secondary syphilis treated with penicillin, the incidence of fever was 50 per cent with the first treatment course and 38 per cent with the second course of therapy.

3. Within a wide range of penicillin dosage (10 to 120,000 u./kg.) the incidence of febrile reactions remained relatively constant (40 to 56 per cent). With extremely small doses of penicillin (1 to 5 u./kg.) febrile reactions were not observed.

4. The temporal pattern of the febrile reaction was quite uniform, and it was independent of the dosage over a wide range.

5. Febrile reactions occurred with single doses of penicillin as little as one-tenth of the amount required to render early syphilitic lesions dark-field negative.

6. With repeated small doses of penicillin (10 to 20 u./kg.) two febrile reactions were produced in the same patient. This double Herxheimer reaction was not observed after repeated large doses of penicillin.

7. The available evidence does not justify the hypothesis that the reaction is due solely to the sudden destruction of large numbers of spirochetes with the liberation of split proteins or endotoxins.

In Vitro Lysis of Leucocytes by Tuberculin and by the Serum of Patients Receiving Adrenocorticotrophic Hormone. C. B. FAVOUR and PAUL FREMONT-SMITH (Introduced by Kendall Emerson, Jr.); Boston, Massachusetts.

The tuberculin type of delayed bacterial hypersensitivity can be passively transferred with white cells from properly sensitized donors. A portion of cells from such donors when exposed to tuberculin (PPD) *in vitro* are lysed within 60 minutes. This phenomenon depends upon the presence of complement and is disease specific, as is the delayed type of skin reaction itself. On the other hand, serum from normal subjects receiving adrenocorticotrophic hormone (ACTH) or serum from an untreated patient with Cushing's disease will lyse a fraction of the leucocytes from normal donors *in vitro* in the absence of complement.

Pneumonitis of Unknown Etiology in a Group of Men Exposed to Pigeon Excreta. (By invitation) HARRY A. FELDMAN and ALBERT B. SABIN, Cincinnati, Ohio.

Twelve men, exposed in various degrees to moistened pigeon excreta in an abandoned water tower in Cincinnati, all developed illnesses of varying severity within 5 to 14 days. Three were only slightly ill with fever for 2 to 5 days while 9 were more severely affected with generalized malaise, headache, chills, non-productive cough, and marked weakness, and were febrile for 8 to 24 days. Although no significant signs were elicited on

physical examination, all of the 12 men exhibited extensive, diffuse, miliary-like infiltrates in both lung fields, giving rise to the most striking feature of this disease, the "snow-storm" roentgenogram. These x-ray changes persisted with varying diminution of intensity for 2 months or longer, but by the end of 5 to 6 months the lungs were almost clear in all but 2 patients, and there was no evidence of calcification. All recovered from the illness, but an opportunity to obtain some idea of the pathological changes of this disease presented itself when one of the men met sudden death 5 months later as a result of an acute myocardial infarction in an arteriosclerotic heart. Although the x-ray of his chest was practically clear 2 months prior to his death, multiple microscopic lesions 1 to 2 m. in diameter were found in the lungs and peribronchial lymph nodes. The lesions were in various stages of organization but in both the lungs and the lymph nodes there were many with central caseous necrosis and "Langhans-type" giant cells *unassociated* with acid-fast bacilli. Inoculation of mice with blood obtained from 11 of the 12 men during the acute stage yielded no infectious agent and serological studies as well as skin tests during convalescence indicated that the etiological agent of this disease was not that of ornithosis, Q fever, coccidioidomycosis, blastomycosis, histoplasmosis or toxoplasmosis.

Red Cell Destruction. CLEMENT A. FINCH, EDWARD D. THOMAS, ROBERT J. WALSH and REX G. FLUHARTY (Introduced by George W. Thorn), Boston, Mass.

Morphological studies have implicated the spleen, liver, and kidneys in blood breakdown. Employing erythrocytes labeled with radioiron and hemoglobin prepared from such cells, it is possible to localize accurately pigment cleared from the blood.

Labeled hemoglobin is rapidly and almost exclusively taken up by renal tissue even when given in amounts below "renal threshold." In contrast, the kidneys of rats transfused with non-viable labeled erythrocytes show only a small amount of radioactivity, while a much greater amount is found in the reticuloendothelial tissue.

For these animals, the two types of blood breakdown are easily distinguished by this technique. With *intravascular hemolysis* hemoglobin, regardless of the plasma level, accumulates in the kidney. Thereafter the radioiron can be traced to storage depots, and eventually appears in circulating red cells. This indicates that free hemoglobin is processed chiefly by the renal tissue and supports the hypothesis that hemoglobin is normally filtered through the glomerulus and re-absorbed by the tubules. In contrast, in *extravascular destruction* of red cells, the reticuloendothelial tissue takes up the damaged erythrocytes. The spleen shows a much greater capacity than the liver to dispose of red cells, as evidenced by the higher unit radioactivity found in the former organ. That this represents cell phagocytosis is indicated by the inability of reticuloendothelial tissue to handle free hemoglobin.

Clinical Experience with the Use of the ACTH Test for Adrenal Cortical Function. (By invitation) PETER H. FORSHAM, GEORGE W. THORN, and (by invitation) LILLIAN RECENT and (by invitation) A. GORMAN HILLS, Boston, Massachusetts.

Validity of the four-hour pituitary adrenocorticotropin (ACTH) response as a simple diagnostic test for Addison's disease has been confirmed in thirty-four classical cases. The mean depression of circulating eosinophils following ACTH administration was 6 per cent (-44 to $+26$) in these cases, 77 per cent (-63 to -97) in ten normals, and 73 per cent (-52 to -98) in forty non-Addisonians. Although mean fasting eosinophil levels in Addisonians (273 per cu. mm.) exceeded the normals (167) and non-Addisonians (181), there was a large overlap.

A mean increase of 21 per cent (0 to 81) in urinary uric acid-creatinine ratio was noted following ACTH administration in the Addisonians, 91 per cent (62 to 130) in the normal group and 89 per cent (28 to 172) in the non-Addisonian group. The fasting uric acid-creatinine ratio was not significantly different in the three groups (0.5).

A patient with Cushing's disease showed a low initial eosinophil count (4) and a high fasting uric acid-creatinine ratio (1.0).

Cases of mild adrenal insufficiency will respond to a forty-eight hour hormone administration in contrast to severe Addisonians. Absence of a response to intravenous epinephrine suggests hypoadrenalism associated with hypopituitarism.

The Disappearance of Edema Through Diuresis Following Artificial Elevation of Plasma Sodium and Bicarbonate. CHARLES L. FOX, JR., D. J. McCUNE, A. H. BLAKEMORE, R. GILDER and R. MOLOSHOK (Introduced by A. R. Dochez), New York, N. Y.

Edema, ascites and oliguria are usually associated with decreased plasma sodium and acidosis (Atchley, J.C.I., 1930, 9, 265). Extracellular water then migrates into cells (Peters, Phys. Rev., 1944, 24, 491; Gamble, Extracellular Fluid, Boston, 1942), resulting in reduction in plasma volume (Darrow, J.C.I., 1935, 19, 419; Winkler, J.C.I., 1944, 23, 111). Impaired excretion of water follows (McCance, Proc. Roy Soc., B, 1935-6, 119, 245). These abnormalities prevailed in one patient during anuria after diabetic acidosis; in one example of Chiari's syndrome after operation to produce porto-caval shunt followed by numerous taps of the peritoneum and pleura; and in 14 patients with the nephrotic syndrome.

Correction of low plasma sodium and bicarbonate might be hoped to augment plasma volume and subsequently increase output of urine and chloride, thereby removing anasarca. Accordingly, sodium lactate and subsequently sodium and potassium acetate were administered orally. Initially body weight increased. Plasma sodiums rose from 120-135 mEq. per liter to above normal; plasma bicarbonates from 9-20 mEq. per liter to above normal. Plasma volumes estimated from falling hematocrit ex-

panded as much as 40 per cent. Daily clearances of sodium, bicarbonate and endogenous creatinine increased several fold. Daily urine flow rose from 0.05 to over 4.0 cc. per minute as urine chloride concentration increased from 0.1 to 1.5 times the plasma value. Anasarca then disappeared.

In the balance studies the recovery of sodium approximated that anticipated from the volume of edema fluid eliminated but the chloride jettisoned was in marked excess.

Sprue—Observations on the Proteolytic Effect of Neutralized Gastric Juice on Protein Substrates, with Reference to the Activity of the Intrinsic Factor. HERBERT J. FOX (Introduced by Jerome S. Harris), Durham, North Carolina.

Previous investigators have shown that mixtures of equal quantities of normal human gastric juice and 1 per cent casein solution when incubated at 37.5° and pH 7.4 would result in progressive increases in the nitrogenous substances in trichloroacetic filtrates of such digests. This activity was found to be absent, or greatly diminished, in the gastric secretion of patients with Addisonian pernicious anemia.

Since the macrocytic anemia of sprue is indistinguishable in many aspects from that of pernicious anemia, it was decided to investigate the *in vitro* activity of gastric juice from sprue patients. The gastric juice was collected following histamine stimulation. Specimens containing traces of bile-stained duodenal contents were discarded. The gastric juice was adjusted to pH 7.4 and mixed with an equal volume of a 1 per cent solution of sodium caseinate, or egg albumin. The mixture was adjusted to pH 7.4 and set in a constant temperature environment of 37.5° C. for 24 hours. Samples were removed at certain intervals for 24 hours and analyzed for progressive increase in nitrogen as well as increase in amino nitrogen, using the methods previously described.

Four cases of sprue in relapse showed proteolytic activity which was reduced in degree below the normal controls. Six cases of sprue in remission produced results similar to the relapse cases. The proteolysis observed, though reduced below normal values, significantly exceeded results seen in pernicious anemia.

The Modifying Effect of Inorganic Iodine Administered to Thyrotoxic Patients Previously Treated with RAI¹³¹. A. S. FREEDBERG and ROBERT BUKA (Introduced by J. E. F. Riseman), Boston, Massachusetts.

Considerable disagreement exists as to the advisability of administering stable iodine after the administration of therapeutic doses of I¹³¹ to thyrotoxic patients. This question is of considerable practical as well as theoretic moment. The effect of continued administration of stable iodine begun one or three days after a dose of I¹³¹ was studied in five patients with thyrotoxicosis. Twenty-four hour urinary I¹³¹ excretion, external thyroid Geiger-Muller counts, and in some cases serum radioactivity were determined for periods of ten to thirty days. Comparable studies were carried out in thyrotoxic patients to

whom stable iodine was not given. Clinical evaluation and serial measurements of basal metabolic rate, serum cholesterol, and circulation time were carried out.

The administration of stable iodine begun twenty-four hours after a dose of I^{131} was associated with a marked increase in urinary I^{131} excretion and a pronounced fall in thyroid radioactivity. The administration of Lugols solution ten minims daily or saturated solution of potassium iodide five minims daily beginning three days after I^{131} dosage was accompanied by a small increase in urinary I^{131} excretion and no appreciable decrease in thyroid radioactivity.

It would appear, therefore, that the early therapeutic effects of stable iodine may be gained by administering it three or more days after I^{131} without interfering significantly with the therapeutic effects of the radioactive material.

The Hemodynamic Effects of Veratrum Viride in Hypertensive Man: Studies of Arterial Pressure, Cardiac Output, Renal and Hepatic Clearances, Peripheral Blood Flow, "Venous Tone" and Vasomotor Reflexes. EDWARD D. FREIS, JOSEPH R. STANTON, JAMES W. CULBERTSON, JULIUS LITTER and MEYER H. HALPERIN (Introduced by Chester S. Keefer), Boston, Massachusetts.

Therapeutic trials of veratrum viride in hypertensive patients have been sufficiently promising in this clinic to stimulate a more extensive investigation of its cardiovascular effects.

Following subtoxic doses of veratrum the fall in arterial pressure (Hamilton) was the result of a decrease in peripheral resistance rather than in cardiac output (direct Fick). Blood flow in the kidneys (PAH), liver (BSP) and limbs (plethysmogram) decreased during the falling phase but then returned to or above control levels during the stable phase of the lowered arterial pressure. "Venous tone" in the limbs decreased but collapse from venous pooling or orthostasis did not occur.

There was no evidence that the hypotensive effects were either sympatholytic or parasympathomimetic. Sympathetic vasomotor reflexes, including vasopressor responses, and digital volume and temperature reactions remained intact. Atropine abolished the bradycardia but not the hypotension after veratrum, while epinephrine or ephedrine abolished both.

Glomerular filtration measured by mannitol clearance was markedly reduced, but by inulin was only transiently decreased. There was always a striking antidiuresis, even without a significant fall in arterial pressure, producing marked increases in the u/P ratio of PAH, mannitol, and inulin.

The Serum Concentration of a Digitalis Glycoside and its Rate of Disappearance in Patients After Parenteral Digitalization. MEYER FRIEDMAN and (by invitation) RENE BINE, JR., San Francisco, California.

By employment of the embryonic duck heart preparation (1), it was found possible not only to detect digitalis

glycoside (Lanatoside C.) in the serum of patients receiving the drug but also to study its rate of disappearance from serum. After preliminary studies had been made of the effects of (1) human blood cells and (2) serum upon the physiological activity of the glycoside, quantitative determinations were made of the glycoside content of the serum of five cardiac patients who had received 1.6 mgm. of Lanatoside C. by vein.

Approximately 0.21 microgram of glycoside per cc. of serum was present in the five patients immediately after its administration. However, the average serum concentration fell rapidly to 0.12, 0.08 and 0.06 micrograms per cc., $7\frac{1}{2}$, 15 and $22\frac{1}{2}$ minutes after injection of the drug. At the end of 30 minutes, the serum of three patients contained 0.05 microgram or less per cc. and in the remaining two patients, no glycoside could be detected in the serum. At the end of an hour, glycoside could not be detected in the serum of any patient. Serum samples taken two, 12 and 24 hours after injection of glycoside also contained no detectable glycoside.

Observations on Intracavitary Electrocardiograms in Man. ARTHUR J. GEIGER and (by invitation) ALLAN V. N. GOODYER, New Haven, Connecticut.

Intracavitary potentials were recorded via a lead passed intravenously in ten subjects including normals and cases of right and left branch block and ventricular hypertrophy.

The changes in P from negative to diphasic to positive as the electrode passed from the superior cava through the atrium into the inferior cava or right ventricle were consistent with the dipole theory of depolarization of muscle. The RS configuration of the normal ventricular complex recorded within the right ventricle was in accord with the view that the septum is depolarized from left to right, assuming that the initial ventricular deflection is of septal origin. Support for this assumption was seen in the entirely negative (QS) character of the ventricular complex in left branch block.

Ventricular extrasystoles excited by the electrode tip in the right ventricle of a case of left branch block closely resembled the natural complexes of the subject.

However, in a case of typical right branch block the triphasic ventricular deflections were of QRs character, implying either that septal depolarization was not from left to right, as ordinarily postulated, or that depolarization of the free wall of the left ventricle preceded depolarization of the septum.

The Effect of Polysaccharides on Virus Activity. (By invitation) HAROLD S. GINSBERG, (by invitation) WALTHER F. GOEBEL, and FRANK L. HORSEFALL, JR., New York, N. Y.

Capsular polysaccharides of Friedländer bacilli inhibit multiplication of mumps virus in the allantoic sac of the chick embryo; as little as 5 μ g. of polysaccharide is effective. Inhibition of multiplication is not due to inactivation of the virus *per se* as shown by both *in vitro* and *in vivo* methods. Polysaccharides active as inhibitors

do not block adsorption of mumps virus by cells of the living allantoic membrane. Inhibition of multiplication is obtained when polysaccharide is injected as long as 4 days after inoculation of mumps virus. Chemical studies on the polysaccharide have shown that the structural configurations responsible for specific serological activity are distinct from those which determine the inhibitory effect relative to mumps virus. The available data indicate that polysaccharide acts upon some intracellular system of the host cells in order to inhibit viral multiplication. Moreover, in addition to the evidence obtained from experiments with polysaccharides and viruses, that obtained in interference experiments suggests that viruses of influenza A, B and Newcastle disease require for multiplication host metabolic systems different from mumps virus or pneumonia virus of mice.

The Study of Myocardial Metabolism and Coronary Blood Flow by Coronary Sinus Catheterization. W. T. GOODALE, J. E. ECKENHOFF, R. J. BING, M. LUBIN, J. H. HAFKENSCHIEL, M. H. HARMEL, W. G. BANFIELD, E. L. FOLTZ and S. S. KETY (Introduced by E. Cowles Andrus), Baltimore, Maryland.

A systematic technique of coronary sinus catheterization has been developed in intact lightly anesthetized dogs, without opening the chest, guided by landmarks visible fluoroscopically in the right anterior oblique view. A modified intravenous catheter, having a small tapered tip with multiple openings, has overcome many of the difficulties of insertion and blood sampling in the coronary sinus, avoiding also any undesirable coronary venous obstruction as indicated by pulse pressure recordings. Diodrast coronary venograms showed the orientation of the catheter and the coronary sinus venous system *in vivo*. The nitrous oxide method of Kety and Schmidt, applied to the coronary circulation by catheter technique, gave coronary blood flow values of 70 to 100 cc./100 Gm./min. Myocardial oxygen consumption and carbon dioxide production were 10 to 12 cc./100 Gm./min., or about 10 per cent of the total oxygen consumption, with coronary A-V differences which were 2 to 3 times the overall systemic differences. Left ventricular efficiency varied from 14 to 21 per cent. Myocardial oxygen consumption was well correlated with blood pressure, but poorly correlated with cardiac output.

A very high myocardial utilization of lactic and pyruvic acid was consistently found, even at basal arterial levels, but only a low and inconsistent glucose utilization. The mean lactate/pyruvate ratio was 7 in both arterial and coronary venous blood. The lactic and pyruvic acid uptake together accounted for 40 to 60 per cent of the total cardiac oxygen utilization, while glucose uptake accounted for an average of only 20 per cent.

Endocardial damage could not be entirely avoided in dogs, after catheterization of not only the coronary sinus, but also the pulmonary artery, although technical refinements have minimized the occurrence and size of lesions. Peculiar to coronary sinus catheterization, however, were coronary venous thromboses or myocardial hemorrhages

which sometimes followed prolonged insertion of a catheter far into the sinus or a cardiac vein, with elevated pulse pressures of 9 to 20 mm. Hg which indicated significant coronary venous obstruction. Coronary venous and myocardial damage were avoided by precautions, including gentle insertion of a small catheter only 1-2 cm. inside the coronary sinus. In this position, there was no evident admixture of coronary blood samples with auricular blood, evidence of trauma to the auricle or coronary sinus ostium was minimal, and pulse pressures were the same or only slightly higher than auricular pressures, indicating that there was no significant coronary sinus obstruction by the catheter. Similar precautions are probably advisable in further applications of this procedure.

Observations on the Impedance Plethysmograph. ALLAN V. N. GOODYER (Introduced by David M. Kydd), New Haven, Connecticut.

An impedance plethysmograph has been constructed following the basic design of Dubois and Nims, except for several modifications which were found necessary in order to achieve reproducible calibration of pulse volume changes in terms of resistance units, using an electrocardiograph as the final recording instrument.

Simultaneous tracings obtained from the fingers and arm with this instrument and with the Burch-Winsor plethysmograph were very similar with regard both to wave contours and to calculated absolute pulse volume changes responsible for the deflections. The versatility of the instrument, claimed by previous workers, was confirmed and its range of sensitivity and ease of application proved a decided advantage over the Burch-Winsor apparatus.

Over 100 records from normal subjects and hospital patients have outlined the range and reproducibility of normal pulse patterns obtained from the digits, extremities and trunk, and have indicated certain variations which may be produced by abnormal cardio-vascular states.

The Relationship of the Precordial Electrocardiogram to the Electrical Field of the Heart. ROBERT P. GRANT, (Introduced by Arthur J. Merrill), Atlanta, Georgia.

The precordial QRS and T have been generally assumed to represent principally the electrical activity of that part of the myocardium directly beneath the exploring electrode. The following experiments were designed to study this relationship.

From precordial V-leads taken along numerous vertical axes on the chest, the pathways of the transitional QRS and T complexes around the chest were determined. Then, in the same subject, the mean spatial vectors representing the size and directions of the forces producing the QRS and T were determined by an adaptation of Wilson's tetrahedral method. The pathways of null points which these spatial vectors would produce on a cylinder of the same dimensions as the patient's chest were then computed. The precordial V-lead transitional pathways were found to coincide closely in all characteristics with the path-

ways calculated for the electrical field of the whole in the eight cases studied. The method was then simplified for routine use and in over 300 consecutive normal and abnormal subjects reasonable agreement was found.

It is concluded that the precordial deflections represent the electrical activity of the heart as a whole, as far as direction of deflection is concerned. Accordingly the distribution of positive and negative precordial QRS and T waves is a function of the directions of the spatial QRS and T vectors. Since these vectors are computed from limb leads, it is evident that the precordial deflections are also functions of the ventricular gradient. By studying this relationship of the precordials to the vectors as manifested in the limb leads the interpretation of abnormal and unusual precordial patterns is much simplified and clarified.

The Uptake of Radioactive Phosphorus by Gastric Carcinoma. (By invitation) SEYMOUR J. GRAY, (by invitation) JOHN SCHULMAN, JR. and (by invitation) MARLENE FALKENHEIM (Introduced by Clifford L. Derrick), Boston, Massachusetts.

Tracer doses of radioactive phosphorus were injected into patients with carcinoma of the stomach and in patients with nonmalignant gastric disease approximately 36 hours prior to gastric resection. The cancerous gastric mucosa and the non-cancer gastric mucosa were analyzed for total phosphorus, acid soluble phosphorus and nucleoprotein content. The radioactivity of each constituent was determined. Results were expressed as standard specific activity [per cent of (injected dose per gm. of body weight) per mgm. of phosphorus]. This expression is proportional to the rate of turnover of phosphorus in the tissue.

In non-cancer stomachs the turnover of phosphorus was uniform. No differences were observed between those areas where cancer is prone to develop and where benign lesions are usually found. In cancerous stomachs the phosphorus turnover of the non-cancerous mucosa was the same as the normal stomach. The turnover of total phosphorus of the carcinoma was 47 per cent greater than the non-cancer mucosa. The turnover of phospholipid phosphorus was 45 per cent greater and the nucleoprotein phosphorus turnover was 56 per cent greater in the cancer than in non-cancer tissue.

Inhibition of Multiplication of Influenza Virus by Tannic Acid. ROBERT H. GREEN (Introduced by Francis G. Blake), New Haven, Connecticut.

Recently several reports describing the inhibition of multiplication of certain viruses have appeared. In some instances the substances which inhibit virus multiplication also inhibit virus hemagglutination. Furthermore, some of these substances are themselves capable of agglutinating erythrocytes. The interrelationships among these phenomena, if indeed any exist, are not clear.

During the course of studies on hemagglutination it was found that tannic acid in concentrations as low as

45 μ g. per cc. agglutinates chicken erythrocytes. Further investigations revealed that tannic acid, in dilutions higher than those which produce hemagglutination, actually inhibits the agglutination of chicken erythrocytes by influenza A virus. Concentrations ranging from 5 to 20 μ g. per cc. inhibit virus hemagglutination. Moreover, tannic acid inhibits the multiplication of influenza A virus *in vivo* and inactivates the virus *in vitro*. When injected into the chorio-allantoic sacs of embryonated eggs one mg. per egg markedly inhibits the multiplication of virus, and smaller amounts produce a less marked but appreciable degree of inhibition. The inhibitory effects of tannic acid would appear to be due, at least partly, to a direct action upon the virus because, *in vitro*, very low concentrations of tannic acid inactivate large amounts of virus.

Right Auricular Pressures in Man at Rest and During Exercise. DAVID G. GREENE, CHARLES E. ROH and ELEANOR DEFOREST BALDWIN (Introduced by Franklin M. Hanger), New York, N. Y.

Subjects with normal cardiac function and subjects with varying degrees of congestive failure were studied by means of right heart catheterization at rest and during supine exercise. Right auricular pressures were measured with Hamilton manometers. The cardiac output was determined by the direct Fick method.

In subjects with normal cardiac function, who responded to the exercise with a definite increase in cardiac output, no significant rise in right auricular mean pressure was observed. On the other hand, in patients with impaired cardiac reserve exercise was associated with a rise in right auricular mean pressure irrespective of any change in the cardiac output. The magnitude of auricular systole and of the negative wave associated with the descent of the base was greater during exercise than at rest in some cases of each group.

Results of Treatment of Patients with Hypertension by Total Thoracic and Partial to Total Lumbar Sympathectomy, Splanchnicectomy and Celiac Ganglionectomy. K. S. GRIMSON and (by invitation) E. S. ORGAIN, Durham, North Carolina.

During the last 8 years 108 patients have been treated by subtotal to total sympathectomy. This operation differs from others currently employed for hypertension in that it includes removal of the stellate and upper thoracic ganglia and therefore denervates the head, arms and thorax as well as the splanchnic visceral area. Usually, only sympathetic pathways to the legs are left intact. Operative mortality occurred in four patients. Two patients died three and five days after reduction of pressure with respiratory arrest; one patient died with uremia and one died with myocardial infarction. At present eleven patients have died since operation. Deaths with three exceptions were caused by sudden cardiac or cerebral vascular accidents. No patient has developed uremia since operation. Varying degrees of clinical improvement or apparent cure have been achieved in the 93 patients

now alive. Supine blood pressure was reduced to normal in 25, reduced but not to normal in 44, and not reduced in 24. Postural hypotension has occurred and has persisted with the exception of a few patients who years after sympathectomy have systolic but not diastolic postural lowering of pressure. Bradycardia has developed after sympathetic heart denervation and has persisted. Retinal hemorrhages and exudates or papilledema were present in more than a third of the patients before operation. With few exceptions these disappeared and have not recurred. Generally symptoms of hypertension have disappeared. Other significant clinical data will be presented and interpreted.

4-Caproylamino Diphenylsulfone, 4'-Aminomethylsulfonic Acid Sodium Salt. Pharmacology and Effect in Experimental Tuberculosis. RICHARD GUBNER, RENÉ J. DUBOS, CYNTHIA PIERCE and HARRY E. UNGERLEIDER (Introduced by William Dock), Brooklyn, New York.

The sodium salt of 4-caproylamino diphenylsulfone, 4'-aminomethylsulfonic acid (Equityl) has been synthesized in an attempt to find a sulfone compound of low toxicity possessing chemotherapeutic activity against the tubercle bacillus. The *in vitro* bacteriostatic effect of this compound is identical with that of diaminodiphenylsulfone, with complete inhibition of growth of human strains of the tubercle bacillus in drug concentrations of one to two mgms. per cent in the Dubos medium. Unlike diaminodiphenylsulfone Equityl possesses no bacteriostatic effect against the streptococcus, staphylococcus, pneumococcus or diphtheria bacillus in concentrations up to 100 mgms. per cent.

The drug exhibits important pharmacological differences from diaminodiphenylsulfone. Whereas diaminodiphenylsulfone given orally to mice causes fatal toxicity in single dosage of 0.25 to 0.5 G./kg. no toxic effects whatever are observed on administering as much as 4 G./kg. of Equityl in single dosage by stomach tube. In chronic toxicity studies in mice no toxic effects were observed when the drug was given daily for thirty-eight days in dosage of 0.25 G./kg., or when given for twenty-one days in dosage of 0.67 G./kg. Similarly in man there has been no evidence of toxicity on oral administration in single dosage of 5 Grams or on protracted daily dosage of 2 to 4 Grams up to ten weeks, as judged by symptoms, weight, blood counts, icteric index, blood chemistry and urinalysis. By the parenteral route, however, Equityl exhibits the same toxicity in mice as diaminodiphenylsulfone. The reason for the lack of toxicity on oral administration appears to be limited absorption of the drug despite its high solubility, for regardless of the oral dosage blood levels above 3.8 mgm. per cent have not been observed. Following a single 5 G. dose in man the drug is rapidly absorbed to its maximum blood level within one hour and is bound to the serum proteins. It is excreted slowly; during the first twenty-four hours urinary concentrations up to 25 mgms. per cent are obtained, with a total twenty-four urinary excretion of approximately 200 milligrams, urinary excretion thereafter falls off

gradually over several days. These pharmacological properties are very similar to findings previously reported by one of us with another caproyl compound, *i.e.*, *N*₄-caproylsulfanilhydroxamide.

The chemotherapeutic effect of Equityl has been investigated in experimental mouse tuberculosis. 0.02 mgm. (dry weight) of a virulent 10-day old H37 strain of tubercle bacillus was inoculated in the tail vein of young Swiss mice. Equityl was mixed with the feed beginning on the day of inoculation in concentrations of 0.25 mgm. per cent and 0.075 mgm. per cent, representing a daily dosage of approximately 0.67 G./kg. and 0.25 G./kg. respectively. All of the control group of ten animals died within fourteen days, with a weight loss averaging 4.3 G. Gross pulmonary tuberculous lesions were present, of the mixed pneumonic, granulomatous, and caseating type. The treated animals were sacrificed after twenty-one days, within which time one death, not due to tuberculosis, had occurred. Pulmonary lesions of minimal degree were present in the majority of the treated animals, less so in the group receiving the larger dosage of drug. In the larger dosage group no weight loss occurred whereas in the smaller dosage group there was an average weight loss of 3.7 G. Equally effective protection could be obtained with diaminodiphenylsulfone although the margin between the therapeutic and toxic dosage was found to be very narrow.

The conclusion is drawn that Equityl possesses chemotherapeutic activity against the tubercle bacillus comparable to diaminodiphenylsulfone, with the advantage of complete freedom from toxicity on oral administration.

Studies on the Mechanism of Hemolytic Anemia and Hemoglobinuria Occurring in Patients with High Concentrations of Serum Cold Agglutinins. THOMAS HALE HAM and (by invitation) FRANK H. GARDNER, (by invitation) PHILIP F. WAGLEY, and (by invitation) S. C. Shen, Boston, Massachusetts.

Patients have been observed with hemolytic anemia associated with high concentrations, in the serum, of cold autohemagglutinins. Studies of mechanical fragility of blood samples containing cold agglutinins, at 15°, 11°, and 4° C., showed increasing hemolysis of normal red cells and red cells from the patients proportional to the increasing degree of agglutination observed at these temperatures. The increased mechanical fragility, observed *in vitro*, on chilled blood containing cold agglutinins, suggested that mechanical trauma to the agglutinated red cells in the periphery of the body might be one of the mechanisms of destruction of red cells in patients with hemolytic anemia associated with cold agglutinins.

In one patient with chronic acquired hemolytic jaundice of 12 years' duration, there was continued high concentration of cold agglutinins (1-5000) observed over a period of four years. The red cells showed a normal osmotic fragility, but a strongly positive agglutination with anti-human serum rabbit serum (Coombs test), and an abnormally increased mechanical fragility at 37° C. without agglutination. The mechanical

fragility was significantly increased at 15° C. Chilling the arm for 20 minutes at 15° with or without stasis, in observations made on two occasions 4 years apart, produced on both occasions hemoglobinemia and hemoglobinuria. At 37° C., using the same procedures, no hemoglobinuria was produced. A similar study was conducted on a patient without anemia who was recovering from atypical virus pneumonia, associated with a high concentration of cold agglutinins (1-5000) in the serum. The red cells were normal as evidenced by normal osmotic and mechanical fragilities and negative Coombs test. Chilling of the arm at 15° C., at which temperature there was a significant increase in mechanical fragility, did not produce hemoglobinemia. Accordingly, hemoglobinemia and hemoglobinuria appeared to result from mechanical destruction *in vivo* of agglutinated red cells during chilling at 15° C., but only in the patient with red cells that were manifestly abnormal.

Three additional cases were observed with high concentrations of cold agglutinins in the serum associated with increased osmotic fragility of the red cells, and, in two instances, with spherocytosis. In one of these patients, there was extreme hemoglobinuria without exposure to cold. The mechanism for these changes is not known.

The Action of Iodocasein on Human Myxedema, with Comparative Studies on the Fate and Distribution of Synthetic Radioactive Iodocasein and of I^{131} during Hypothyroidism and Euthyroidism. (By invitation) C. FERRILL HAMILTON, (by invitation) A. ALBERT, (by invitation) MARSCHELLE H. POWER, (by invitation) SAMUEL F. HAINES and F. RAYMOND KEATING, JR., Rochester, Minnesota.

Tracer doses of I^{131} and of synthetic radio-iodocasein, comparable in total iodine and specific radioactivity, were administered before and after myxedema in a patient was completely alleviated according to conventional criteria by daily administration of 60 mg. iodocasein. This dose was equivalent by bio-assay to 100 mg. strong thyroid. The fate and distribution of I^{131} and radio-iodocasein were determined by radioactive measurements of urine, feces and blood, and by *in vivo* measurements over thigh, liver and thyroid areas.

During myxedema, I^{131} was distributed in urine (91 per cent), feces (2 per cent) and in blood, where an appreciable fraction was protein-bound. Thyroid and liver areas showed no concentration of radioactivity. After administration of radio-iodocasein, however, urine contained 40 per cent of the radioactivity, feces 59 per cent and blood only small amounts, most of which was protein-bound. Considerable radioactivity was concentrated only over the liver. When euthyroidism was attained, repetition of each tracer yielded qualitatively similar results respectively but the proportion of protein-bound radioactivity in blood was diminished.

These studies indicate that (1) intermediary metabolism of organic iodine may occur in the liver and (2) human myxedema can be corrected by synthetic iodocasein.

Arterial Pressure Response to the Valsalva Test: an Indicator of Sympathetic Activity. ESTHER HARDENBERGH, JAMES L. WHITTENBERGER and STANLEY J. SARNOFF (Introduced by David D. Rutstein), Boston, Massachusetts.

Changes in femoral arterial pressure resulting from a simulated Valsalva experiment (extrathoracic and intrapulmonary pressures of 40 mm. Hg for 30 seconds) have been observed 357 times in 10 dogs. Measurements have been made with an electronic strain gauge, direct writing oscillograph, and reveal the following:

(1) The response consists of six components (A, B, C, D, E, F).

(2) Component E, the overshoot of arterial pressure above the prestimulus level following cessation of the stimulus, is of major importance because: (a) it is consistently present in normal and vagotomized animals; (b) it is diminished in direct proportion to the degree of interference with sympathetic activity accomplished by graded segmental spinal anesthesia or tetraethylammonium chloride; (c) it is increased by elimination of vagal activity accomplished by vagotomy or the administration of atropine; (d) it is greatly diminished or abolished by interference with carotid sinus activity accomplished by previous bilateral occlusion of both common carotid arteries.

These results explain the mechanism of the arterial pressure response to the Valsalva test and indicate the basis for its use clinically in the determination of the extent of sympathetic activity and denervation.

Experiments with Pteroylglutamic Acid and Pteroylglutamic Acid Deficiency in Human Leukemia. ROBERT W. HEINLE and (by invitation) ARNOLD D. WELCH, Cleveland, Ohio.

Administration of pteroylglutamic acid (PGA) to three patients with chronic myeloid leukemia was attended by rapid hematologic and clinical relapse in each instance. In one of these patients, hematologic improvement accompanied the withdrawal of PGA on two occasions. Administration of PGA to patients with chronic lymphoid leukemia was not associated with relapse. One patient with chronic myeloid leukemia was placed on a regimen of diet low in PGA, a crude antagonist of PGA, and succinylsulfathiazole. After one hundred days, marked hematologic remission with drop of leukocyte count from 150,000 to 12,000 per c.mm. occurred with concomitant decrease in platelet count from normal values to 10,000 per c.mm. Upon subsequent administration of PGA and withdrawal of the antagonist, relapse occurred and the patient died, although reinstitution of the original regimen was followed by evidence of hematologic improvement just before death. With the rise in white count there was also an increase in platelet count to 150,000 per c.mm. While these experiments are not conclusive, they indicate the desirability of further study of the role of pteroylglutamic acid in white cell genesis in general and leukemia in particular.

Pulmonary Capillary Pressure in Man. (By invitation) HARPER K. HELLEMS, (by invitation) FLORENCE W. HAYNES, (by invitation) JOHN F. GOWDEY and LEWIS DEXTER, Boston, Massachusetts.

A cardiac catheter with the hole on the tip has been introduced into a small branch of the pulmonary artery so as to obstruct the arterial lumen and pressures have been recorded with Hamilton and saline manometers. The pressure existing in the lumen of the artery distal to the obstruction is a result of the retrograde transmission of pressure from the next significant collateral branch entering the pulmonary artery. Anatomically, this is the pulmonary capillary bed of the lung. Physiologically, this is also the case, as indicated by the fact that blood fully saturated with oxygen can be withdrawn through the catheter. Furthermore, pressures recorded through catheters wedged into the pulmonary artery and pulmonary vein are in essential agreement.

In normal individuals the pulmonary capillary pressure, thus measured, varies from 7 to 15 mm. Hg with a mean average of 10. In emphysema, pulmonary vascular disease, Eisenmenger's Complex, with elevated pulmonary artery pressure, the pulmonary capillary pressure is within normal limits, indicating that the resistance to blood flow is in pulmonary "arterioles" and not in the capillaries. In mitral stenosis and other cardiac abnormalities producing so-called left heart failure, the pulmonary capillary pressure is elevated at rest and increases further during exercise.

The Sertoli Cell. CARL G. HELLER, and (by invitation) WILLIAM O. MADDOCK, (by invitation) EDWIN O. JUNGCK, and (by invitation) WARREN O. NELSON, Portland, Oregon.

In each of 32 patients having azoospermia or oligospermia, with or without eunuchoidism, it was noted that some seminiferous tubules were devoid of all cells of the germinal series, revealing only the supporting cells of Sertoli. The percentage of tubules containing Sertoli cells only varied from 10 to 100 per cent, and were usually associated with some degree of thickening or hyalinization of the tunica propria. Varying degrees of germinal activity were encountered, from instances in which the majority of tubules contained germinal cells to instances (5) in which 100 per cent of the tubules contained Sertoli cells only. This suggests that the condition of "Sertoli cells only" is the result of death of the germinal cells.

The clinical appearance of these patients, varying from completely eunuchoidal to normal, could be correlated with the histological appearance of the Leydig cells, which varied from severe degeneration to normal.

The Sertoli cell does not appear to secrete a hormone capable of inhibiting the secretion of pituitary gonadotrophins, since urinary gonadotrophins appeared in greater than normal amounts in the urine of each patient.

Lack of inactivation of follicle stimulating hormone due to lack of spermatogenic activity is suggested as the

factor accounting for the rise in urinary gonadotrophin excretion.

Procaine Penicillin: an Experimental and Clinical Evaluation. WALLACE E. HERRELL, and (by invitation) DONALD R. NICHOLS and (by invitation) FORDYCE R. HEILMAN, Rochester, Minnesota.

This study concerns itself with the efficacy of procaine penicillin in prolonging the action of this antibiotic. Various types of suspensions of procaine penicillin have been studied. These include procaine penicillin in cottonseed oil, in peanut oil and in sesame oil, as well as aqueous suspensions. After single intramuscular injections of 1 cc. of the material (300,000 units per cubic centimeter) adequate therapeutic blood levels are maintained for twenty-four hours or longer. In some instances therapeutic levels of penicillin in the serum have been maintained for as long as forty-two hours following a single injection.

The report includes observations on the pharmacologic action of this material, including absorption, excretion and diffusion.

The therapeutic results obtained in the treatment of a variety of infections owing to microbes susceptible to the action of penicillin are also included in the report.

Postural Changes in Cardiac Output in Orthostatic Hypotension. JOHN B. HICKAM (Introduced by J. M. Ruffin), Durham, North Carolina.

The fall of blood pressure in postural hypotension may be explained by lack of normal arterial constriction or by a greater than normal postural fall in cardiac output. Failure of arterial constriction in response to a fall of blood pressure has been found in cases of postural hypotension, but there is little information on variation in cardiac output with change of body positions.

Cardiac outputs were measured by the Fick method, and intracardiac and peripheral arterial pressures were manometrically recorded. Determinations were made in the supine and semi-erect positions on 4 cases of idiopathic postural hypotension and in 5 patients with postural hypotension produced by lumbo-dorsal sympathectomy for hypertension.

In 4 partially sympathectomized patients there was a large drop in blood pressure in the foot-down position, but the cardiac output showed no more than the normal postural fall. In 3 cases of non-operative postural hypotension and in one sympathectomized patient there was a postural fall in both cardiac output and mean arterial pressure to approximately 50 per cent of the supine values. One patient who frequently had postural hypotension showed, at the time of study, only a negligible fall in blood pressure but a 50 per cent drop in cardiac output in the foot-down position. In the cases of non-operative postural hypotension and in one sympathectomized patient a rapid infusion of albumin in saline prevented more than a normal postural fall in cardiac output and blood pressure.

It is concluded that a large drop in cardiac output, as

well as failure of compensatory arterial constriction, is a factor in the postural fall in blood pressure in certain cases of orthostatic hypotension. The mechanism of the drop in cardiac output is unexplained. The restoration of the output and the blood pressure on acutely increasing the blood volume suggests that in certain patients with postural hypotension failure of normal venoconstriction may play a part.

The Effect of a Nitrogen Mustard on Whole Blood Coagulation Time. L. O. JACOBSON, (by invitation) J. G. ALLEN, (by invitation) T. R. SMITH, (by invitation) C. L. SPURR, and (by invitation) M. H. BLOCK, Chicago, Illinois.

Allen and Jacobson recently reported that ionizing radiations produced a prolonged whole blood coagulation time in humans and animals as a result of the appearance in the blood of an anticoagulant biologically indistinguishable from heparin. This phenomenon was also observed in five patients with neoplastic disease given therapeutic doses of a nitrogen mustard (methyl bis (B chloroethyl) amine hydrochloride). A prolonged whole blood coagulation time has also been produced in rabbits by the intracardial injection of this drug in a dose of 3 and 4 mg. per kilogram of body weight. In both humans and rabbits a pancytopenia, prolonged bleeding time, and prolonged whole blood coagulation time (Lee White) are associated with the syndrome, whereas the prothrombin time is normal.

Usefulness of "Gamma Globulin" Determinations in Estimating Duration of "Activity" in Streptococcal Infections and in Rheumatic Fever. B. V. JAGER, J. F. WALDO and H. H. HECHT (Introduced by Maxwell M. Wintrobe), Salt Lake City, Utah.

In an attempt to find a more sensitive index of persistent activity in streptococcal infections and in rheumatic fever than is afforded by the erythrocyte sedimentation rate, a simple chemical method has been devised for measuring "gamma globulin."

Repeated clinical and laboratory examinations have been carried out in 15 patients with beta hemolytic streptococcal pharyngitis at intervals over a period of 6 weeks to 1 year. Five patients showed clinical evidence of non-suppurative complications. In these 5 and in 3 others without clinical findings, an elevation of the "gamma globulin" was demonstrable for prolonged periods, often in the absence of other abnormal laboratory findings.

In 15 patients with acute rheumatic fever, repeated studies have been made for a period of 6 to 18 months. In this group, the "gamma globulin" fraction was frequently greater than normal in the absence of other abnormal findings. Moreover in some patients whose infection was judged inactive, cyclical recurrent rises occurred in this fraction, suggesting persistence of the process at a less intense level. Such activity, ordinarily unrecognized, may account for the progressive cardiac changes which are so apt to occur long after the rheumatic attack has apparently subsided.

"Gamma globulin" and antistreptolysin O titer are being measured periodically in normal individuals with the object of determining whether by this means subclinical streptococcal infections can be detected.

Studies on Dicumarol in Human Beings: Its Neutralization by Vitamin K₁ Oxide, Menadione Bisulfite, Synkayvite and Blood. DAVID F. JAMES, JOHN J. BUTLER, IVAN L. BENNETT, JR., and PERITZ SCHEINBERG (Introduced by Marshall N. Fulton), Atlanta, Georgia.

In order to establish a broader clinical basis for the control of dicumarol effect, vitamin K₁ oxide, menadione bisulfite and synkayvite were administered in large single doses to patients with hypoprothrombinemia induced by dicumarol. The effect of fresh and bank blood transfusions was evaluated. One hundred and ten patients were given dicumarol in the usual dosage. When the prothrombin time exceeded that of normal plasma diluted to 20 per cent the patient was either allowed to return to his normal prothrombin level or was given large single doses of the test substances. Blood samples taken frequently during the succeeding 24 hours, and daily thereafter, were studied for prothrombin activity.

The efficacy of these substances was tested on two bases: the time elapsing until (1) the conversion of marked to moderate hypoprothrombinemia and (2) the appearance of a prothrombin level consistent with the possibility of intravascular clotting. Vitamin K₁ oxide was markedly superior in both respects. Patients given 0.5 gram or more of this material intravenously required an average time of 4 hours to be changed from that of marked to moderate hypoprothrombinemia. An average of 13 hours elapsed until the appearance of a prothrombin level consistent with intravascular clotting.

Bank and fresh blood were equally effective, 500 cc. transfusions having a minor, temporary effect.

The requirement of an individual for dicumarol is approximately predictable from his prior response to this agent. An exception to this situation occurs shortly after the administration of vitamin K₁ oxide, following which patients are relatively insensitive to dicumarol. This signifies storage of vitamin K₁ oxide for several days.

Studies on Prolonged Suppurative Injection in Man. Observations on the Blood. (By invitation) GEORGE W. JAMES, III, (by invitation) LILLIAN A. RIBLET, (by invitation) JOSEPH C. ROBINSON, (by invitation) ROBERT E. JOHNSON, and ROBERT M. KARK, Chicago, Illinois.

Eighty-six young men with chronic suppurative infections of the bones, kidneys or soft tissues were studied by clinical and laboratory techniques. Despite vigorous therapy with blood and plasma transfusions, sulfonamide derivatives and antibiotics, chronic suppuration persisted with frequent breakdowns. When first observed infection was severe in eleven and moderate in the remainder. The average duration of illness was 24 months and the average loss of weight was 7.9 kilograms. No clinical evidence of vitamin or protein deficiencies existed.

Distribution curves for plasma proteins, hemoglobin, hematocrit, white and red cells were within normal limits. Slight deviations from the normal were noted in the M.C.H.C., and M.C.V. The red cells of patients with severe infection showed decreased osmotic resistance. Serum iron concentration was diminished with increased serum copper concentration, especially when severe infections existed.

Blood volume per kilogram body weight was normal in 13 patients with moderate, and in ten with severe, infection. In the latter total circulating hemoglobin was reduced despite transfusions, while circulating plasma protein levels were maintained or increased even in the face of a marked reduction in body mass (from 14 to 24 per cent). Periodic determinations of serum copper and iron made in the severely ill showed a return to normal levels concomitant with clinical improvement. The shift in copper came earlier and was more marked than the shift in iron.

Observations on the Bone Marrow of Persons with Chronic Hepatic Insufficiency and Macrocytic Anemia.
(By invitation) THOMAS JARROLD and RICHARD W. VILTER, Cincinnati, Ohio.

Macrocytic anemia commonly observed in persons with chronic liver disease has been linked in theory to the erythrocyte maturation factor deficiency anemias. This relationship has not been tested by studies of bone marrow morphology and there are several reasons for questioning it. We wish to report studies on the peripheral blood and bone marrow performed repeatedly in twenty unselected patients with advanced portal cirrhosis confirmed in the majority of instances by biopsy or autopsy.

Moderate or severe anemia, usually macrocytic and normochromic, was found in seventeen subjects. Blood smears revealed slight anisocytosis and poikilocytosis, and normal differential nucleated cell counts. Reticulocytosis up to 13 per cent was common and could not be explained by recent blood loss in the majority of patients.

The bone marrow was hypo- or normally cellular with a relative increase in normoblasts. Megaloblasts and early erythroblasts were found in only two subjects both of whom had good evidence of extrinsic factor deficiency.

Plasma cells and lymphocytes were found in strikingly increased numbers, many times as high as 20 per cent for each cell type. The degree of plasma cell and lymphocyte hyperplasia correlated roughly with the degree of hyperglobulinemia suggesting a causal relationship.

In no instance did intensive therapy with liver extract, folic acid, amino acids or B complex vitamins affect the peripheral blood or bone marrow dramatically. Additional reticulocytosis did not occur.

These data suggest that a metabolic abnormality other than lack of storage or utilization of the erythrocyte maturation factor must account for the macrocytic anemia in chronic liver disease. In an occasional patient, extrinsic factor deficiency may superimpose a hematologic pattern resembling pernicious anemia.

Radio-active and Stable Iodine in Peripheral Tissues.

MACALISTER W. JOHNSTON (Introduced by William T. Salter), New Haven, Connecticut.

It is well established that the protein-precipitable iodine of plasma reflects thyroid activity. A similar correlation can be demonstrated with peripheral tissue iodine when the inorganic fraction is separated from the organically bound. Studies in rats and cats show a species difference in iodine concentrations; but both yield values lower than normal in hypothyroidism (produced by thiouracil) for muscle, liver, kidney, heart and brain. Higher values than normal are found in animals treated with thyroxine.

The organically bound iodine of peripheral tissues (e.g., skeletal muscle) can be isolated in association with certain characteristic protein fractions.

In observations involving man and animals, when measurement of radio-activity is combined with classical studies of stable (ordinary) iodine, the resulting ratio (i.e., "specific radio-activity") indicates the rate of metabolic turnover under appropriate conditions. The same comparative procedure can be applied to the thyroid gland and blood plasma.

After treatment with radio-active iodine, peripheral tissues also contain radio-active iodide (inorganic). If this be present for appropriate periods of time at high concentrations, tissue damage will result.

The Renal Tubular Reabsorption of Salt with Exercise in a Patient with Cardiac Failure and Normal Controls.

A. KATTUS, B. SINCLAIR-SMITH, J. GENEST and E. V. NEWMAN (Introduced by A. M. Harvey), Baltimore, Maryland.

Simultaneous clearances (C) of inulin (In), para-amino-acetylhippuric acid (PACA), chloride, sodium, potassium and phosphate were determined on three occasions in a young patient with congestive failure due to rheumatic valvular disease during mild exercise. On normal subjects the effect of walking at different rates on simultaneous clearances of inulin or creatinine (C_r), and electrolytes was observed. The patient at rest had a low normal C_{In} with an abnormally high filtration fraction (FF). Exercise caused a fall in C_{In} with no change in FF and a marked fall in ratios C_{Na}/C_{In} and C_{Cl}/C_{In}. The ratio C_K/C_{In} fell slightly with urine flow and C_{In}. During recovery, C_{In} returned to control level before the C_{Na}/C_{In} and C_{Cl}/C_{In} ratios.

Normal subjects walking showed unchanged C_{In} or C_{Cr}, but the ratios C_{Na}/C_{In} and C_{Cl}/C_{In} decreased consistently and sometimes as markedly as in the cardiac patient. The ratios C_K/C_{In} and C_{HPO₄}/C_{In} fell slightly with the urine flow.

Thus, increased renal sodium chloride retention is a normal response to exercise due to increased tubular reabsorption of filtered electrolytes, not necessarily related to fall in filtration rate, but possibly elicited more readily and intensely in cardiac failure.

The Significance of Aortic and Pulmonary Artery Wall Movements, Electrokymographically Recorded, in the Study of Acute Circulatory Disturbances. CALVIN F. KAY, (by invitation) JAMES W. WOODS, JR., and (by invitation) HARRY F. ZINSSER, Philadelphia, Pennsylvania.

Border movements of the aorta and pulmonary artery were continuously recorded by the electrokymograph in 18 normal subjects during the period of acute change in intrathoracic pressure produced by voluntary straining. Brachial artery pressure was simultaneously recorded with a capacitance monometer and, in several subjects, stroke volume was estimated with the ballistocardiograph. Pulsation amplitude changes recorded from the aortic knob were directly related to changes in brachial pulse pressure and inversely related to the pulse rate. In pulsations recorded from the pulmonary artery, a striking increase in amplitude immediately followed cessation of straining, as observed in pressure recordings from this vessel by others. We employed procedures to estimate the method as a measure of the movements of the vessel walls and to estimate the relation of vessel wall movements to diameter changes. It is concluded that the electrokymographic method provides a measure of relative stroke change in aortic and pulmonary artery diameter. From the electrokymographic records alone, the cardiovascular disturbances produced by straining may be deduced. The interpretation so obtained is in accordance with that previously derived by the combined application of many methods. It is a rapid, simple, and painless method by which cardiovascular dynamic changes are immediately and sharply recorded. It is now proving useful in the study of a variety of cardiovascular problems.

The Cerebral Circulation in Essential Hypertension and the Effects of Differential Spinal Sympathetic Block. (By invitation) SEYMOUR S. KETY, (by invitation) BENTON D. KING, (by invitation) JOSEPH H. HAFKENSCHIEL, (by invitation) STEVEN M. HORVATH, and WILLIAM A. JEFFERS, Philadelphia, Pennsylvania.

Quantitative measurements of cerebral blood flow, cerebrovascular resistance and cerebral oxygen consumption have been made in a series of patients with essential hypertension by means of the nitrous oxide technique. Cerebral blood flow and oxygen consumption are within normal limits, but there is a striking increase in cerebrovascular resistance. Because of the frequency of cerebral symptoms following the acute reduction of blood pressure in this condition it was deemed of interest to perform these quantitative observations during a period of relative hypotension produced by differential spinal block. A fall in mean arterial blood pressure was obtained, accompanied by a significant reduction in cerebral blood flow. There was no change in cerebral oxygen consumption or in cerebrovascular resistance. The cerebral nutritive index (ratio of oxygen supplied to oxygen consumed), determined independently of cerebral blood flow, showed a moderate decrease during the hypotension and a striking reduction where the blood pressure fell markedly and

cerebral symptoms became apparent. All changes reported are statistically significant.

These findings indicate that the high degree of vascular tone present in the brain in essential hypertension is not readily released even in response to a fall in blood pressure of a severity sufficient to compromise the cerebral blood flow.

Studies in Methionine and Sulfur Metabolism in the Presence of Liver Damage: I. Rate of Utilization and Urinary Excretion of the D and L Isomers Following Intravenous Administration. LAURANCE W. KINSELL, HAROLD A. HARPER and HARRY C. BARTON (Introduced by Theodore L. Althausen), San Francisco, California.

It was postulated that intravenously administered methionine would be anabolized and catabolized at a different rate in patients with liver damage than in normal humans.

To test this hypothesis, 1.5 grams of DL-methionine has been administered to normal individuals, and to patients with acute and chronic liver damage. Plasma L and DL-methionine, urinary L and DL-methionine, and urinary inorganic and ethereal sulfate have been determined before, and at frequent intervals following the methionine infusion. Microbiologic assay procedures have been utilized for methionine quantitation.

Such studies to date have demonstrated:

1. Significant diminution in the rate of methionine utilization in patients with liver damage, as compared to normals, with reversion to normal as liver function improves.
2. Insignificant urinary L-methionine, but very considerable D-methionine excretion.
3. Urinary inorganic sulfate excretion appears to give significant information as to the relative anabolism or catabolism of administered methionine. A persistent catabolic response may be a grave prognostic sign.
4. Studies in methionine-sulfur metabolism in other metabolic disorders will be presented if time permits.

Vitamin A Studies in Middleaged and Old Individuals. ESBEN KIRK and MARGARET CHIEFFI (Introduced by William B. Kountz), Saint Louis, Missouri.

An investigation was made of the total carotene, α & β carotenes, and vitamin A concentration of plasma in 155 middleaged and old individuals, offered a diet adequate in vitamin A, and in 47 younger subjects. The vitamin A analyses were performed on 20 ml. plasma samples, using a modification of the technique recommended by the Association of Vitamin Chemists. The total carotene concentration was obtained by use of a Dubosque colorimeter, the α & β carotene value after preliminary adsorption to an aluminum oxide column and subsequent elution with benzol-benzene. Definitely higher total carotene and α & β carotene concentrations were found in the younger (16-39) age group (average values 330 and 190 micrograms per cent) than in the middleaged and old individuals (average values 210 and 110 micrograms

per cent). The vitamin A concentration of plasma averaged 20 micrograms per cent and showed no significant change with age.

In the patients presenting a low plasma vitamin A value (1-15 micrograms per cent) and the incidence of conjunctival pathology and of toad skin was significantly higher than in the individuals in whom a high (30-60 micrograms per cent) vitamin A plasma value was found. No certain difference was observed in the daily output of epithelial cells in the urine or in the percentage frequency of cornified cells in conjunctival smears. The evaluation of the dark adaptation values was rendered difficult by the presence of lenticular opacities and retinal arteriosclerosis.

The Relation of Growth Dispersion to Growth Inhibition of M. Tuberculosis by Subtilin and Other Chemotherapeutic Agents. VERNON KNIGHT and RALPH TOMPSETT (Introduced by Walsh McDermott), New York, New York.

A preparation of subtilin highly inhibitory to pneumococci, streptococci, and tubercle bacilli *in vitro*, was also shown to possess high *in vivo* activity in experimental pneumococcal and streptococcal infections. It was further observed that under suitable experimental conditions, persistence of antimicrobial activity against tubercle bacilli in the serum of treated animals could be demonstrated by biologic assay. Nevertheless, the course of tuberculous infection in mice was not inhibited by the continued administration of subtilin in daily doses which were much larger than those necessary for protection against pneumococcal or streptococcal infections.

Investigation of the mechanism of this paradoxical phenomenon revealed that it is associated with an unusual property of *M. tuberculosis*. In contrast with most other disease-producing bacterial species, *M. tuberculosis* grows *in vitro* as macroscopic aggregates, unless non-ionic wetting agents are added to the medium. It was observed that tubercle bacilli growing as aggregates were not inhibited by subtilin. Conversely, when the addition of wetting agents converted growth to the dispersed form characteristic of other bacteria, the cells of *M. tuberculosis* were highly sensitive to minute concentrations of subtilin, as well as to certain other chemotherapeutic agents. Presence of the same wetting agents in diffusely growing cultures of other bacterial species produced no appreciable effect upon the usual sensitivity of the cells to subtilin or other antimicrobial drugs. It was also observed that when tween, one agent used for dispersion of growth, was antagonized by serum, the tubercle bacilli grew in aggregates and were not inhibited by subtilin. This effect of serum could be neutralized by the addition of sufficient wetting agent to permit dispersed growth.

It is not known whether the aggregates of tubercle bacilli present *in vivo* are in any way comparable in their drug sensitivity to the aggregates which occur *in vitro*. It was observed, however, that the few chemotherapeutic agents which are anti-tuberculous *in vivo*, are highly active against the aggregated organisms growing *in vitro*

and display relatively little increase in activity when tested under conditions of dispersed growth.

Dipolar Nature and Duration of the Regression Process in the Human Heart. CHARLES E. KOSSMANN, New York, N. Y.

In records made of the action potential in the heart of any given species under physiologic conditions, the deflections resulting from regression are partly obscured by the larger and more rapid deflections resulting from accession. By warming the sinus venosus of the frog, it has been possible to separate the two sets of deflections, and to demonstrate that the former, like the latter, are dipolar in nature, but of reversed polarity and approximately twenty times greater length (Macleod, 1938).

In two different sets of observations in man similar features of the regression process were demonstrated in the right atrium, and in the ventricles.

In the first of these observations an electrogram was made after introducing a small exploring electrode into the cavity of the right atrium of a patient with sinus rhythm and complete auriculoventricular block. Deflections of atrial recovery could be observed without distortion by oscillations of ventricular excitation. The entire auricular complex was composed of an initial positive and negative deflection followed by a slower pair of waves of lower voltage and reversed polarity (Figure 1). From the record, the tripartite nature of the early part of the action potential was easily discerned. The duration of increasing activity, disregarding the error introduced by the distance of the electrode from the atrial endocardium, was 0.005 second; of complete activity 0.0028 second; and of receding activity 0.075 second. Assuming the rate of conduction in the human atrium to be approximately 2000 mm. per second (Kossmann, *et al.*, 1947), the length of accession was 10 mm., of complete activity 56 mm., and of regression 150 mm.

In addition, a terminal, slow, small positive deflection, comparable to the U wave in ventricular records, was observed.

At necropsy sometime later, the right atrium was found to be greatly dilated, so that the figures cannot be accepted as representative of the normal.

In a second set of observations electrocardiograms were made in patients whose body temperature was purposefully reduced to approximately 80° F., by cooling in air. In addition to other changes (Kossmann, 1939), several patients displayed an unusual ventricular T wave consisting of two parts, both upright, one of which occurred just after the QRS, the other in the usual location at the end of electrical systole (Figure 2). The first of these was in the expected direction but the second was not, presumably because of a ventricular gradient.

The two experiments were interpreted to mean that in man, as in lower species, the regression process in the auricles and in the ventricles is essentially dipolar in nature, and of considerably greater length than the accession process.

The Motility of the Esophagus in Cardiospasm and Scleroderma. (By invitation) PHILIP KRAMER and FRANZ J. INGELFINGER, Boston, Massachusetts.

Esophageal motility was studied by fluoroscopy and balloon-kymograph recordings in normal subjects, 3 patients with cardiospasm and 4 patients with scleroderma.

In both cardiospasm and scleroderma cases, fluoroscopy demonstrated definite but not excessive esophageal dilatation ending abruptly near the cardia. In scleroderma, motility was minimal. In cardiospasm, motor activity was present, but uncoordinated and non-propulsive. Though degree of stasis in patients with cardiospasm and scleroderma was comparable, esophageal symptoms were minimal in scleroderma cases.

Motility records revealed marked atonicity and diminished wave pattern in both cardiospasm and scleroderma. Acetyl-beta-methyl-choline, 10 mg. i.m., increased motility moderately in normal subjects, exerted little effect on the hypomotility of scleroderma, but produced a tetanic and lumen-obliterating contraction of the esophagus in cardiospasm. This reaction was also observed fluoroscopically.

These observations support the concept that cardiospasm is a neuromuscular disorder of the entire esophagus, not of the cardia alone. The violent esophageal reaction to cholinergic stimulation may be the hypersensitive response of a denervated organ and suggests that the distal parasympathetic pathways are interrupted in cardiospasm. Though superficially alike, the esophageal disorders of cardiospasm and scleroderma do not appear similar with respect to pathogenesis or function.

The Relation between Infant Birthweight and Subsequent Development of Maternal Diabetes Mellitus. (By invitation) JOSEPH P. KRISS and PALMER H. FUTCHER, Saint Louis, Missouri.

Analysis was made of birthweight data on infants born to 100 women destined later to develop diabetes and on infants born to 100 non-diabetic (control) women of comparable age and parity. In the 2 groups there were 144 infants weighing 10 pounds or more; 77.1 per cent of the 144 were born to pre-diabetic women. Of 52 infants weighing 12 pounds or more, 90.3 per cent were born to pre-diabetic women. Single and repeated births of abnormally large infants occurred far more commonly in the pre-diabetic mothers than in the control mothers. As reported by H. C. Miller, the average birthweight of the infants born to the pre-diabetic mothers was significantly greater than that of infants born to control mothers. The period between the birth of the first abnormally large infant and the development of clinical diabetes in the mother averaged about 24 years, with a range from 1 to 46 years.

According to Spiegelman and Marks, it may be predicted that 4 per cent of women of childbearing age will develop diabetes. The data on our small group of subjects indicated that diabetes developed in over 50 per cent of women giving birth to one baby weighing over 13 pounds or to 3 babies weighing more than 10 pounds.

Experimental Studies on Spread of Pain. E. CHARLES KUNKLE, GEORGE C. ARMISTEAD and HELEN GOODSELL (Introduced by Harold G. Wolff), New York, New York.

In 125 experiments upon 23 adult subjects cyclic pain induced by immersion of a finger in water maintained at 0° C. was almost always found to overflow to adjacent areas, particularly to neighboring digits. Features common to this phenomenon were a "latent" period, "facilitation" in subsequent phases of the pain cycle, "tapering" of intensity, "incomplete segmental filling," and absence of contralateral spread. Pain failed to spread from thumb to jaw (in cortical sequence). Overflow of pain was unaltered by preliminary interruption of the circulation to the arm or by procainization of an area into which spread of pain was to occur.

The extent of spread showed moderate intra- and marked inter-individual variation. In a minority of instances the spreading pain "migrated" during the experiment, "skipped" a digit, or reached a higher intensity than that of the primary pain.

These listed features can readily be identified also in clinical experience, notably in patients with angina pectoris. It is inferred that such overflow of pain is a central phenomenon and probably occurs at the segmental level in the cord. This mechanism contrasts sharply with spread of pain due to peripheral effects, as in secondary contraction of skeletal muscle or with sensory nerve root or trunk lesions.

The Metabolic Effects of Chorionic Gonadotrophins in Young Men. RICHARD L. LANDAU and KATHRYN KNOWLTON (Introduced by Allan T. Kenyon), Chicago, Illinois.

The anabolic effects of testosterone are established but it has not been shown that the testis of the mature male is capable of participating in anabolic adjustments by an increased rate of secretion of its hormone. To study this possibility chorionic gonadotrophins were administered to two normal men and one eunuchoid.

One normal man received 500 to 3000 I.U. of chorionic gonadotrophins daily for six days. Pronounced nitrogen retention of 60 mg./Kg. body weight daily was obtained. There was parallel retention of inorganic phosphorus and administered creatine. 17-ketosteroids rose an average of 7 mg. daily for ten days. Another received 500 to 1500 I.U. daily for twelve days. Nitrogen retention (22 mg./Kg. daily) was moderate, as was that of phosphorus. 17-ketosteroids showed only a faint suggestion of a rise.

The eunuchoid was given 500 to 3000 I.U. daily for six days without effect on the urinary constituents determined. However, 5 mg. of testosterone propionate daily produced nitrogen retention of 28 mg./Kg. per day. The effects of the gonadotrophins described are accordingly mediated through the testis.

The normal adult testis is thus sensitive to suitable stimulation.

The Relation of Renal to Non-renal Vascular Resistances in "Essential" Hypertension; and the Effect of Sympathectomy. (By invitation) M. LANDOWNE, A. S. ALVING and (by invitation) W. ADAMS, Chicago, Illinois.

Studies of renal dynamics were made upon twelve subjects before and up to twenty-eight months after radical sympathectomy. In nine of these, non-simultaneous cardiac output was determined under comparable basal conditions. For simultaneous measurements the ratio of renal to non-renal blood flow would be $RBF/(CO - RBF)$, and the ratio of renal to non-renal resistances (R_k/R_n) would be approximately the reciprocal of this. For non-simultaneous measurements this ratio (R_k/R_n) has been derived from the calculated renal resistance (R_k) and the total resistance (R); since in parallel arrangement

$$\frac{1}{R} = \frac{1}{R_n} + \frac{1}{R_k},$$

therefore

$$\frac{R_k}{R_n} = \frac{R_k}{R} - 1.$$

Renal resistances were calculated by Lampion's formulae, using the sum of "afferent" and "efferent Arterioles" resistances. Total resistances were expressed, in the same units, as $P_m/CO \times 1000$.

The average of the preoperative ratios R_k/R_n was 4.27. Twenty-nine postoperative determinations gave an averaged value of 4.17. The result of sympathectomy upon the blood pressure is not the same in all patients. In those of our series with lower R_k 's ($R_{k+} < 32$ units/ $1.73 m^2$) the blood pressure fell. Two of the nine cases were in this group; their preoperative R_k/R_n was 2.85, and postoperatively fell to 1.42. Five cases had temporary reduction in blood pressure after operation. Their averaged R_k/R_n was 4.00 before, and 3.83 after operation. Two cases did poorly. In these the preoperative R_k/R_n was 6.4, and the postoperative R_k/R_n was 7.8. The significance and limitations of the data will be discussed.

Physiological Studies of Polycythemia Vera. JOHN H. LAWRENCE, and (by invitation) R. LOWRY DOBSON, (by invitation) WM. E. BERG, (by invitation) LOUIS R. WASSERMAN, (by invitation) JAMES R. ROBERTSON, and (by invitation) ROBERT L. ROSENTHAL, Berkeley, California.

A method employing a mass spectroscopie for analysis of expired gas mixtures was used to measure the rate of pulmonary denitrogenation, taken as a measure of pulmonary efficiency. As the patient changed from breathing air to inhaling pure oxygen a continuous record of nitrogen concentration in exhaled air was continuously recorded. No marked difference was found between polycythemia patients and normal controls in the group studied.

Using the microgasometric technique of Roughton and Scholander, arterial blood oxygen saturation was found to be within normal limits in 51 resting patients with polycythemia.

Determinations of prothrombin, bleeding and clotting times and studies of clot retraction by electrical resistance methods in polycythemic patients gave normal values.

Arm-to-tongue circulation times and blood viscosity were found to be elevated in patients having high hematocrits. In general they fell to normal as the hematocrits approached normal with treatment.

Sternal marrow studies showed the characteristic pattern for polycythemia vera to be a relative increase in nucleated red cells.

Using a thermal conductivity method, it was found that after exercise polycythemic patients have a normal rate of return to normal of oxygen consumption but an abnormally slow return to normal of CO_2 production.

The Incidence of Reaction Following Administration of Crystalline Aqueous Penicillin, Penicillin in Oil and Beeswax and Procaine Penicillin in Oil. (By invitation) MARK H. LEPPER, HARRY F. DOWLING, (by invitation) JAY A. ROBINSON, and (by invitation) THOMAS E. STONE.

This study reports the relative incidence of local and allergic reactions resulting from use of aqueous penicillin in peanut oil and beeswax (POB) and procaine penicillin in sesame oil (PPO).

The incidence of local reactions recorded as mild, moderate and severe was obtained. During 317 courses of treatment, 232 patients receiving aqueous penicillin, there were 27 mild, one moderate and two severe reactions. Similarly, during 272 courses of therapy with POB in 170 patients similar reactions occurred in 64, 21 and 9 patients respectively. With PPO there were 72 courses and 54 patients with only 4 reactions, all mild. With all preparations there was a greater incidence of reaction with higher doses and the difference is greatest in the POB treated group. With the aqueous and POB preparations the number of reactions increased with longer administration, but this trend has not been seen as yet in the PPO patients. There is a comparable percentage of patients receiving high doses and long continued treatment with each preparation. POB is more apt to cause local reactions and the dosage and duration of use are limited by this fact.

In evaluating allergic reactions, many of the patients were given a second course of the same preparation. However, the reaction rate is very small, there being two such reactions in the aqueous, one in the POB, and none in the PPO patients discussed above.

The Physiologic Activity of Tetrabrom- and Tetrachlor-thyronine. JACOB LERMAN and (by invitation) C. R. HARRINGTON, Boston, Massachusetts.

One of the actions of thyroid hormone is to depress the function of the thyroid. This is accomplished in two ways: 1. Indirectly by depressing pituitary activity, and 2. Directly by depressing the thyroid follicle. Advantage has been taken of this property to depress the overactive thyroid in Graves' Disease. However, the high calorigenic action of thyroid hormone makes it hazardous to

use it in large doses over a long period of time. The desired compound is one which has little or no calorigenic activity and yet may retain the property of depressing the thyroid.

Two such compounds have been made available by Harington, namely tetrabromthyronine and tetrachlorthyronine. Each compound has been assayed in two patients with spontaneous myxedema, and the results compared with our standard assays of thyroxine and thyroxinopoly-peptide. In each case, there was a rise in metabolism, improvement in the myxedematous state and reduction in serum cholesterol. That iodine did not participate in the metabolic effect produced by tetrabrom- and tetrachlorthyronine is indicated by the fact that the protein-bound iodine of the blood remained unchanged. The activity of tetrabromthyronine is about 1/15th, and of tetrachlorthyronine about 1/300th that of thyroxine.

A preliminary trial with tetrabromthyronine in a patient with Graves' Disease caused a slight drop in metabolism but a marked drop in protein-bound iodine from 24 γ to 8.8 γ per cent.

Studies of Phosphorus Metabolism in Man: II. A Study of the Permeability of the Human Erythrocyte to Inorganic Phosphate in Vitro and in Vivo by the Use of Radioactive Phosphate (P^{32}). S. M. LEVENSON, M. A. ADAMS and F. H. L. TAYLOR (with the technical assistance of Mary Kendrick) (Introduced by George Richards Minot), Boston, Massachusetts.

Phosphate exchange between the plasma and erythrocytes of human blood was studied *in vitro* and *in vivo*. The *in vitro* studies were conducted over a period of 4 hours. In both instances P^{32} was used as a means of tagging the phosphorus. In the *in vitro* studies, unlike former studies on this subject, no phosphate was added other than the isotopic preparation which was of high specific activity.

The *in vitro* studies showed that inorganic phosphate exchanged freely between plasma and erythrocytes at 37.5° C. Minimal transfer occurred at 7° C.

Essentially all the P^{32} in the plasma remained in the inorganic form. Most of the P^{32} which passed into the erythrocyte was found in the inorganic fraction, less than 30 per cent of the amount found in the erythrocyte after 4 hours being in the organic form. The transfer to the organic fraction was confined entirely to the acid soluble portion.

Following the intravenous administration of tracer amounts (100 to 200 microcuries) of P^{32} in man, the exchange and distribution of the isotope followed closely those observed *in vitro*.

The Study of Hemoglobin Metabolism in Man with the Aid of the Isotope Technique. IRVING M. LONDON, DAVID SHEMIN and D. RITTENBERG (Introduced by R. West), New York, New York.

The administration of glycine labeled with N^{15} to humans affords a physiologic method for studying the rate

of formation and the pattern of destruction of the human erythrocyte. In three normal adults the average life span of the erythrocyte has been found to be 127, 116, and 118 days. A patient with sickle cell anemia has shown a random disappearance of labeled heme from the peripheral blood which is consistent with either a random destruction of the erythrocytes or a random synthesis and degradation of hemoglobin in the peripheral blood. In investigating this question, the whole blood of sickle cell anemia patients has been found to synthesize heme from glycine *in vitro*. Blood from normal individuals and from patients with elevated reticulocyte counts due to other blood dyscrasias produced no significant heme synthesis. These studies will be considered in relation to our earlier studies in pernicious anemia and polycythemia vera.

Crystalline stercobilin has been isolated from the feces of one of the normal subjects in order to study the relationship of hemoglobin destruction to bile pigment production. The data indicate that a portion of bile pigment is derived from a source other than the hemoglobin of circulating red blood cells. The origin of this portion of bile pigment will be discussed.

The Pathogenesis and Histopathology of Air-Borne Pneumonitis Virus Infection in Mice: The Effect of Penicillin G upon the Developing Lesion. CLAYTON G. LOOSLI and (by invitation) MERLE H. RITTER, Chicago, Illinois.

Fatal pulmonary infections were produced in mice by allowing them to breathe air for 1 hour in a 60-liter chamber into which was atomized 4 cc. of 10^{-4} dilution of mouse-lung suspension of mouse pneumonitis virus which is related to the psittacosis-lymphogranuloma group. Animals died of extensive pulmonary consolidation from 10 to 16 days following exposure to the infected atmosphere. The development of the pulmonary lesion was studied in mice killed at increasing intervals after exposure. Grossly small focal lesions appeared on lung surfaces in from 3 to 4 days. These enlarged by directed extension until the greater majority of the lung substance became consolidated when death occurred. There was evidence microscopically that the virus "central body" and "plaque" develop extracellularly on the surface of the alveolar walls, an observation which is in agreement with that of Weiss and others. The intracellular virus vesicle is confined principally to the attached septal cells of the alveolar walls. Daily injections of Penicillin G (1000 units) given subcutaneously in 4 doses prevents the growth of the primary pulmonary lesion. The effect of the penicillin on the developing virus bodies in the lung will be shown.

Induced Insulin Resistance in the Rabbit. FRANCIS C. LOWELL and (by invitation) WILLIAM FRANKLIN, Boston, Massachusetts.

A number of rabbits, which were shown to be susceptible to small doses of insulin, were injected with

large doses of beef and pork insulin incorporated in an emulsion of falba and mineral oil containing acid-fast organisms. Four months after injections were begun one animal developed a high degree of insulin resistance which persisted for at least 5 months. A single intravenous dose of 16 units of insulin, equivalent to 400 units in a human subject, was tolerated without symptoms and the blood sugar fell only moderately. On the other hand small doses of *human* insulin have caused a pronounced fall in blood sugar. Diabetes has not developed and a glucose tolerance test was normal. The resistance to insulin, therefore, is species specific and is probably due to the development of an antibody for beef and pork insulin.

Further experiments have shown that beef insulin treated chemically so as to destroy its activity as a hormone, still acted as though it combined with the animal's antibody for insulin. It is concluded that resistance to insulin on an immunologic basis may be induced in the rabbit, that such resistance may be species specific and that the antibody formed is not a true anti-hormone. It appears that experimentally induced resistance to insulin may provide a valuable immune system for experimentation as well as a new means for studying insulin. Finally, it is probable that these findings have a bearing on resistance to insulin as it occasionally occurs in diabetic individuals.

The Relationship between the Plasma Protein Level, the Renal Excretion of Sodium, and Edema. JOHN A. LUETSCHER, JR., and (by invitation) ALASTAIR D. HALL, Baltimore, Maryland.

The anomalous behavior of certain nephrotic patients after albumin therapy suggested that renal retention of sodium might be as important a cause of edema as the reduced plasma colloid osmotic pressure. Both increased circulating protein and diuresis of sodium and water are apparently necessary to raise the concentration of plasma protein to normal, but either factor alone may increase the plasma protein concentration to a limited extent. The plasma volume rises when circulating protein is increased, but decreases during diuresis.

In acute hemorrhagic nephritis, edema may be associated with renal sodium retention without significant reduction in the plasma proteins, and diuresis may result in a sharp drop in plasma volume with increasing concentration of the circulating proteins.

Dogs on protein-free diets for 3-4 months show a profound fall in glomerular filtration rate and some impairment of sodium excretion. Specific depletion of plasma protein to similar levels by plasmapheresis is associated with minimal reduction in filtration rate and sodium excretion.

These data suggest that either protein depletion or failure of renal sodium excretion may lower the plasma protein concentration. When the two factors coincide in nephrosis, intractable hypoproteinemia and edema follow. The specific sodium retention may be attributed to active nephritis or to prolonged protein deficiency.

Observations on the Dumping Syndrome and Relief of Symptoms by Atropine. THOMAS E. MACHELLA, Philadelphia, Pennsylvania.

In some patients following subtotal gastric resection, symptoms of varying severity occur after the ingestion of meals; these may consist of sweating, vertigo, palpitation, weakness, nausea and even collapse. It is generally accepted that the rapid entrance of food into the jejunum is somehow responsible for the manifestations. The mechanism of their production has been variously ascribed to mechanical distention of the jejunum, to hypoglycemia and also to hyperglycemia.

Observations on 4 patients manifesting symptoms of the "dumping syndrome" reveal that the symptoms occur toward the end of a meal or immediately thereafter during which period a hyperglycemia exists. They are accompanied by a rise in blood pressure and an increase in pulse rate. The manifestations can be reproduced by the administration of glucose orally but not when the glucose is administered intravenously. The symptoms, but not the rise in blood sugar, in blood pressure or in pulse rate, are prevented by the administration of atropine before meals. The results of mechanical distention of the jejunum by inflation of a balloon will be presented.

Observations on the Apparent Acquisition of Streptomycin-Fastness. MANSON MEADS (Introduced by George T. Harrell, Jr.), Winston-Salem, North Carolina.

Methods of preventing drug-fastness in clinical infections are suggested by observations made on strains of *Kl. pneumoniae* exposed to streptomycin. When the number of organisms and the antibiotic concentration were varied independently, in liquid or solid media, a small number of progeny of originally sensitive cells grew in streptomycin. This number was inversely related to the drug concentration up to a point where the population was large. A constant number of highly resistant cells then appeared. Variants surviving small drug concentrations gave rise to variants of greater streptomycin resistance. Sulfonamide and penicillin sensitivities were unaffected. Variants occurred only during active cell division. Resistant variants are reported to appear following exposure of bacteria to sulfonamides, bacteriophage, penicillin, and gramicidin.

A rapidly developing high degree of streptomycin resistance occurs more frequently, clinically, than a step-like slowly developing resistance. Gram negative pathogens tend to focalize and produce large populations. The frequency of drug-fastness should be reduced if: (1) the number of infecting organisms can be reduced prior to specific therapy; (2) *bacteriostatic* drug concentrations are maintained in the infected site; and (3) another specific *bacteriostatic* drug, or antiserum, is used concurrently. The second drug should retard growth of the few variants of high resistance specifically to streptomycin.

A New Approach to the Vascular Problem in Diabetes Mellitus. (By invitation) R. MEGIBOW, (by invitation) S. MEGIBOW, (by invitation) K. OSSERMAN, (by invitation) J. BOOKMAN, (by invitation) S. FEITELBERG, and HERBERT POLLACK, New York, New York.

A new direct writing photoelectric microplethysmograph capable of recording volume changes of magnitudes less than 1 mm.³ has been employed to obtain plethysmograms from the great toes of 53 diabetic patients ranging from 6 to 66 years in age.

Plethysmographically the presence of structural vascular disease is manifested by a reduction in peripheral blood flow as measured by the venous occlusion method, and by a reduction in the amplitude of the volume pulse waves after the release of vasomotor tone by nitroglycerine and tetraethylammonium. Since blood flow through these vessels represents the ultimate circulation, the combination of a normal oscillometric index and of an abnormal plethysmogram, if present, would suggest that the initial vascular alterations in diabetes develop in the arterioles and capillaries.

Such a combination of clinically unsuspected but plethysmographically demonstrated vascular disease was noted in 10 of 53 patients. In an attempt to elucidate what factors might initiate these capillary and arteriolar changes, the plethysmograms were correlated with the age of the patient, the duration of the diabetes, the type of diet, the dosage of insulin, the adequacy of control, and the level of the blood cholesterol. The results are discussed, and the implications from both the therapeutic and pathogenetic viewpoints are stressed.

The Effect of Anemia and Polycythemia on Digital Intravascular Blood Viscosity. MILTON MENDLOWITZ (Introduced by Louis J. Soffer), New York, New York.

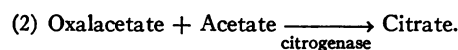
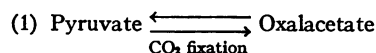
The calorimetric method for measuring digital blood flow was used to study changes in intravascular blood viscosity with varying erythrocyte concentration in patients with anemia and polycythemia. In each observation the blood vessels were dilated maximally by indirect heating. Change in the ratio of pressure to flow with increasing erythrocyte concentration was used as a measure of change in viscosity, the factor of vascular caliber having been maintained relatively constant. Pressures were corrected for "yield value" which varied with erythrocyte concentration. Flow values were corrected for the specific heat of the blood which also varied with erythrocyte concentration. The final observations confirmed similar studies in animals, indicating that intravascular blood viscosity differs from *in vitro* measurements. The gradient of decrease in viscosity with decreasing erythrocyte concentration in anemia was moderate. The blood viscosity in polycythemia increased gradually with moderate increase in erythrocyte concentration and more steeply at higher levels. The blood viscosity was found to be 80 per cent of normal at a hematocrit level of 17 and 169 per cent of normal at

a hematocrit level of 73, these being the extremes of anemia and polycythemia observed.

Studies on Pyruvate and Citrate Metabolism in Man and Animal. MAX MILLER, (by invitation) ERNEST BUEDELING, and (by invitation) R. O. STRAUCH, Cleveland, Ohio.

Few of the individual steps of intermediary metabolism have been demonstrated in the intact animal. Consequently, some of the metabolic reactions involving glucose, alanine, citrate, succinate, acetate, and pyruvate were studied *in vivo*. Blood pyruvate rose from 50 to 375 per cent following citrate, glucose, alanine, and succinate injections, the substances being arranged according to increasing effect. Acetate initially caused a fall in pyruvate, with a subsequent rise. Simultaneous administration of glucose and acetate abolished the initial rise in pyruvate produced by glucose alone, but greater rises than with either occurred after 60 minutes. Plasma citrate fell significantly after glucose and alanine injections, elevations resulted after succinate and acetate.

The rises in pyruvate coincide with observations *in vitro* that pyruvate is an intermediary in the metabolism of glucose, alanine, citrate and succinate. The greater rise after succinate and alanine can be explained by fewer intermediary reactions leading to the formation of pyruvate. The initial fall in pyruvate after acetate is consistent with the hypothesis that a C₂ compound related to acetic acid condenses with oxalacetate formed by CO₂ fixation from pyruvate:



The secondary rise in pyruvate after acetate injection could be due to the subsequent conversion of citrate to pyruvate.

The rises in citrate after succinate and acetate infusions indicate that these compounds are metabolized by the same intermediary reactions (tricarboxylic acid cycle) as *in vitro*. The fall in citrate levels after glucose and alanine cannot be satisfactorily explained by the above schemes and other possible pathways will be discussed.

The Role of "Insulinase" in the Regulation of Carbohydrate Metabolism. I. ARTHUR MIRSKY and (by invitation) R. H. BROH-KAHN, Cincinnati, Ohio.

In another communication we have described the occurrence, distribution and properties of an enzyme system which is capable of inactivating insulin during *in vitro* incubation and which, for descriptive purposes, we call "insulinase." In order to determine its role in the regulation of carbohydrate metabolism in the intact organism, it seemed desirable to investigate the influence of various procedures on the content of this system in the liver. Toward that end, the insulinase content of the liver of

normal well-fed rats was compared with that of copper treated and fasted animals.

In accordance with the observation that the addition of copper inhibits its activity *in vitro*, the liver insulinase content of rats injected subcutaneously with copper sulphate was found to be significantly lower than that of untreated rats. Further, when rats were fasted for 48 hours or more, their liver insulinase content underwent a significant decrease which could be restored to normal values within 48 hours after cessation of their fast. In many instances, a positive correlation could be established between the insulin sensitivity of an animal and its liver insulinase content. The clinical application of these findings will be discussed.

Oxygen Tension in the Skin of the Extremities. HUGH MONTGOMERY and (by invitation) ORVILLE HORWITZ, Philadelphia, Pennsylvania.

Method: Oxygen tension of the intact skin of toes was derived from measurements made by a modification of the exposed tip electrode method of Davies and Brink. The circuit comprised a sharp platinum electrode, diameter 0.25 mm., a moist indifferent electrode, a calomel half-cell, a galvanometer, and a source of suitable polarizing voltage. When O_2 diffusion coefficient and temperature were kept constant, current varied directly with PO_2 in known solutions. The platinum electrodes were calibrated for use in intact skin by insertion into excised skin in 0.9 per cent NaCl of known PO_2 . Corrections for variations in skin temperature were resolved, and were included in the method.

Results: The work (unpublished) of Hodes and Larabee was confirmed, showing current increasing with warmth of skin, increasing several fold when the subject breathed pure O_2 , and becoming zero when the circulation to the limb was arrested by pressure.

By means of calibrated electrodes, the PO_2 of skin was measured. Skin of normal toes averages 100 mm. Hg. during vasodilatation, 50 mm. during vasoconstriction, and 500 mm. during vasodilatation when the subject breathed pure O_2 . Severely ischaemic skin of toes of patients with arteriosclerosis had PO_2 as low as 5 mm., and little or no increase resulted from the breathing of O_2 .

Methods and Interpretations in the Study of Intracellular Biochemistry by Isotope Dilution Technics. FRANCIS D. MOORE, Boston, Massachusetts.

Fluid phase partition in human patients has been extended by the use of deuterium to measure total body water (H_2O). Total solid elementary constituents may also be measured by isotope dilution; in this study the measurement of the total exchangeable potassium (K_2O) has occupied our attention.

Technical problems, biological limitations and factors which determine interpretation of data derived by these methods, will be discussed relative to the findings on seventy-five hospital patients.

Resistance to the Action of the Endotoxins of Enteric Bacilli in Man. HERBERT R. MORGAN (Introduced by Maxwell Finland), Boston, Massachusetts.

The intravenous injection of 0.001 mg. of purified, toxic, somatic antigens (endotoxins) of *Salmonella typhosa*, *S. schottmuelleri* and *Shigella dysenteriae* in man produced chills, fever, headache, muscle aching and generalized malaise and in some instances nausea and vomiting. Daily injections resulted in a progressive decrease in the severity of these reactions until 5 or more times the original dose could be administered without any reaction. Patients who developed this tolerance to the toxic effects of any of these three antigens following its repeated injection were found to show the same resistance following the injection of either of the other two endotoxins. This tolerance was not related to the presence of specific circulating antibody, since patients becoming resistant to injections of the antigen from *S. typhosa* showed no reaction to the administration of *Sh. dysenteriae* when antibodies were detectable only for *S. typhosa*.

The acquired tolerance disappeared in 4-6 weeks, although homologous antibody was still detectable. Some mechanism other than an antigen-antibody reaction is probably responsible for this phenomenon of tolerance.

A patient convalescent from typhoid fever was resistant to the toxic effects of these somatic antigens.

Muscle Electrolytes in Patients with Potassium Depletion. GILBERT H. MUDGE (Introduced by Robert F. Loeb), New York, New York.

Muscle electrolytes were studied by analysis of biopsies obtained from five patients who showed evidence of potassium depletion. Three patients had chronic renal acidosis and osteomalacia and two had gastric alkalosis. In three of these simultaneous sodium, potassium, chloride and nitrogen balances were studied.

Biopsies showed that intracellular water (calculated as non-chloride water) contained decreased potassium and increased sodium concentrations. These intracellular cation changes were similar in both acidosis and alkalosis. In one patient with chronic renal acidosis the biopsy was obtained when the patient had severe voluntary muscle paralysis. Serum and intracellular potassium concentrations were low but did not differ significantly from the non-paralyzed patients, suggesting that the changes in potassium concentration, in themselves, were not the direct cause of this type of paralysis.

Balance data, calculated by the method of Darrow on the assumption that chloride remains extracellular, demonstrated shifts of sodium and potassium which were in general agreement with the changes found by biopsy, although some inconsistencies were noted.

The Splanchnic Oxygen Consumption of Man in the Normal and Diseased States, with Observations on the Effect of the Intravenous Amino Acids. J. D. MYERS and B. C. HOLLAND (Introduced by Eugene A. Stead, Jr.), Durham, North Carolina.

The simultaneous measurement of the hepatic blood flow and the arterial-hepatic venous oxygen difference, by

the method of catheterization of the hepatic veins, provides an estimation of the splanchnic oxygen consumption (hepatic blood flow \times hepatic A-V oxygen difference). Under conditions of rest and fasting, the splanchnic oxygen consumption, which is the oxygen consumption of the liver plus those viscera drained by the portal vein, is probably reflective of the true hepatic oxygen consumption.

The splanchnic oxygen consumption has been measured under various circumstances in which it might be suspected of being altered—cardiac failure, severe anemia, hyperthyroidism, and after the rapid intravenous administration of amino acid solution. The results are compared with data obtained in a series of 12 individuals without significant disease.

Study of 13 patients with heart failure and low cardiac outputs has shown a *proportionate decrease* in hepatic blood flow, as measured by the bromsulphalein technique. This decrease in flow is compensated by an increase in arterial-hepatic venous oxygen difference so as to maintain a normal splanchnic oxygen consumption. In 5 subjects with hemoglobin levels of less than 8 gm. per 100 ml., all of whom showed increased cardiac outputs, there was a *proportionate rise* in liver blood flow and again a normal splanchnic oxygen consumption. Four patients with hyperthyroidism have shown increases in splanchnic oxygen consumption in keeping with their increases in total oxygen consumption. This was accomplished largely by an increase in hepatic A-V oxygen difference; there has been mild if any increase in hepatic blood flow.

A well-tolerated solution of amino-acids (Vuj-nIX solution, Merck) has been given rapidly intravenously in a dose of 25 to 50 gm. (250 to 500 ml.) to 12 individuals (controls 4, cardiac failure 3, anemia 3, and hyperthyroidism 2). This was accompanied, in all of the subjects except those with anemia, by a striking increase in splanchnic (and presumably hepatic) oxygen consumption. The increase was accomplished primarily by a rise in hepatic A-V oxygen difference. Certain individuals, such as those with heart failure and hyperthyroidism, had such marked unsaturation of hepatic venous blood in the fasting state that not much further increase in oxygen extraction was possible. These persons, then, supported their increased splanchnic oxygen consumptions after amino acids by augmenting the liver blood flow by as much as 50 per cent of the basal.

The Effect of Changing Plasma Concentration on Clearances of Diodrast (C_D), Para-aminohippuric Acid (C_{PAH}) and Para-aminoacetylhippuric Acid (C_{PACA}) in Dog and Man. E. V. NEWMAN, J. GENEST, A. GENBCIN, E. CALKINS and J. MURPHY (Introduced by Benjamin M. Baker, Jr.), Baltimore, Maryland.

Clearances were determined on fasting, resting dogs and patients after single intravenous injections producing continuously falling plasma concentration. In dogs the C_{PAH} and C_{PACA} were constant and identical from 8 to 1.0 mgm. per cent plasma concentration. Renal ex-

traction of PACA was 80–90 per cent, determined from renal vein plasma in an explanted dog kidney.

In man the C_D and C_{PAH} fell progressively as plasma concentration fell from 10 to 1.0 mgm. per cent. The fall in C_{PAH} in man was accompanied by increased proportion of conjugated PAH (C_{PAH}) in urine. The C_{CPAH} was always higher than the C_{PAH} .

The C_{PACA} in man showed no self depression with plasma concentration up to 7 mgm. per cent and did not show progressive fall with falling plasma concentration.

No de-acetylation of PACA and PAH was found in dog and man, and no conjugated PAH was found in dogs.

The filtration rate was constant as the C_{PAH} and C_D fell in man.

The C_D and C_{PAH} are not independent of falling plasma concentration in man, but the C_{PACA} is; the C_{PAH} and C_{PACA} are independent in the dog.

Hereditary Hypercholesterolemia: A Factor in the Genesis of Coronary Atherosclerosis. Studies of Patients Under Age of 50. ALBERT D. PARETS and DAVID ADLERSBERG (Introduced by Ernst P. Boas), New York, New York.

Study of 122 unselected, consecutive patients with proven coronary artery disease under age of 50; 108 males and 14 females. The average serum cholesterol for the entire group was 316 mgms. per 100 ml. Arcus senilis was exhibited by 22, xanthelasma by 12, and xanthomatosis by 3; the great majority with these stigmata had hypercholesterolemia. Fifty families of these patients were available for studies. In 15 families, all or most of the siblings showed hypercholesterolemia, in 9 families there was an equal number of siblings with normo- and hypercholesterolemia. Only concentrations of serum cholesterol above 300 mgms. per 100 ml. were considered abnormal. The findings suggest that a hereditary disturbance of lipid metabolism may play a significant part at least in young individuals with coronary artery disease.

The Action of Penicillin on Staphylococcus. The Effect of a Short Exposure to Penicillin on Growing Cells. R. F. PARKER, Cleveland, Ohio.

When a growing culture of staphylococcus is exposed to an appropriate concentration of penicillin, growth is promptly inhibited. Earlier work with a single strain indicated that if after a short interval the cells were transferred to penicillin free broth at 37° C. no appreciable killing of organisms occurred. On the other hand, such penicillin treated cells failed to resume growth for a considerable period.

In the present experiments the observations have been extended to include 29 strains, and it has been found that the effect is consistently produced. Experiments indicate that when staphylococci sensitive to inhibition by 0.25 unit of penicillin per ml. in the standard test are exposed for 15 minutes to 1.0 unit of penicillin per ml.,

and the penicillin is then removed, multiplication is prevented for (on the average) 2½ hours.

If similar effects occur *in vivo*, at least part of the reason for the paradoxical efficiency of intermittent administration of penicillin may be accounted for, since serum concentrations of this order are easily attained after intramuscular injections of 50,000 units of penicillin.

Hemolysis of Human Red Cells by Hemologous Complement, in the Presence of Tannic Acid. JOHN L. PECK and LEWIS THOMAS (Introduced by H. W. Josephs), Baltimore, Maryland.

It has long been known that tannic acid in high dilutions renders erythrocytes susceptible to lysis by complement. A study of this phenomenon was undertaken. Human cells treated with tannic acid were lysed by complement from the same individual. The effective range of tannic acid was from 0.06 to 0.008 per cent. The optimal concentration of sodium chloride was 0.7 per cent, with 1 per cent red cell suspensions.

Studies on the factors influencing the reaction were undertaken. Sensitization occurred only after exposure of red cells to tannic acid for at least 5 minutes. If tannic acid were mixed with complement before the addition of red cells, lysis did not occur. Small amounts of protein in the red cell suspension prevented the action of tannic acid. When cells had been sensitized with tannic acid, they could be washed without losing their susceptibility to lysis by complement. Inhibition of lysis was caused by heparin and congo red. Cells sensitized with tannic acid were more susceptible to lysis by detergents than normal cells.

Using tannic acid, human complement and human red cells as the indicator system, complement fixation tests were performed with various antigen-antibody mixtures. The results were comparable to those obtained in the standard test with guinea pig complement, sheep cells and rabbit amboceptor.

Antihyaluronidase Studies in Rheumatic Fever. ROBERT W. QUINN (Introduced by J. R. Paul), New Haven, Connecticut.

The early work of Friou and Wenner on the antihyaluronidase test as a diagnostic measure of activity of infection in rheumatic fever, has been confirmed in these studies. Their method which was originally described by McClean (which is a mucin-clot prevention test) has been modified to determine the antihyaluronidase titre of sera from patients with rheumatic fever in different phases of activity, patients convalescent from beta hemolytic streptococcal infections, non-streptococcal infectious diseases, rheumatoid arthritis and normal individuals.

It was found that the mean antihyaluronidases titre of sera from patients with rheumatic fever was significantly higher than the mean titre of sera from any other group of patients or normal individuals. The most important result in this study was the finding that the mean antihyaluronidase titre of sera from patients with *active*

rheumatic fever was significantly higher than the mean titre of sera from patients in any other phase of rheumatic fever or any other group of patients studied.

The rise and fall of serum antihyaluronidase titre during the active and inactive phase of rheumatic fever is also demonstrated.

Possible mechanisms involved in this test are discussed.

Relationship of Antibody Response Following Hemolytic Streptococcus Sore Throat to Development of Nonsuppurative Complications. LOWELL A. RANTZ (by invitation) ELIZABETH RANDALL, and (by invitation) HELEN H. RANTZ, San Francisco, California.

A large number of cases of Group A hemolytic streptococcus sore throat were studied in great detail. Serial antistreptolysin "O" and antifibrinolysin determinations were made over a period of 4 or more weeks. The results of this investigation demonstrate that the magnitude or frequency of the antibody response was greater when a nonsuppurative complication was a sequel to the initial acute respiratory illness. The mean increment of antistreptolysin in uncomplicated infections was 210 units per ml. When arthritis, late fever, carditis or nonsuppurative pneumonitis supervened the mean increase in this antibody was 434 units.

Similarly, the frequency of antifibrinolysin response increased from 25.3 per cent to 45.5 per cent in the presence of these poststreptococcal disorders. The results just described are statistically highly significant.

Analysis indicates that these variations are not the result of differences between the antibody stimulating properties of the hemolytic streptococci responsible for the initial infection. It is believed that the augmented formation of antibody by human beings who develop poststreptococcal nonsuppurative disease reflects an immunological hyper-reactivity on the part of these individuals.

Data will be presented in appropriate tables and charts in support of these statements, and the significance of these observations will be discussed.

The Mechanism of Rapid Fibrinolysis in Chronic Hepatic Disease. OSCAR D. RATNOFF (Introduced by G. Canby Robinson), Baltimore, Maryland.

The frequency of rapid fibrinolysis, described by Goodpasture in patients with cirrhosis, was investigated. The lysis time of recalcified plasma clots of 25 of 28 patients with cirrhosis, and 9 of 17 patients with hepatic damage secondary to other pathology, was two days or less, but was three days or more in all of 12 patients with acute hepatitis and 6 patients with obstructive jaundice, and 164 of 175 other controls.

The mechanism controlling the rate of fibrinolysis was investigated. The rate was unrelated to spontaneous, chloroform-activated, or fibrinolysin-activated plasma proteolytic activity, or to the inhibitory activity of fresh plasma or serum against plasma proteolytic enzyme. However, the inhibitory activity of all of 38 plasma tested against plasma protease decreased, during incuba-

tion at 37° C., to a constant minimal level. The time this level was reached coincided roughly with the clot lysis time. The deterioration of inhibitory activity was independent of the presence of calcium or fibrin. Thus, the rapid fibrinolysis observed in patients with chronic liver disease seemed to depend not on the presence of more proteolytic activity in such bloods, nor on a poverty of proteolytic enzyme inhibitor, but rather on the rate of inactivation of the labile inhibitor.

The Renal Extraction of Mannitol and Para-aminohippurate Compared to their Excretions in Normotensive and Hypertensive Subjects. FRANÇOIS C. REUBI (Introduced by Carl V. Moore), St. Louis, Missouri.

A comparison was made between the clearances of para-aminohippurate and mannitol and the simultaneous renal extraction of these substances before and after the injection of epinephrine and histamine in human subjects. The right renal vein was catheterized and blood samples obtained simultaneously from the femoral artery or antecubital vein and the renal vein. The apparent clearances, as measured by the formulae $C_M = \frac{U_M V}{P_M}$ and $C_M = E_M \frac{C_{PAH}}{E_{PAH}}$ were compared. Considerable discrepancies were found. In one normotensive subject the clearance calculated from the extraction was as much as 54 per cent higher than that calculated from the urinary excretion. This was true to a lesser degree in one hypertensive subject with good renal function. One subject, with a possible hypernephroma and only one kidney, showed no discrepancy. Two hypertensive subjects, with a reduced apparent renal blood flow, showed the reverse: The clearance, calculated from the extraction, was as much as 31 per cent lower than that calculated from the urinary excretion. When histamine or epinephrine was injected subcutaneously, these discrepancies were reversed in all cases only to return 30 to 40 minutes later. The effect of histamine on renal blood flow, as measured by the clearance technique, was found in five hypertensive and five normotensive subjects to act somewhat similarly to that of epinephrine. Since $\frac{U_M}{P_M - R_M}$ does not equal $\frac{U_{PAH}}{P_{PAH} - R_{PAH}}$, and since this discrepancy can be altered by the injection of these vasoactive drugs, it is possible that under some conditions mannitol may be metabolized or reabsorbed through lymphatic vessels, and under other conditions para-aminohippurate may be lost in the same manner. Renal arterio-venous by-passes do not account for these differences.

The Thyroid Inhibiting Properties of Tetrabromthyronine. (By invitation) CHARLES E. RICHARDS, (by invitation) ROSCOE O. BRADY, (by invitation) OLIVE JONESON, (by invitation) DOUGLAS S. RIGGS, and RULON W. RAWSON, Boston, Massachusetts.

The thyroid inhibiting properties of tetrabromthyronine have been evaluated by observing the effects of this agent

on the development of goiters in rats receiving thiouracil. These properties have been compared with the antigoitrogenic effects of thyroxine.

It has been observed that tetrabromthyronine, when administered in a daily dose of three hundred micrograms, has an antigoitrogenic effect comparable to that of thyroxine administered in a daily dose of twenty micrograms. Tetrabromthyronine in part prevented the loss of thyroid iodine, though to a lesser degree than did thyroxine.

These thyroid inhibiting properties of tetrabromthyronine were observed even though the blood protein bound iodines fell to levels comparable to those found in rats being treated with thiouracil alone. In the rats receiving thiouracil and thyroxine there was a significant increase in the blood protein bound iodine levels.

The pituitaries of animals treated with these agents have been assayed for thyrotrophic hormone by injecting suspensions of pooled pituitaries into cockerels and examining the thyroids microhistometrically. The pituitaries of rats treated with thiouracil alone were found to possess no demonstrable thyrotrophic activity. The coadministration of tetrabromthyronine or of thyroxine with thiouracil prevented any loss of thyrotrophic activity from the pituitaries.

Differentiation of Distribution- from Diffusion-Impairment in Pulmonary Emphysema and Fibrosis. R. L. RILEY and J. H. McCLEMENT (Introduced by D. W. Richards, Jr.), New York, New York.

Recently developed methods permit the estimation of the oxygen partial pressure gradient between alveolar air and arterial blood. The factors contributing to the alveolar-arterial pO_2 gradient are distribution, diffusion and venous admixture. "Distribution" refers to variations in alveolar pO_2 in different parts of the lung, hence to the ratio of alveolar ventilation to alveolar perfusion. "Diffusion" refers to the resistance of the alveolo-capillary membrane to the passage of oxygen, hence to both permeability of the tissue-fluid barrier and total area of the blood-gas interface. "Venous admixture" is a relatively insignificant factor in the absence of congenital anomalies. It is possible to differentiate impaired diffusion from impaired distribution by estimating the alveolar-arterial pO_2 gradient at high and low levels of oxygenation. Owing to the characteristics of oxyhemoglobin dissociation the distribution factor is preponderant at or near full arterial oxyhemoglobin saturation and the diffusion factor is preponderant at approximately 70 per cent. Findings in a patient with a type of fibrosis causing impaired alveolo-capillary diffusion are contrasted with those of an emphysematous patient in whom alveolar ventilation and alveolar perfusion are poorly correlated.

Studies on the Role of Histamine in Hypersensitivity to Cold. BRAM ROSE, Montreal, Canada.

Studies on the histamine content of the blood and plasma were made on eight patients with hypersensitivity to cold, following the administration of histamine and immersion of the hands and fore-arms in ice-water, both

before and after the previous administration of antihistamine compounds. In four of these patients, symptoms were not reproduced, nor was the blood histamine altered. In the remaining four, exposure to cold resulted in marked swelling of the immersed parts. In three of these, the symptoms appeared to be due to local histamine release, since marked increases of the total blood and plasma histamine occurred, and coincided with the peak of the drop in blood pressure, and increase in the pulse rate. Furthermore, the symptoms could be inhibited by the previous administration of an antihistamine compound. In the fourth patient, in addition to the swelling, there was a profound drop in the blood pressure, a marked bradycardia and syncope. The blood histamine was unchanged, and antihistamine compounds were without effect. It was concluded that histamine was not a factor in this case. These results will be discussed in relation to the histamine theory of allergy, and the effect of antihistamine compounds on the liberation and action of histamine.

Inactivation of Viruses by Secretions of the Respiratory Tract. HARRY M. ROSE and (by invitation) ELEANORA M. PRINCE, New York, New York.

The sputums of patients suffering from a number of diseases affecting the respiratory tract have been found to contain variable amounts of a substance which will inhibit the agglutination of erythrocytes by influenza virus. Sputum and sputum extracts containing a high titer of this inhibitory substance have neutralized up to 1000 minimal lethal doses of influenza virus in mice, and have also neutralized from 100 to 1000 minimal infectious doses of herpes and vaccinia viruses in chick embryos. Agglutinin inhibition tests with sputum and serum from the same patient indicate that the titer of circulating influenza antibody is not related to the concentration of inhibitor in the sputum.

Measurable amounts of the inhibitory substance have not been found in fresh or autolyzed suspensions of human liver, kidney, spleen, pancreas, salivary gland and voluntary muscle. Partially purified material has been obtained from sputum by extraction with chloroform, followed by fractional precipitation with alcohol and acetone.

The nature and significance of the virus inhibitor are unknown, but its presence in secretions of the respiratory tract suggests that it may function as a direct mechanism of defense against certain viral agents.

Variation Occurring in Group A Streptococci During Human Infections. SIDNEY ROTHBARD and ROBERT F. WATSON, New York, New York.

A study of the variation in group A streptococci which occurred during the natural course of infection in man was made. From 50 patients with 52 infections, 234 strains of recognized serological types, isolated at weekly intervals, were tested for their capacity to resist the bacteriostatic action of normal human blood and to synthesize the type-specific M protein. In 42 per cent of the infections, strains isolated in the convalescent and

carrier stages showed an increasing susceptibility to bacteriostasis correlated with a progressive loss of M substance; whereas, in the remaining 58 per cent resistance to bacteriostasis and the capacity to produce M protein were maintained throughout the observation period.

In 3 different infections, strains completely lost their capacity to synthesize the M protein and concomitantly became highly susceptible to bacteriostasis. Spontaneous reversion did not occur, but serial mouse passage re-established these functions. These degraded variants had the same T antigen as their respective original strains, which is further evidence the variants developed in the host from the initially isolated strains.

Studies were made to correlate this phenomenon with (a) the appearance of type-specific bacteriostatic antibodies in the patients' sera, (b) the serological type of streptococcus, (c) the production of streptococcal proteinase, (d) the therapeutic administration of sulfadiazine, and (e) the development of purulent complications or rheumatic fever. The possible relationship of these observations to the problem of the "dangerous carrier" of hemolytic streptococci is also discussed.

Excretion Rhythms of Water and Electrolytes in the Nephrotic Syndrome. DAVID A. RYTAND and (by invitation) J. M. CRISMON, San Francisco, California.

In a girl four years of age, the nephrotic syndrome began abruptly during a serum-sickness-like reaction to bee-sting. It was possible to examine individually some 85 consecutively voided specimens of urine (only a few were lost) through three spontaneous cycles of exacerbation and remission within a short time. Determinations included specific gravity, pH, and rates of excretion of water, sodium, potassium, chloride, and protein.

In general, a rise of urinary pH was the earliest indication of an approaching remission. This was soon followed by water diuresis, which in turn was succeeded by simultaneous increases of sodium and chloride excretion, including both concentration and rate. Urinary potassium concentration tended to be high when that of sodium was low, and vice versa. During the remissions, there was a diurnal cycle in excretion of water, sodium, and chloride in that each was excreted more rapidly early in the morning. Similar cycles have been reported by others in normal individuals.

These findings, together with those of others, suggest that chronological differences in behavior of water and electrolytes may be characteristic both of formation and disappearance of edema.

Polymyxin: Experimental and Clinical Investigations. EMANUEL B. SCHOENBACH, (by invitation) MORTON S. BRYER, (by invitation) ELEANOR A. BLISS and (by invitation) EARL OTT, Baltimore, Maryland.

"Polymyxin" is an antibiotic substance derived from cultures of *B. polymyxa* and described by P. G. Stansley, R. G. Shephard and H. J. White. It is active only against Gram-negative organisms. It is probably a basic polypeptide and appears to be similar if not identical

with "Aerosporin," an antibiotic recently described by G. C. Ainsworth, A. M. Brown and G. Brownlee in England, which was obtained from cultures of *B. aerosporus*. *In vitro*, polymyxin is active against a wide range of Gram-negative organisms and, in many instances, 0.15-0.3 micrograms per cubic centimeter has been bactericidal. The L.D. 50 of this antibiotic following injection of mice via the subcutaneous route is 0.3 gram per kilogram. Dogs tolerate 15 milligrams per kilogram administered as a single intravenous dose and 10.0 milligrams per kilogram injected intramuscularly twice daily for seven days. When 1.25 milligrams per kilogram was injected intravenously into a rabbit polymyxin was detected at two but not at three hours in the blood.

Polymyxin has not been detected in the spinal fluid after intramuscular administration. It is excreted slowly in the urine in which, 24 hours after its administration, bactericidal concentrations of the drug are noted. Polymyxin is very effective (much more so than streptomycin) against experimental infections with *Kl. pneumoniae* Type A and *H. influenzae* Type b. It also is of interest that to date, despite repeated attempts, it has not been possible to produce resistance to polymyxin *in vitro*.

Polymyxin in total daily dosage up to 5 milligrams per kilogram, given in divided doses at intervals of 3 hours, has been used for therapy of patients ill with infections due to *Ps. aeruginosa*, *Kl. pneumoniae*, and *Br. abortus*. The results thus far have been promising.

Pressor Substances in Extracts of Hypertensive Blood.

HENRY A. SCHROEDER (by invitation) MELVIN L. GOLDMAN and (by invitation) NORMAN S. OLSEN, St. Louis, Missouri.

Alcoholic extracts of hypertensive and normotensive arterial blood were prepared, concentrated, extracted with petroleum ether, and purified by subsequent alcoholic extraction. They were further purified by adsorption on anionic and cationic exchange resins and by the formation of picrates. These extracts were tested for pressor activity in the whole anesthetized rat. Their adsorption spectra and their ability to potentiate the topical action of epinephrine on the rat's mesoappendix were also determined. The color formed by Richter's method for amine picrates was also measured. Those patients (15) exhibiting arterial hypertension with renal disease, either primary or secondary but without nitrogen retention, were found to contain in their blood substances which gave a prolonged pressor response in the rat. In extracts made from the blood in all but three of fifteen exhibiting "neurogenic hypertension" no such response was found. The extract of the blood of one normotensive subject out of fifteen gave the response. The picrate color was found to be usually increased in the blood of hypertensive subjects, the average being three times as much as was found in most normotensive subjects. The extract from hypertensive subjects almost uniformly potentiated the topical action of epinephrine on the rat's mesoappendix, while that from normotensive subjects usually did not. It can be concluded that pressor sub-

stances can be demonstrated in the blood of some hypertensive individuals.

Nitrogen Balance Studies on the Kempner Rice Diet.

WILLIAM B. SCHWARTZ and JEROME K. MERLIS (Introduced by Maurice B. Strauss), Framingham, Massachusetts.

Kempner's report that nitrogen balance is achieved on a rice, fruit, and fruit juice diet with a nitrogen intake estimated to be 3.2 gm. per day is not in accord with other data on minimal nitrogen requirements. In Kempner's studies no analyses of food or fecal nitrogen were reported. Nitrogen balance studies were carried out on six normotensive subjects who adhered strictly to the Kempner rice regime for eight days following a four-day period on a nitrogen depletion diet. One patient with severe hypertension was studied for a 90-day period on the rice regime alone.

The actual nitrogen content of the rice regime, determined by macro-Kjeldahl analysis, was 2.63 gm. rather than Kempner's estimated 3.2 gm. On the eighth day of the rice diet the average total N excretion (urinary plus fecal) was 5.85 gm. in the normotensive subjects, giving a negative N balance of 3.22 gm. per day. The curve of urinary nitrogen excretion indicated that basal values had been closely approximated. On the 90th day the hypertensive patient had a total N excretion of 5.30 gm. per day with a negative balance of 2.67 gm. per day.

The Metabolism of Silver. (By invitation) K. G. SCOTT and J. G. HAMILTON, San Francisco, California.

A study of the metabolism of carrier-free radioactive silver has been made in the rat at intervals from 1 to 64 days. The total quantity of silver, containing the radioactive silver, administered to each animal was less than .001 microgram. Parenteral administration was followed by rapid elimination, most of which took place by way of the liver, the excreted silver appearing in the feces. Absorption by way of the digestive tract was noted to be less than .1 per cent of the administered dose. It has been shown that the normal route of excretion takes place by way of the bile, since ligation of the bile duct reduces the fecal excretion by a factor of more than 10. When the carrier-free radio-silver was diluted by the addition of inert silver, in the range of .1 to 1 milligram of silver administered to each animal, the distribution in the tissue and excreta became very different, there being a ten to one hundred-fold increase at the earlier time intervals of radio-silver in organs such as liver, kidney, spleen, skin, bone, and muscle; and a marked decrease of its rate of excretion. It appeared that the deposition in these tissues was proportional to the total amount of silver administered. A marked degree of decrease in the excretion of silver by way of the liver took place following 3 hours of light chloroform anesthesia. This effect was found to be transient with return to the normal rate of excretion within six days after the administration of the anesthetic. It is suggested that these results point the way for the de-

velopment of a liver function test. It was found that *in vivo* and *in vitro*, most of the carrier-free silver in the blood is bound in a globulin fraction and is not dialyzable to any extent through cellophane.

The Synergistic Action of Streptomycin and Sulfadiazine in the Therapy of Experimental Brucella Infection in the Developing Chick Embryo. (By invitation)

JAMES M. SHAFFER and WESLEY W. SPINK, Minneapolis, Minnesota.

Investigations in this clinic have revealed that combined therapy with streptomycin and sulfadiazine is the most effective treatment available to date in both bacteriologically proved human brucellosis and experimental *Brucella* infection in the chick embryo. This report is concerned with the mechanism whereby such a therapeutic combination is more effective than when either agent is used alone. It has been shown that the superiority of the combined therapy is due to a typical synergistic action of the two therapeutic agents. This synergism is present in experimental infections established with *Br. abortus*, *Br. suis* or with *Br. melitensis*.

The synergistic action of streptomycin and sulfadiazine has been demonstrated by treating infected chick embryos 24 hours after infection with small doses of streptomycin or sodium sulfadiazine alone, and with the two combined. Typical experimental results against *Br. Abortus* show that 80 micrograms of streptomycin or 0.12 milligram of sodium sulfadiazine will not eliminate *Brucella* from any of the embryos, but when these drugs are given together in these doses *Brucella* are eradicated from 40 per cent of the infected-treated chick embryos. By doubling the above doses, the combined therapy produced 75 per cent negative cultures as compared to 30 per cent for sodium sulfadiazine alone, and 10 per cent for streptomycin alone. Such experimental results provide supporting evidence for the use of streptomycin and sulfadiazine in human brucellosis.

The Low Potassium Syndrome in Chronic Nephritis.

(By invitation) SOL SHERRY, LUDWIG W. EICHNA and DAVID P. EARLE, JR., New York, New York.

A patient with persistent hypokalemia (1.5-2.5 meq./L.), hypochloremia (85-94 meq./L.), and hypotension (80/50) exhibited transient muscular weakness, abnormal cardiac rhythms, and electrocardiographic abnormalities. Evidence is presented that the clinical syndrome was due to a faulty mechanism of the renal tubules for the handling of potassium, secondary to renal disease. Ammonium chloride administration revealed little defect in ammonia or titratable acidity production, but a low potassium diet promptly led to a negative potassium balance, weakness and cardiac abnormalities. Normal serum potassium levels could not be attained by the prolonged daily administration of 25 grams of KCl.

Potassium depletion affected the heart in two ways, (a) by increasing the vagal effect and (b) by flattening and broadening the T wave of the electrocardiogram. These effects could be separated by atropine.

The height of the T wave of the electrocardiogram could be correlated with the serum potassium level in acute experiments after potassium administration. However, in the post absorptive state the correlation was poor. A single dose of potassium produced a transient rise in serum potassium level, whereas a slow and progressive improvement in muscle strength began several hours later. The evidence after potassium administration suggested a rapid distribution of potassium into certain spaces, followed by a slower redistribution into others.

The Effect of "Tracer Doses" of Radioactive Iodine on the Function of Chick Thyroids. BENGT N. SKANSE, PRISCILLA MERRILL and ROBLEY D. EVANS (Introduced by Oliver Cope), Boston, Massachusetts.

We have studied the effect of radioactive iodine (I^{131}) on the thyroid's growth, iodine content and response to thyrotrophic hormone in cockerels. These effects were studied sixteen and twenty-four days after administering the I^{131} .

Thyroids which collected 0.1 microcurie were not altered in growth or iodine concentration. Growth of the thyroids which collected 1 and 5 microcuries was significantly inhibited. Iodine concentration of the 1 microcurie group was not altered; however, there was a significant decrease in concentration of thyroid iodine in the 5 microcurie group.

All irradiated animals responded to thyrotrophic hormone as measured by increase in thyroid weight and loss of iodine sixteen days after administering I^{131} . However, at the twenty-four-day interval there was demonstrated a dissociation in response to thyrotrophic hormone between the 1 and 5 microcurie groups. In the first group a loss of iodine was observed but no increase in thyroid weight. In the latter group there was no effect on either iodine loss or thyroid weight.

We have demonstrated that so-called tracer doses of I^{131} may alter normal functions of the thyroid and that these functions vary in their sensitivity to irradiation with this isotope.

Cardiovascular Dynamics in Experimental Embolism of Restricted Portions of the Lungs. JOHN R. SMITH and (by invitation) MASAKI HARA, St. Louis, Missouri.

Studies of experimental pulmonary embolism indicate that small single or multiple emboli may produce marked elevation of pulmonary arterial tension and death, with intense dilatation of the right cardiac chambers. Excluding massive pulmonary arterial obstruction, these dynamic changes from smaller emboli suggest "reflex" pulmonary vascular spasm.

In open-chest dog preparations, carotid arterial and pulmonary arterial pressures were recorded. Flexible rubber catheters were introduced into the main pulmonary artery and directed into a selected lobar arterial branch. The injection of small quantities of barium sulfate or potato starch suspensions into the selected lobar artery provoked a striking rise of pulmonary arterial tension, a fall of systemic pressure, and death, with evidence of

overwhelming right heart failure. Microscopic study indicates embolization of the pulmonary capillaries. The experiments suggest that pulmonary vascular reflex spasm may be induced by capillary embolization of highly restricted lung portions.

In other experiments, catheters were placed in selected lobar arteries, but the main artery to the corresponding lung was ligated. Embolization with barium or starch was then ineffective. Subsequent removal of the ligature resulted promptly in death with right heart failure. The experiments suggest that reflex pulmonary spasm may be abolished by interruption of nerve tracts contained in the pulmonary arterial walls.

Acceleration of Flow in the Veins of Human Limbs by the Local Application of Pressure. (By invitation)

JOSEPH R. STANTON, (by invitation) EDWARD D. FREIS and ROBERT W. WILKINS, Boston, Massachusetts.

The velocity of blood flow in the veins of the limbs was determined fluoroscopically, or with serial roentgenograms, by timing the progression of 4 cc. of 35 per cent diodrast injected in a distal vein. Following control observations in which the pattern as well as the velocity of venous flow was noted, the extremity was evenly pressurized by the inflation of cuffs smoothly applied to the limb prior to the experiment. At pressures of 12-40 mm. Hg the velocity of flow was increased above that of the control observations. Likewise, in three experiments with both lower limbs studied simultaneously, an increase in velocity of venous flow occurred in the pressurized as compared with the unpressurized extremity. The distribution of the diodrast in the venous bed was not significantly altered by the application of pressure although the diameter of the individual veins was decreased.

These observations, which seem pertinent to the clinical problem of phlebothrombosis in both medical and surgical patients, suggest that the velocity of venous flow in the limbs may be increased by mild local compression. The apparent explanation for the observed acceleration is that such compression decreases the total cross-sectional area of the venous bed proportionately more than it reduces the volume of blood flow as previously reported from this laboratory.

Effect of Sodium Chloride Depletion on Blood Pressure and Tetraethyl Ammonium Chloride Response in Hypertension. WILLIAM W. STEAD and MORTON F. REISER (Introduced by M. A. Blankenhorn), Cincinnati, Ohio.

Temporary autonomic ganglion block can be produced by tetraethyl ammonium chloride (TEAC), thus leaving a "floor" pressure which is probably maintained by intrinsic vascular and humoral mechanisms.

Blood pressure and TEAC responses were studied in 11 patients with severe progressive hypertension during: (1) control periods, (2) salt deprivation (0.25 gm. dietary sodium per day), and (3) re-salting. In patients without severe renal insufficiency the sodium deprivation was supplemented by mercurhydrin thrice weekly. In all

patients de-salting produced a comparable degree of dehydration and fall of serum sodium, but the changes in blood pressure and TEAC response fell into two distinct groups:

(1) Gradual fall in resting pressure and even greater fall in the TEAC "floor" during sodium deprivation and return to control values during re-salting. This response occurred in ten experiments in five patients. All but one had large initial TEAC response.

(2) No essential change in either resting or "floor" pressure. This occurred in eight experiments in six patients, generally with renal impairment, only one patient having fairly adequate renal function at the outset. None had large initial TEAC response.

The data suggest variations in the contribution of neural and humoral factors in different patients. When the humoral component was predominant de-salting produced little effect, but it was effective when neural factors were in the foreground.

Potassium Deficiency and the Role of the Kidney in its Production. (By invitation) R. TARAIL and J. R. ELKINTON, New Haven, Connecticut.

Potassium was administered without cardiotoxic effects in daily doses of 1.43 to 3.65 milliequivalents per kilogram to six adult patients maintained on parenteral fluids. Five of the patients were losing gastro-intestinal fluid, and the sixth had had a cerebral vascular accident. Two normal subjects were given 3.42 and 4.37 milliequivalents of potassium per kilogram, as controls. The exchanges of electrolytes and nitrogen were measured.

In 4 of the patients the concentrations of potassium in serum were abnormally low. All of the patients retained administered potassium in the cellular phase in "excess" of nitrogen, in amounts varying from 1.20 to 4.61 milliequivalents per kilogram. Only one patient received potassium long enough to show that the maximum degree of retention had been reached. The 2 normal subjects retained only 0.29 and -0.14 milliequivalents per kilogram.

During periods of low potassium intake more potassium was lost in urine than in gastro-intestinal fluid. In 4 patients the quantity in urine was greater than during periods when the intakes were high and the concentrations in serum were normal. The minimum amounts in urine in 3 of the patients deprived of exogenous potassium and maintained in nitrogen equilibrium, were 28, 27, and 6 milliequivalents per day. The renal tubules did not reabsorb potassium completely under these conditions of maximum need for conservation of the ion. The data indicate the primary role of the kidney in the production of potassium deficiency in these patients.

Studies on the Mechanism of the Schwartzman Phenomenon. LEWIS THOMAS and CHANDLER A. STETSON, JR. (Introduced by Harold E. Harrison), Baltimore, Maryland.

Approximately two hours after intravenous injection of Schwartzman's meningococcal filtrate in rabbits, exten-

sive hemorrhagic reactions in the abdominal skin resembling Shwartzman reactions could be induced by the intradermal injection of cysteine or BAL (2,3, dimer-captopropanol). These substances did not cause hemorrhages in normal animals. Hemorrhages were not produced by Na ascorbate, glutathione, or by any of a large number of unrelated compounds. Hemorrhages with the thiol compounds could only be elicited between two and five hours after intravenous injection of bacterial filtrate.

Similar but more extensive hemorrhages occurred when papain was injected intradermally two hours after intravenous bacterial filtrate. In control animals, papain caused much smaller areas of localized necrosis, or produced no reaction.

When skin was prepared for the Shwartzman reaction by intradermal bacterial filtrate, a single application of bromobenzene to the area at any time during the next 20 hours caused complete inhibition of the reaction. Other lipid solvents had a similar effect.

It is postulated that the Shwartzman phenomenon may be due to the action on blood vessels of a tissue protease, activated by sulfhydryl groups. One phase of the reaction may consist of the withdrawal of protease-inhibitor from the involved tissue.

Elaboration of Hyaluronidase by Pneumococci Isolated from Bacteremic Pneumococcal Pneumonia Patients.

ROBERT T. THOMPSON and FRANCES E. MOSES (Introduced by Morton Hamburger, Jr.), Cincinnati, Ohio.

Previously reported rises of antihyaluronidase titer in the sera of patients with bacteremic pneumococcal pneumonia indicate that pneumococcus hyaluronidase was elaborated early in these infections. These findings pose the question: Will pathogenic pneumococci which elaborate hyaluronidase retain this property during culture in ordinary artificial medium? Pneumococci from nine bacteremic pneumonia patients were passed through 0.05 per cent glucose broth every eighteen to twenty-four hours, and then were tested at intervals for the ability to elaborate hyaluronidase by subculture into 0.20 per cent hyaluronic acid broth.

Five of the nine pneumococci tested elaborated hyaluronidase at the first subculture into hyaluronic acid broth, as follows: Four pneumococci were first tested eighteen hours after culture from the patients, and three of these elaborated hyaluronidase; three were first tested thirty-six hours after culture from the patients, and two of these elaborated hyaluronidase; two were first tested forty-eight hours after culture from the patients, and neither elaborated hyaluronidase.

Four of the same five pneumococci which elaborated hyaluronidase on first subculture into hyaluronic acid broth failed to do so on second subculture at intervals of two days, two days, three days, and four days respectively after culture of the pneumococci from the patients. The other pneumococcus which elaborated hyaluronidase on first subculture was not subsequently tested.

These findings indicate that pathogenic pneumococci which elaborate hyaluronidase lose this property in ordi-

nary broth medium approximately forty-eight hours after removal from the pneumonia patient.

Urine "Corticosteroids" in Toxemia and Hypertension.

LOUIS TOBIAN, JR. (Introduced by Tinsley R. Harrison), Dallas, Texas.

Urinary "corticosteroids" were extracted with ethyl acetate and determined by the Loewenstein method which is not necessarily specific. All measurements in pregnant patients were made in the 31-40 weeks.

The results obtained were as follows:

1. In normal late pregnancy, "corticosteroids" were twice the nonpregnant value.
2. Women with twins excreted approximately 40 per cent more than comparable single-fetus women.
3. Pregnant women with excessive edema, with or without toxemia, excreted 50 per cent more "corticosteroid" than pregnant women with minimal or no edema.
4. Mild preeclampsics with minimal or no edema excreted no more "corticosteroid" than nontoxemics.
5. Edematous mild preeclampsics excreted as much "corticosteroid" as equally edematous women with more severe preeclampsia.
6. Nonpregnant patients with essential hypertension, one diabetic, and one nephrotic, all had essentially normal "corticosteroid" excretion.

The results obtained would suggest that increased excretion of "corticosteroids" is correlated, not with hypertension but with pregnancy, and more especially, with edema developing during pregnancy. Although this conclusion cannot be considered established until a larger series of patients has been studied, the findings may afford a partial explanation for the similarity of preeclampsia to desoxycorticosterone intoxication.

Acetylcholine and Neuronal Activity in Craniocerebral Trauma.

(By invitation) DONALD B. TOWER and DONALD MCEACHERN, Montreal, Canada.

During studies on the presence of acetylcholine and cholinesterases in cerebrospinal fluids of over 100 neurological patients, interesting observations have been made on a group with craniocerebral trauma. Detailed methods and results are given elsewhere. Patients fall into 3 groups: (a) Epileptics—"normal" cholinesterases, acetylcholine present. (b) Craniocerebral trauma patients—cholinesterases abnormal, acetylcholine present in varying amounts. (c) Normal individuals and patients with various diseases—cholinesterases "normal," acetylcholine absent.

Only the second group of 14 craniocerebral trauma cases is considered in detail here. Serial observations have been possible in some cases. Low CSF cholinesterase activity and reversal of normal cholinesterase ratios characterize the group. In severe cases acetylcholine is present in the cerebrospinal fluid in large amounts. Recovery is associated with reversal of the above changes. In 3 cases correlation is illustrated between cholinesterase pattern, acetylcholine level, EEG and the clinical state of

the patients. Reference is also made to 6 psychiatric patients undergoing electroshock therapy (a form of craniocerebral trauma) who evidenced similar changes.

Bornstein showed in animals the presence of acetylcholine and abnormalities of the EEG following artificially induced craniocerebral trauma. Our studies in man indicate a correlation between chemical and electrographic findings and the clinical state of the patient and thus contribute to the understanding of brain injury.

Zinc and Carbonic Anhydrase Content of Red Cells in Normals and in Pernicious Anemia. BERT L. VALLEE (Introduced by John G. Gibson, 2nd), Boston, Massachusetts.

Zinc is a component of the enzyme carbonic anhydrase. The zinc content (measured by dithizone), and the carbonic anhydrase activity (measured by the velocity of CO₂ evolution), of normal packed red cells, have a constant relationship. Normal unit values for packed red cells range from 11 to 19 gamma of zinc, averaging 14.7; and from 2.6 to 5.1 E units of carbonic anhydrase, averaging 3.9 per cc.

In the anemias due to iron and dietary deficiency, infection and uremia, unit values of both zinc and carbonic anhydrase are within normal limits. There is a marked increase in both the metal and enzyme in untreated pernicious anemia. Values obtained in 8 patients ranged from 19.0 to 30.0 gamma of zinc, averaging 24; and from 5.9 to 12.7 E units of carbonic anhydrase, averaging 8.0. The ratio of the components, therefore, was comparable to that found in normal red cells. Under successful liver therapy both components return to within normal limits in about 60 days; the relative proportion of metal and enzyme is identical to that of normal cells. Under maintenance therapy values remain normal.

In secondary anemias, zinc and carbonic anhydrase decrease on a slope parallel to that of the drop in hemoglobin. In contrast, in pernicious anemia, the increase of zinc and carbonic anhydrase is inversely proportional to the fall in hemoglobin. This may indicate that the hemoglobin and carbonic anhydrase systems are structurally discrete although functionally related.

Susceptibility of Red Cells and Serum Factor in the Mechanism of Hemolysis in Paroxysmal Nocturnal Hemoglobinuria. PHILIP F. WAGLEY and MAURICE D. HICKEY (Introduced by William B. Castle), Boston, Massachusetts.

In patients with paroxysmal nocturnal hemoglobinuria, the number of red cells that are susceptible to hemolysis may be determined by the repeated incubation for 45 minutes of the cells in samples of fresh human serum at pH 6.4 until no more hemolysis occurs. In one patient the presence of hemoglobinuria correlated with the number of such susceptible red cells. The susceptible cells varied from 3 to 33 per cent of the total red cell population. Hemolysis of such cells is enhanced *in vitro* when the physiological pH range is decreased from 7.4 to 7.22.

The factor in human serum required for the hemolysis of red cells from patients with paroxysmal nocturnal hemoglobinuria is inactivated by procedures known to inactivate the complement required for hemolysis of sheep cells sensitized by amboceptor. However, no complement fixation is observed in the hemolytic mechanism in paroxysmal nocturnal hemoglobinuria and the hemolytic activity of human serum is rapidly diminished with only slight changes in complement activity when fresh human serum is diluted with serum previously heated to 57° C. for 30 minutes. Following the restoration of pH to approximately 6.3 of sera previously incubated at 37° C. at a pH of 5.1, 6.2, 7.4, complement activity for sensitized sheep cells was still demonstrable. However, for the hemolytic system of red cells from a patient with paroxysmal nocturnal hemoglobinuria, hemolysis was irreversibly inactivated by the incubation of serum at a pH of 5.1 and 9.2; hemolysis was not restored by the addition of guinea pig complement to the system adjusted to pH 6.4. The factor in human serum required for hemolysis in paroxysmal nocturnal hemoglobinuria is not identical with the complement required for hemolysis of sensitized sheep cells.

The Effects of Histamine Administered Intravenously on the Peripheral Circulation in Man. (By invitation) KHALIL G. WAKIM, (by invitation) GUSTAVUS A. PETERS, (by invitation) JEAN C. TERRIER and BAYARD T. HORTON, Rochester, Minnesota.

The effects of the continuous intravenous administration of histamine diphosphate on skin temperature, blood pressure, heart rate and blood flow were studied among patients who were receiving the drug therapeutically. The drug was administered to each patient in a solution of 1:250,000 in saline at successive rates of 0.004, 0.008, 0.016 and 0.024 mg. of histamine per minute, respectively. The duration of infusion at each rate was twenty minutes. Control values for skin temperatures, heart rate, blood pressure and blood flow were established before the infusion of histamine was started, and the observations were repeated at regular intervals thereafter for each of the periods of infusion at each of the four infusion rates and for five to fifteen minutes after the infusion was stopped. The blood flow in all four extremities was determined by means of the plethysmograph with a compensating spirometer recorder. The cutaneous temperatures were recorded galvanometrically by means of skin thermocouples applied to the forehead, to the skin over the right and left deltoid muscles, and over the right and left quadriceps femoris muscles.

Histamine produced a cutaneous vasodilatation which appeared first over the face and neck of the patient and gradually extended downward over the upper extremities and thorax, reaching the lower extremities only toward the end when the higher rates of infusion were used. There was a definite increase in skin temperature and in heart rate, and a slight decrease in blood pressure.

The blood flow in the four extremities gradually increased until at the highest rate of infusion of 0.024 mg.

histamine per minute, the average increase in blood flow in the 12 subjects was 182 per cent in the forearms and 45 per cent in the legs, over the control values. However, five minutes after the infusion of histamine was stopped, the blood flow averaged only +46 per cent in the forearms and +27 per cent in the legs. The changes in skin temperature, blood flow, heart rate and blood pressure gradually subsided, and the values returned toward the control level shortly after cessation of the infusion of histamine.

The Balance of Sodium and Potassium in Repair Solutions. WILLIAM MCLEAN WALLACE (Introduced by James L. Gamble), Boston, Massachusetts.

The administration of sodium has long been known to depress the potassium balance of the body and vice versa. The loss of intracellular potassium in the fasting-thirsting state has been shown to have significance with respect to the efficacies of repair solutions. The quantity of potassium which can be provided for replacement of this loss is limited by the concentration which is considered safe as regards cardiac function and the maximal practicable volume. The question then presents: to what extent should the provision of sodium for repair of deficit be limited in order to obtain the most efficient utilization of potassium? As a part of studies of infants receiving treatment for severe diarrhea and acidosis, attempt has been made to answer this question by daily measurements of balance for the individual electrolytes over periods of treatment in which differing quantities of sodium were provided along with 3 m.mol of potassium per kg. of body weight in a volume of 200 cc. per kg.; taken as limits in terms of safety and practicabilities. The data describe the desirability of reduction of the quantity of sodium ordinarily used in fluid therapy to an extent which permits an approximately parallel progress of replenishment of sodium and potassium deficits.

Influenza Virus Associated with Bacterial Pneumonia. THOMAS G. WARD, ELIZABETH STARBUCK MAXWELL and THOMAS E. VAN METRE, JR. (Introduced by Thomas B. Turner), Baltimore, Maryland.

It is well known that an increase in pneumonia cases accompanies epidemics of clinical influenza. Evidence presented herein suggests that influenza virus is one of the causative agents in cases of pneumonia previously considered primarily bacterial in origin. Sputum was obtained from 69 cases of bacterial pneumonia and studied for influenza virus by the chick embryo technique. Of 33 cases occurring during non influenza periods one yielded an influenza "B" virus. Of 36 cases occurring during the period when influenza "A" was prevalent in Baltimore 13 yielded influenza virus which were serologically similar to influenza "A" strains isolated from clinical cases of influenza occurring at the same time.

Acute and convalescent blood specimens were secured on 53 of these same cases and a third specimen was obtained about five months later on 25. Four cases showed

evidence of positive hemagglutination-inhibition antibody response but failed to yield virus.

Thus, a total of 17 of 36 cases (47 per cent) of bacterial pneumonia occurring during an influenza "A" epidemic gave evidence, by virus isolation or serologic techniques, of the presence of influenza virus associated with bacterial pneumonia.

The significance of these findings in the pathogenesis of bacterial pneumonia will be discussed.

Studies on the Action of the Heart by Means of a Cine-radiographic Technique. J. V. WARREN, (by invitation) H. S. WEENS and (by invitation) D. F. JAMES, Atlanta, Georgia.

Radiographic contrast visualization of the heart is a means of extending our knowledge of cardiac activity in health and disease. The value of serial angiocardigrams is limited since they depict only isolated phases of the cardiac cycle. More complete information may be obtained utilizing slow motion cineradiography.

Small mongrel dogs were used for the present experiments. Under pentobarbital anesthesia contrast medium (diodrast or thorotrast) was injected rapidly into the superior vena cava through an intravenous catheter. Motion pictures were made of the image produced on a high speed fluoroscopic screen by x-rays generated at 90 kilovolts and 100-150 milliamperes. Utilizing cameras equipped with large aperture lenses it was possible to record 30 to 40 frames per cardiac cycle on either 16 or 35 mm. green sensitive film. Although projection of the motion pictures permits an overall slow motion demonstration of cardiac activity, more detailed analysis must be based upon the study of individual frames.

Twenty observations have been made on normal anesthetized dogs. Despite variations in the position of the animal and the medium injected, the results were essentially the same in all. The superior vena cava and right atrium were opacified almost immediately following injection of the contrast medium. In proper succession visualization of all heart chambers, the major pulmonary vessels, and the aorta was obtained. In many instances the position and motion of the atrioventricular valves could be determined. Of particular interest was the incomplete emptying of all heart chambers which was noted in every instance. The amount of residual blood in the ventricles, as well as in the atria, during systole was more than anticipated. This may well be of importance in explaining the ability of the heart to undergo the extremely rapid changes in cardiac output known to occur. Increases or decreases in stroke volume may be the result of alterations in the amount of residual blood.

Metabolic Studies on Protein Depleted Patients Receiving a Large Part of their Nitrogen Intake from Human Serum Albumin Administered Intravenously. CHRISTINE WATERHOUSE and JACOB HOLLER (Introduced by Samuel H. Bassett), Rochester, New York.

The availability of purified albumin preparations has led to studies on their utilization in man. The conversion of

albumin to tissue protein, variations dependent on routes of administration, and the induced changes in renal function have been demonstrated by other investigators. That important variations in individual response can occur is illustrated by the following experiments.

Each of three subjects received a daily dose of 60 gm. of concentrated Na free human albumin for 10 or more days. Balances of N, Ca, P, and K were made during control, albumin, and post-albumin periods. Concomitant observations of serum protein fractions, plasma volume and renal function were made.

Subject 1, a man convalescent from rheumatic fever and without evidence of impaired renal function, developed an intense proteinuria by virtue of which he was in negative nitrogen balance on the 10th day of therapy. In subject 2, an emaciated woman with fever of unknown etiology and probable increase in capillary permeability, about 40 per cent of the injected albumin appeared to leak into the extracellular fluid, while 50 per cent was catabolized. The remainder was excreted in the urine or converted to tissue protein. There was marked retention of water with edema, hydrothorax and pericardial effusion. Subject 3, a young woman, was in fair health except for moderate undernutrition. Her response in most respects followed along the lines reported by other investigators, *i.e.*, an immediate, marked retention of the albumin with subsequent slow conversion of 50 per cent of the quantity injected to tissue protein; catabolism of 40 per cent; excretion of 1.6 per cent in the urine with the rest chiefly in the plasma. After the eleventh day of therapy signs of cardio-respiratory embarrassment were noted.

Proteinuria appeared to bear no relation to kidney damage as judged by measurements of glomerular filtration and renal blood flow. It is suggested that this phenomenon may be expected to occur whenever large doses of albumin are administered for a sufficient period of time.

Coronary Flow in Experimental Auricular and Ventricular Tachycardias. RENÉ WÉGRÉ and (by invitation) RICHARD P. KEATING, New York, New York.

Coronary flow and arterial blood pressure were recorded in anesthetized dogs during experimental auricular and ventricular tachycardias. A rate of stimulation equal to that of the spontaneous rhythm was first employed, then it was progressively increased.

In auricular tachycardia of rates approximating the spontaneous rate, no change occurred. With rates higher than the spontaneous rate, a transient drop in flow and pressure was followed by their return to control levels and, when the rate was not excessive, the flow reached a level above its control. As the rate of tachycardia increased, flow and pressure decreased more markedly and even remained below control levels. When tachycardia produced initially a drop of flow and pressure, its termination was followed by an increase of flow and pressure. The higher the rate of tachycardia, the greater was the increase in flow and pressure upon the termination of tachycardia.

In ventricular tachycardia, essentially similar phenomena occurred but the decrease in flow was more marked and lasted longer.

The mechanisms of the phenomena observed are discussed.

Some Effects upon Nitrogen Balance of the Independent Variation of Protein and Calories in Man. SIDNEY C. WERNER, New York, New York.

In most nutritional studies involving reduction of calories or of protein, both variables have been altered concurrently. The effect of change of either of these factors independently has needed detailing. Such a study has been carried out. The results appear to have significance in respect to outlining intravenous as well as oral feeding programs and in respect to the interpretation of the mechanism behind the loss of nitrogen from the body following trauma or disease. The present study has been divided into four parts:

1. A reduction of calories at constant protein intake. This results in negative nitrogen balance of a degree to equal that resulting from most traumatic reactions.

2. The restitution of nitrogen balance at low caloric intakes. This can be done by increasing the protein nitrogen intake despite a simultaneous reduction in carbohydrate intake necessitated thereby to keep calories constant.

3. A study of the effect of equicaloric fat versus carbohydrate reduction at a constant nitrogen intake level. There is a greater negative nitrogen balance with carbohydrate reduction as opposed to fat reduction reaffirming the greater nitrogen sparing effect per unit of carbohydrate over fat even at relatively high intake levels of both.

4. A study of the effect of protein reduction after high protein intakes, with constant caloric intake. A sharp negative nitrogen balance occurs even at high caloric levels, the duration of which may exceed a week.

From these data it is concluded that much of the loss of nitrogen after injury may result from caloric reduction and from an adaptation to a high protein nitrogen turnover level. This high level may be the result of absorption of protein nitrogen from injured tissues. These data also offer possible suggestions in respect to the goal of treatment for pre- and post-operative nitrogen feeding.

An Analysis of the Unresponsiveness to Mercurial Diuretics Observed in Certain Patients with Severe Chronic Congestive Failure. RAYMOND E. WESTON and DORIS J. W. ESCHER (Introduced by Louis Leiter), New York, New York.

In a series of cardiac patients who no longer gave satisfactory responses to organic mercurial diuretics, renal clearances of sodium, chloride, mannitol (GFR), and PAH (R.P.F.) were determined before and after administration of mercuzanthin, and again after the rates of sodium and chloride filtration were increased by either the rapid intravenous administration of aminophyllin (0.48 - 0.72 grams) or the continuous infusion of 4.5 per

cent NaCl (at times, plus molar Na lactate). A similar procedure was carried out on one non-edematous, hypertensive patient in whom a very low GFR was produced by the Kempner rice diet.

In nearly all cases, the very low control water and salt excretion rates were not significantly affected by the mercuzanthin alone. However, after giving the mercuzanthin, if the filtration of sodium and chloride was increased by injection of aminophyllin or concentrated salt solution, there was a marked rise in urinary water and salt output, in some instances to values approximating those observed in cardinals responsive to mercurials. It is concluded that the previous failure of these patients to respond to mercurial diuretics was due not to the usually postulated renal tubular resistance to mercury, but rather to the marked decrease in sodium and chloride filtered. The significance of these data with respect to the relationship between impaired renal hemodynamics and salt retention in chronic congestive failure will be discussed.

Familial Incidence of Neurocirculatory Asthenia ("Anxiety Neurosis," "Effort Syndrome"). (By invitation) EDWIN O. WHEELER, (by invitation) PAUL D. WHITE, (by invitation) ELEANOR REED and MANDEL E. COHEN, Boston, Massachusetts.

Family histories from patients with neurocirculatory asthenia (N.C.A.) have suggested that it is a familial disorder. To investigate further the familial incidence of N.C.A. the sons and daughters of patients with N.C.A. were examined to determine whether or not they had N.C.A.

The family study was based on 50 patients in whom the diagnosis of N.C.A. had been made 20 years before its verification in this study. 22 families had 45 children over 18 years of age. The 37 available children from 18 families were examined. For control data, the prevalence of N.C.A. was determined from 5 groups comprising 234 individuals, 129 women and 105 men. The diagnosis of N.C.A. was based on its characteristic symptoms.

The prevalence of N.C.A. in the sons and daughters of parents with N.C.A. was 48.6 per cent. In contrast, the prevalence was only 5.6 per cent in the control groups. This difference is highly significant statistically, the significance ratio being 5.1 (Odds: 1.7×10^4 to 1). These data do not reveal whether the disorder is hereditary or on an acquired household basis.

It is concluded that the prevalence of N.C.A. in the sons and daughters of patients with N.C.A. is significantly higher than in the general population.

A Source of Error in Metabolic Rate Determinations Resulting in Falsely Low as well as Falsely High Values. HAROLD N. WILLARD and GEORGE A. WOLF, JR. (Introduced by David P. Barr), New York, New York.

Apparent metabolic rates varying from more than minus one hundred to plus one hundred as measured by the Benedict-Roth closed spirometer apparatus could be produced voluntarily by a trained subject. These tests

were classified as satisfactory by experienced technicians after inspection of the patient and the tracing.

Patients and normal controls were studied using pneumographs around the abdomen and chest, the tilt table and its effect on the diaphragm, and the estimation of complementary air before and after metabolic rate determinations.

Progressive change in the chest volume occurring during the determination of the metabolic rate, rather than change in the oxygen consumption, was shown to cause the marked discrepancy between the apparent and the true metabolic rate.

The relation of these observations to the value and interpretation of clinical determinations of basal metabolic rate will be discussed.

Reciprocal Relationships of Radioiodotherapy and Thyroid Function. ROBERT H. WILLIAMS and (by invitation) HERBERT JAFFE, (by invitation) WALTER F. ROGERS, JR., (by invitation) BEVERLY T. TOWERY, and (by invitation) RENE TAGNON, Boston, Massachusetts.

Studies conducted with 175 individuals and several hundred rats, considered in conjunction with previous reports, indicate that the turnover of radioiodine in the thyroid gland is influenced by many factors, e.g., (a) the size and structure of the thyroid, (b) the amount and duration of thyrotoxicosis, (c) severe trauma, infection, emotional reactions, starvation, and extreme changes in temperature, (d) the amount of iodine ingested before and after the radioiodine, and (e) the amount, duration, and interval of cessation of treatment with antithyroid drugs. Some of the details of these studies will be presented.

Therapeutic doses of radioiodine have been given to 105 patients, consisting of 101 unselected subjects with thyrotoxicosis, 2 with non-toxic nodular goiter, and 2 with malignant adenoma. All patients were given I^{131} except for 3 who received I^{130} . Each of these 3 subjects were administered 25 or 30 millicuries and has been free of thyrotoxicosis for more than one year. The remaining 98 patients with hyperthyroidism were given an average of approximately 8.5 millicuries of I^{131} in from 1 to 6 doses. In 18 cases therapy has been too recent to afford much evaluation. Seventy-six patients have been in a euthyroid state for from 3 to 12 months, while 4 are myxedematous. The individuals with myxedema had received a total of from 4 to 7 millicuries, but each had been treated with one of the thiouracils for more than one year.

Some of the patients experienced an exacerbation in the thyrotoxicosis during the 2 weeks following therapy. Treatment with one of the thiouracils before and with iodide after the radioiodine helped to prevent these reactions. The largest quantity of protein-bound radioiodine in the serum was found approximately 7 days later, the concentrations gradually decreasing during the next 5 weeks. Patients given potassium iodide for 5 days after the I^{131} obtained maximal concentrations of protein-bound radioiodine approximately 2 weeks after the I^{131} .

It required about 6 weeks or longer to obtain the maxi-

mum response in the thyrotoxicity. In most of the cases treated the goiter disappeared and no evidence of damage to other tissues has been found. A moderate reduction in the size of the thyroid resulted in the 2 patients with non-toxic goiters. All palpable thyroid tissue in the cases with malignant adenoma disappeared.

The plan of therapy with I^{131} that we now use for most of the thyrotoxic patients is as follows: (a) one of the thiouracils, and no iodide, is given for about 5 weeks, (b) 4 days after cessation of this therapy an average of 100 microcuries of I^{131} , with 0.5 mg. of potassium iodide, is given orally, (c) beginning one day later 3 drops of a saturated solution of potassium iodide is given twice daily for 5 days, and (d) another dose of I^{131} is given approximately 6 to 8 weeks later if hyperthyroidism exists.

Effects of Attitude and Conditioning on Action of Chemical Agents in Human Subjects. The Pharmacology of Placebos. STEWART WOLF, New York, New York.

Fifty experimental observations were carried out on twelve human subjects in an attempt to obtain quantitative data concerning the "placebo" action of chemical agents. The meaning of "placebo" is extended to apply to any action of a substance other than that attributable to its pharmacologic properties.

The chief subject was Tom, a man with large gastric fistula, whose stomach lining was accessible to view. In this individual the effects of drugs on the stomach were measured by kymographic recordings of motor activity, analysis of gastric juice and color photography of the gastric mucosa as well as by direct visualization.

It was found that pharmacologically "inert" substances such as distilled water and lactose exert a readily measurable "placebo" action. For example, under experimental circumstances after suitable conditioning with prostigmine it was repeatedly observed over a period of four weeks that the administration of a lactose capsule induced hyperaemia, hyperacidity and hypermotility in the stomach and hypermotility in the colon of greater degree and duration than was observed following the prostigmine itself. Furthermore, measurable "placebo" effects could be demonstrated in the case of pharmacologically active agents such as atropine and benedryl. At times the "placebo" effect of a drug cancelled out or appreciably outweighed its usual pharmacologic action. For example, at a time of anxiety concerning the experimental procedure, the action of atropine occasioned, instead of its usual inhibiting effect, hyperaemia, hyperacidity and hypermotility in the stomach.

Simultaneous Studies of Intraradial and Intrafemoral Arterial Pressure Before and After Corrective Surgery for Coarctation of the Aorta. E. H. WOOD, G. E. BROWN, JR., H. B. BURCHELL and O. T. CLAGETT (introduced by C. F. Code), Rochester, Minnesota.

Continuous and simultaneous recordings of intraradial and intrafemoral arterial pressures, venous pressure, electrocardiographic data and respiration have been obtained from 6 normal subjects and from 27 patients who had

coarctation of the aorta, with these persons at rest in the horizontal position and during various cardiovascular tests. When the patients were in the horizontal position: (1) systolic and, in most instances, diastolic, pressure in the radial artery was elevated above the range of values obtained in the normal subjects, (2) systolic pressure in the femoral artery was reduced or within the range of values obtained in normal persons, while diastolic pressure was, in most instances, above the normal range, (3) the femoral/radial systolic pressure ratio and the femoral/radial pulse pressure ratio were below the range of the normals, (4) the onset of the femoral pulse wave was nearly always delayed beyond the onset of the radial pulse wave and (5) the period of time elapsing between the onset and the attainment of the peak in the femoral pulse wave was, with one exception, beyond the range of the comparable period of time as obtained among normal subjects.

Postoperative studies have been carried out among 12 patients. The data demonstrate that the cardiovascular dynamics of patients who have coarctation of the aorta may be altered toward the normal state, and the data constitute an objective measure of the degree of this alteration.

Observations on Hemolytic Reactions Produced in Dogs by Transfusion of Incompatible Dog Blood. LAWRENCE E. YOUNG and (by invitation) CHARLES L. YUILE, (by invitation) DONALD M. ERVIN and (by invitation) EDWARD VON HASSELN, Rochester, New York.

Dogs systematically transfused with dog erythrocytes containing a factor lacking in their own red cells developed isohemagglutinins and hemolysins that exhibited characteristics of immune antibodies. Dogs thus immunized were transfused under controlled conditions with incompatible whole blood in order to provide opportunities for studying the pathological physiology of hemolytic reactions.

In each instance base-line observations were made and followed by closely spaced post-transfusion measurements of hematologic, immunologic and chemical alterations. These measurements included total white cell and differential counts, determinations of osmotic and mechanical fragility of red cells, coagulation time, prothrombin concentration, serum antibody and complement titers, serum and urinary potassium, plasma hemoglobin, urea nitrogen, bilirubin and electrophoretic pattern, clearances of hemoglobin, mannitol and creatinine and estimations of effective renal plasma flow.

The transfused cells were tagged with Fe^{59} which made it possible to determine accurately the rate of destruction of donated corpuscles and the rate of excretion of the hemoglobin thus liberated. The disappearance of transfused cells was also followed by the technique of differential agglutination (Ashby). Studies are in progress on the effects of dehydration and acidosis and the administration of various therapeutic agents that may aid in correcting the sequelae of rapid red cell destruction.

This type of controlled transfusion experiment in dogs provides a new approach to the investigation of both immediate and delayed effects of the combination of hemoglobinemia and antigen-antibody reactions under conditions closely simulating those encountered clinically.

The Role of Muscle Mass and of Renal Reabsorption in Creatinuria in Man. (By invitation) K. L. ZIERLER, (by invitation) J. W. MAGLADERY, (by invitation) B. P. FOLK and J. L. LILIENTHAL, JR., Baltimore, Maryland.

Consideration of the main pathways concerned in the normal metabolism of creatine suggests that creatinuria may be the result of accelerated synthesis of creatine, extrusion of intracellular creatine, inadequate disposition of creatine, or diminished renal tubular reabsorption of creatine. The role of two of these factors was evaluated in human subjects.

(1) Determinations of nitrogen balance, guanidoacetic acid excretion, serum concentrations of creatine and of creatinine, and urinary excretion of creatine and creatinine, spontaneously and under creatine loads, in obsolete anterior poliomyelitis, were interpreted as indicating that reduction in muscle mass alone is an adequate cause of creatinuria.

(2) Simultaneous measurements of creatine clearance and of glomerular filtration rates revealed that the ability of the renal tubule to reabsorb creatine was diminished (a) during the administration of thyroid substance in hypothyroidism, (b) during prolonged administration of desoxycorticosterone acetate, and (c) during the puerperium.

It is concluded that the creatinuria may be independent of altered muscle metabolism. Furthermore, it would appear, from the examples discovered in the case of creatine, that speculation concerning extra-renal mechanisms may not be justified by simple measurement of urinary

excretion unless appropriate determinations of renal function have been undertaken.

The Flow Through the Coronary Bed in Normal and Abnormal Human Hearts by the Method of Kerosene Perfusion. P. M. ZOLL and D. T. DRESDALE (Introduced by H. L. Blumgart), Boston, Massachusetts.

The rate of inflow into each coronary artery and the partition of outflow via the right and left chambers were measured. The hearts were then studied by the Schlesinger technique.

Under standard conditions and constant pressure the rate of inflow is an index of the resistance of the entire coronary bed.

1. In the presence of coronary occlusions, the rate of inflow per gram weight of heart was reduced in contrast to normal hearts; the rate per gram of tissue did not increase with cardiac hypertrophy.

2. The rate of inflow into one coronary artery increased up to 15 per cent when perfusion through the other artery was stopped. This increment was not affected by the presence of occlusions.

3. When one coronary artery was perfused, the outflow from the uninjected coronary artery varied from 1-12 per cent of the inflow. Transmitted pressures up to 18 mm. of mercury were observed in the latter artery.

4. The aortic outflow in normal hearts was less than 5 per cent of the total outflow, possibly representing small left-sided Thebesian flow; in hearts with occlusions, it was usually increased, from 14 to 37 per cent, and radio-paque mass injected into the coronary arteries was found occasionally in the left ventricle.

5. These observations indicate that narrowing or occlusion of a coronary artery leads to increased luminal-coronary communications as well as the previously described interarterial collateral channels.