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PROCEEDINGS OF THE THIRTY-SECOND ANNUAL MEETING OF THE AMERICAN SOCIETY FOR CLINICAL INVESTIGATION HELD IN ATLANTIC CITY, N. J., MAY 6, 1940

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Research Article

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READ BEFORE THE SCIENTIFIC SESSION

PRESIDENTIAL ADDRESS

Functions and Dysfunctions of Learned Societies

By Isaac Starr

In times of intellectual activity men with common interests have always organized themselves into societies. I propose that we examine the raison d'etre of such societies, ask what the aims are, and then, changing from the general to the particular, ask ourselves how well we are accomplishing the aims we have in mind.

Certainly we are not a club whose aim is the entertainment of the members. We do not come together for mutual admiration and we are not concerned with perpetuating the past. We are concerned with the present and the future, and the proper aim of learned societies, as I see it, is a double one: first, to set a standard; and second, to provide a service. What do we aim to accomplish in these directions and how successful are we in attaining our objectives?

The presidential address of our first president, Dr. Meltzer, was published in the Journal of the American Medical Association (J. A. M. A., 1909, 53, 508). I hope that you have read or will read it. In a fighting speech he defends the claims of clinical research against attacks emanating from two directions; first, the inertia of those in authority; second, the lure of what he calls the "golden calf" of practice. Though it is nowhere explicitly stated, Meltzer's ideal for this society stands out plainly; it is to be composed of young men who *will* have the truth at any personal sacrifice. May this remain our ideal still!

But times have greatly changed since 1909. The interest in research has increased until it is now a matter for newspaper headlines and the only criticism that could be made of those in authority, who are so often among the founders of our society, is that in certain places there seems to be some lack of discrimination between the search for truth and the writing of papers. But today all pay lip service to research, if they pay no more. So we find ourselves in a situation quite different from that existing when our society was founded and it is time to reconsider our aims.

The service we aim to supply may be considered under three headings. Let us take first that rendered by the Journal of Clinical Investigation. To those of us who are considered to be clinicians by physiologists, biochemists, and immunologists; and considered to be physiologists, biochemists, or immunologists by most clinicians; the existence of this journal has been a godsend. Without any particular effort to direct the subject matter submitted, it has become the locus of the papers concerned with clinical investigations made by quantitative methods, and so it is in the forefront of that change from descriptive and qualitative methods to the more exact quantitative measurements, a change which has made possible the great advances of physics and chemistry and which may well produce as great a revolution in medical practice. Let us pause to pay tribute to the Rockefeller Foundation whose financial support made the starting of our Journal possible, to the medical clinics, and to the Chemical Foundation which assisted it at a time of need, and especially to the editors who, entirely without financial recompense, have given so much time and effort to making the Journal what it is.

Our second method of service is in these meetings. I find that any attempt to read the medical literature systematically is overwhelming. I am counting more and more on meetings such as this to keep me on the firing line. But I sometimes wonder whether greater service might not be possible. Our programs have contained very little of what may be called synthetic thinking. It is true that 100 years ago, and more, medical speculation was almost wholly fanciful. From this we were rescued by the great pathological school with its insistence on demonstrated facts, and as a result the promulgations of theories became not quite comme il faut. But, on the other hand, facts are not of equal importance. In every investigation there is a period when one must decide which facts are worth discovering. To do this logically, one must picture to himself what the situation is. In this connection I want to point out a difference between clinicians and other scientists which is sometimes a cause of misunderstanding. Chemists, physiologists, and the like, working in pure science, are under no pressure to make up their minds. If their grasp of any situation does not please them, they can wait any length of time before committing themselves. But a clinician, confronted with a patient, must come to a decision, and to act intelligently he must create a picture of the situation, even though the evidence on which to base it is scanty indeed. Hence, clinical theories are, by the very nature of things, less firmly based than those in the branches of pure science. But they are not less important and, in my opinion, our program would be improved by studying the methods of the great English school of physi-

ology whose members have never been afraid to attempt to synthesize the facts into simplifying theories.

It is true that some persons, like imaginative children, seem quite unable to distinguish the facts from the figments of their imagination, but this is no excuse for failing to try to synthesize the facts we have. Scientists who have never made an observation or conducted an experiment may contribute signally to our understanding of nature. If one were only clever enough what might not be gleaned from the multitude of observations and experiments in the medical literature and from the long stacks of hospital records now gathering dust? We are spending much time, effort, and money in our clinics accumulating records, apparently in the pious hope that some day somebody is going to synthesize something useful from the multitude of data they contain.

Our third method of giving service is less tangible, but I believe that it is very important. It consists of the advantage that comes with a wide acquaintance among scientific investigators. The ideal doctor, like the philosopher, should have at his command the sum total of all knowledge and any idea that one man can cover the field of modern knowledge applicable to medicine is preposterous. We must cooperate. I hope that membership in this society makes it easier for young investigators to ask questions and obtain criticism from those whose experience and effort are in a different direction from theirs. I am convinced that a few questions asked of just the right people will usually secure a nearer approximation to the truth than can be discovered in many months of patient search of the literature. I hope that personal contact at our annual meetings may make such things easier.

If investigators would think of their confreres not as rivals but as friends cooperating against common difficulties, much would be gained for science in America. It is my hope that this society will bring about friendships of this sort and so avoid the silly acrimonious controversies which have so plagued some branches of science.

I think few people have any doubts about the value of the services rendered by this and other learned societies, but the difficulties begin when they start to exercise their other function, that of setting a standard.

We set standards when we select members for our society, and here our standards have changed. When this society was four years old the secretary sent out a circular letter urging the members to nominate friends who might be interested. Now the waiting list far exceeds the present constitutional limit of membership! In the earlier days interest in research was deemed sufficient. Now we demand tangible evidence of accomplishment. The descriptive essays which have played so large a part in medical literature are not good enough for us now.

The tremendous growth of research interest in America has greatly increased the number of available candidates and from those your council must try to select the best on the basis of the candidate's publications, his academic rank, and the letters from members about him. As is inevitable, institutional pride and personal friendship color the recommendations so that the council has a hard time deciding. One problem is particularly bothersome. Candidate A has worked in a laboratory known to be highly productive, and its resources have been at his command. His production is superior to that of B, but B has been working without either scientific or financial support. Which is the better man? Time will tell but until it does I do not think the question can be answered with confidence, and when I admit this I admit that mistakes in the application of our standard are inevitable.

A second method of setting our standard is in the selection of papers for the program. This duty of the president must be performed by inspection of abstracts in a very short period of time. Again mistakes are inevitable. The selection is not always on the basis of intrinsic merit; general interest, timeliness, and the ability of the author to present his work clearly, must be considered. But due to the energy and cooperativeness of the members who annually submit about four times the number of titles which can be accommodated, I do not believe that there is another medical program of comparable size which, year in and year out, contains so much of real interest.

Our third method of maintaining a standard is by the selection of papers for our Journal. With this I personally have had no experience, but several facts should be brought to the attention of the members. Like the other scientific journals owned by learned societies, the Journal of Clinical Investigation was not born because of a widespread demand on the part of the membership. In its early days it was proper and inevitable that control should reside with the group who initiated it and who were in a position to finance it. But now, although our Journal is self supporting, the membership as a whole has neither taken the interest it should nor exerted the authority it possesses in the Journal's affairs. I suppose that this indicates complete satisfaction with things as they are. If it does not, it is the fault of the membership itself. Helpful criticism by members has been conspicuous by its absence and it might do much to strengthen the Journal.

During the foregoing discussion of the functions of learned societies, perhaps my next point has already occurred to you. It is that the two chief functions of learned societies are, in a measure, in conflict. Thus there are some who think that the membership should be enlarged and the program expanded. Their aim is to improve the service given by the society. This is opposed by others who point out that such a change would lower our standard of excellence.

Too much emphasis on standards is a cause of decay, often it is a psychological defense mechanism set up by persons no longer productive. The organizations which become more and more exclusive tend to die of dry rot. Mistakes made in the enforcement of the standard make them ludicrous.

I often reflect on our own shortcomings. The young

Pasteur, if nominated to this society, would probably have been turned down because he was a chemist; the young James Mackenzie because he was not connected with a medical school.

Nevertheless, while undue insistence on standards causes difficulties, abandoning them too far in the interest of service brings troubles of another sort in its train. For then the door is opened for the man whose real aim is personal advertisement rather than the search for truth. Uncensored programs are likely to be too long. Societies with low entrance requirements become so large that friendship between the members becomes impossible and the personal service on which I lay so much value is non-existent.

Somewhere, therefore, between the aim of setting a standard and the aim of giving a service, a compromise must be made. It is not for me as your presiding officer to dictate any line of conduct but I am going to suggest that the members, in attacking this and the other problems which confront learned societies, keep two principles in mind.

To illustrate the first I have, under the urge of a sense of duty as your representative, constructed a model of the society's activities.* Here I have a representation of our society radiating its beneficent influence in almost every direction. Now this timepiece is an integral part of the model for it indicates that the influence of our society extends, and will extend, throughout time. But the timepiece has another purpose which is important, for by means of it I am entitled to claim that our model is a four dimensional one and that it is therefore one (dimension) up on the model produced by my friend, the past president of the Association of American Physicians, at the last meeting of that distinguished body (DuBois, E. F., Tr. A. Am. Physicians, 1939, **54**, 1).

But, in spite of all this, I stated that my model was designed to illustrate a point in my argument. The point is this: in dealing with learned societies, let us preserve our sense of humor. In some of the letters received by the secretary a sense of humor has seemed strangely lacking. The errors of today, if they be errors, can and must be corrected tomorrow.

As a final point I suggest a larger use of the ordinary processes of democracy in the solution of our problems. There has been a tendency in American learned societies to let the officers make all the decisions behind closed doors. The attendance at business meetings has become smaller and smaller and the proceedings more and more routine. In my opinion this is an unhealthy tendency, for I conceive that it is the duty of the officers to keep the members informed of the problems which concern them and that the members have an obligation to assist in making the necessary decisions. If our society is to be made maximally effective, it must truly represent the best thought of the younger minds in medical investigation. The decision concerning its policies rests with you. And these decisions are important because there is no reasonable doubt that nowhere in this war tried world is there a group of young men whose opportunities for the advancement of medical research can be compared with those which have been granted to you.

The Chemical Properties of Scarlet Fever Toxin. By E. S. GUZMAN BARRON and (by invitation) GEORGE F. DICK and CARL M. LYMAN, Chicago, Ill.

The chemical properties of the scarlet fever toxin purified by Dick and Boor were studied by using skin reactions in human subjects to measure the activity of the toxin.

The toxin, as shown by other investigators, is very resistant to heat, for it can be heated for 1 hour up to 90° C. and for 45 minutes up to 100° C. with no loss of activity. Nor was there any loss of activity when it was subjected to the action of trypsin and pepsin for 24 hours. The toxin is also resistant to pH changes, for it remained active when kept for 24 hours at 25° C. from pH values of 1.08 to 11.18. It is resistant to the action of oxidizing agents such as H_2O_2, copper, and oxidized glutathione, and to that of reducing agents such as cysteine, glutathione, $Na_2S_2O_4$, and H_2 activated with Pt. black. Iodine and porphyrindin destroyed it by destroying free amino groups. Neither sulfanilamide nor its oxidation product obtained by irradiation with ultraviolet light had any action on the toxin. The isoelectric point determined with Theorell's cataphoresis cell at 3° C. was at pH 5.48. At pH 4.5 the toxin migrates to the cathode and the protein impurity to the anode branch of the cell, permitting further purification. The toxin is destroyed by 30 minutes' treatment with ketene and nitrous acid, showing that the presence of amino groups is essential for activity. On ultrafiltration through graded collodion membranes, the toxin filtered through membranes of a porosity that did not let cytochrome C pass through (molecular weight of cytochrome C, 13,000); on the other hand, membranes that let clupeine through (molecular weight about 2500) did not let the toxin through.

It may be concluded that scarlet fever toxin is a polypeptide with a molecular weight between 13,000 and 4000, its activity being determined by the presence of free amino groups.

The Significance of Antibodies Against Epidemic Influenza Virus. By E. R. RICKARD and EDWIN H. LENNETTE (by invitation) and FRANK L. HORSFALL, JR., New York, N. Y.

The respiratory disease experience of a representative suburban population of 800 individuals has been studied for 2 years. Blood specimens were obtained from all individuals in this group in 1938 and again in 1939. The titer of antibodies against the PR8 strain of epidemic influenza virus was determined on all these sera both by means of the neutralization and complement fixation tests

* At this point the president drew forth a curious looking object which at a distance resembled an orange thrust through with a multitude of long steel knitting needles that radiated from it in all directions. This he placed beside a clock.

and was found to differ markedly from one individual to another.

In the first 3 months of 1939 a small epidemic of influenza occurred in this population. The incidence of clinical cases, in which the diagnosis was confirmed by the isolation of influenza virus or by a significant increase in antibodies, was 10 times greater among persons who possessed low neutralization titers than among those whose titers were high.

With the sera of 600 individuals who did not have influenza during the epidemic and who presented no evidence of subclinical infection, it was found that individual antibody titers, irrespective of their initial level, remained constant for a period of 1 year.

Rat Bite Fever With Arthritis Due to Streptobacillus Moniliformis. By THOMAS MCPHERSON BROWN and JOHN C. NUNEMAKER (introduced by Perrin H. Long), Baltimore, Md.

A 49-year-old-farmer was bitten by a rat and 18 days later was admitted to the Johns Hopkins Hospital because of fever and arthritis. The streptobacillus moniliformis was isolated from the joint fluid and blood. Severe arthritis localized in the left knee, with destructive changes by x-ray, and also marked laryngeal changes were the chief clinical features. No definite improvement was noted from aspirin or sulfanilamide; there was apparent benefit with gold therapy. Streptobacillus moniliformis has been agglutinated in high titer by patient's serum during a four months' period, also by serum from immunized rabbits.

L_1 pleuropneumonia-like organism of Klieneberger has been isolated from cultures of the streptobacillus moniliformis. L_1 colonies have remained constant on solid media, but have always reverted to streptobacillus form when transferred to liquid media, and then back to solid media.

Migratory polyarthritis has been observed in mice injected both intravenously and intraperitoneally with the streptobacillus moniliformis. The experimental arthritis has been illustrated by photographs, x-rays and sections; also by diagrammatic drawings of joints involved, indicating degree of involvement and migratory character of the arthritis. Gold prevents infection of mice with this strain of streptobacillus moniliformis. Sulfanilamide and sulfapyridine produce no therapeutic effect.

The Occurrence and Significance of a Factor Which Annuls the Bacteriostatic Action of Sulfonamide Compounds. By C. M. MACLEOD and G. S. MIRICK (introduced by O. T. Avery), New York, N. Y.

The presence of a substance in peptone which greatly diminishes the bacteriostatic action of sulfonamide compounds *in vitro* was observed first by Lockwood. The occurrence of this material in the peptones used in the preparation of the usual bacteriological media has made comparative bacteriostatic tests difficult to interpret, since different lots of media prepared under apparently identical conditions may contain different amounts of the sulfonamide inhibitor. However, the presence of this substance is not restricted to peptones since it has now been found to exist in certain body tissues. Increased amounts of the inhibiting factor are associated with the occurrence of autolysis in tissues and exudates. Thus, fresh muscle contains only a small amount, but if autolysis takes place a great increase in inhibitor occurs. Purulent exudates obtained from patients with staphylococcal, pneumococcal and streptococcal infections, as well as guinea pig liver containing caseous tuberculous lesions, yield large amounts. Fresh spleen is rich in the substance, but none has been demonstrated in fresh liver. This inhibitor is of importance, therefore, not only with respect to *in vitro* bacteriostatic tests but also in relation to the lack of bacteriostatic action of the sulfonamide compounds observed clinically in the presence of purulent lesions.

Sulfapyridine and Vomiting. An Experimental Study of the Mechanism in Dogs. By JOSEPH F. SADUSK, JR. and JOHN W. HIRSHFELD, with technical assistance of ANNE SEYMOUR (introduced by Francis G. Blake), New Haven, Conn.

Vomiting in dogs following the administration of sodium sulfapyridine intravenously is ordinarily produced when the blood level of sulfapyridine reaches 20 to 30 mgm. per cent. This vomiting level is not materially changed if, preceding the intravenous injection of sodium sulfapyridine, the installation into the stomach of as high as a one per cent suspension of sulfapyridine is done.

Experiments carried out following total gastrectomy, and even total removal of the gastro-intestinal tract, revealed no change in the blood level at which vomiting occurred. A preliminary experiment concerning the local effect of sulfapyridine and apomorphine upon the vomiting center in the medulla would seem to indicate that the vomiting is not primarily central in origin.

With the data noted above, it would appear that the mechanism of vomiting in dogs following sulfapyridine administration is dependent on a reflex stimulation of the vomiting center from some organ other than the gastro-intestinal tract.

The Clinical Significance of Gastro-Intestinal Pressure Changes. By W. O. ABBOTT and (by invitation) H. K. HARTLINE, J. P. HERVEY, F. J. INGELFINGER, A. J. RAWSON and L. ZETZEL, Philadelphia, Pa.

The movement of contents within the gastro-intestinal tract occurs in response to changes in the internal pressure of the gut just as the movement of blood is governed by the relation of arterial to capillary and venous pressures. A new method has been devised which makes it possible to record the pressures simultaneously at several selected points along the alimentary tract at two-second intervals. Normal movements of the intestinal contents are observed by the fluoroscope while the pressures are being recorded. Thus the gradients of pressure in the intestinal canal and the movements engen-

dered by them may be observed directly in normal subjects and in patients suffering from digestive disorders. The records obtained are interpreted in the light of normal and abnormal gastro-intestinal reactions, and the diagnostic value of such data is presented.

An Investigation of the Mechanism of Experimental Nephritis Produced in Rabbits by the Use of Anti-Nephrotoxic Duck Serum. By CALVIN F. KAY (by invitation) (introduced by WARFIELD T. LONGCOPE), Baltimore, Md.

A study was first made of the relationship between the appearance of antibodies to duck serum and the appearance of nephritis in rabbits injected with nephrotoxic serum. It was found possible by appropriate means either to shorten or to lengthen the interval between the onset of nephritis and the appearance of antibodies. The duration of this incubation period was found to be related to the development of the antibodies to duck serum. Evidence is presented to indicate that antibody formation by the rabbit is essential for the development of the nephritis. An hypothesis is presented to explain the mode of action of the nephrotoxic serum.

The Use of Radioactive Sodium as a Measure of the Volume of the Extracellular Fluids of the Body. By NOLAN L. KALTREIDER, GEORGE R. MENEELY, JAMES R. ALLEN, STANLEY N. VANVOORHIS and VINCENT F. DOWNING (introduced by Wm. S. McCann), Rochester, N. Y.

Radioactive sodium was produced by the bombardment of sodium chloride with deuterons. Its half life is 14.8 hours. The quantity of radio sodium present in a sample was determined by a measurement of its ray activity, using a Geiger-Müller counter. By means of this artificially produced radioactive substance, the authors were able to measure the amount of fluid available for the dilution of sodium. Simultaneously, for comparative purposes, the volume of fluid through which thiocyanate is distributed was estimated after intravenous injection of sodium thiocyanate. The plasma volume was measured concurrently by the dye (T — 1824) method.

In normal subjects it is apparent that the attainment of diffusion equilibrium for radio sodium and thiocyanate between plasma and the interstitial fluid was reached in 3 hours. The average value for the "sodium space" of 8 normal subjects was 19.55 liters, or 26.5 per cent of body weight, with extreme values of 23 and 29 per cent. The amount of available fluid appeared to be more closely related to the body surface area than to the weight.

In order to attain equilibrium of radio sodium between plasma and various transudates in patients with congestive heart disease, 6 to 12 hours were required. During congestive failure both the plasma and interstitial volumes were increased and, as improvement took place, both volumes diminished. During recovery the decrease in the volume of extracellular fluid paralleled the loss of body weight. Both in normal subjects and in patients who showed an accumulation of fluid, the volume measured by radio sodium was higher than that found by thiocyanate. In contrast to thiocyanate, radio sodium diffused into the subarachnoid space.

The Action of Adrenalin on the Ischemic Kidney and the Response of Hypertension to Tyrosinase. By HENRY A. SCHROEDER (by invitation) and ALFRED E. COHN, New York, N. Y.

Blood pressure in anesthetized dogs was recorded by Hamilton's manometer, and renal blood flow by a thermostromuhr. Records were made during various degrees of constriction of the renal artery, the animals being watched for several hours. It was found that small doses of adrenalin given intravenously resulted in prolonged and sustained falls of blood flow in the affected kidney when the renal artery was constricted, producing no demonstrable effect in the other kidney. One-hundredth of the dose of adrenalin necessary for transient reduction in blood flow in the normal kidney resulted in marked vasoconstriction for 5 to 30 minutes when the kidney was ischemic. This effect was noticed with amounts as low 0.05 *r* per kgm. of dog. The greatest response occurred when the renal artery was constricted to a point at which intrarenal vasodilatation, described previously, was maximal.

In eight of eleven dogs systemic blood pressure became significantly elevated for the duration of the experiment (3 to 6 hours) after constriction of the renal artery and further reduction of renal blood flow by small doses of adrenalin, while constriction of the artery alone resulted in little change in blood pressure. The intravenous injection of tyrosinase, a pure phenolic oxidase prepared by and obtained from Prof. J. M. Nelson, lowered blood pressure raised by this method. Likewise, tyrosinase, when given intravenously to fifteen hypertensive rats with unilateral renal affections, lowered blood pressure consistently, this effect appearing 5 to 15 minutes after injection and lasting as long as the rats were followed (in five animals—1, 5, 14, and 17 days). The injection of this enzyme into twenty normal rats gave inconsistent results. Intravenous and intramuscular injections in four hypertensive dogs lowered systolic blood pressure for 3 to 48 hours, there being little effect beyond an immediate one in the normal. The effect on diastolic pressure was of lesser degree. It appears possible that these results are produced by the alteration of a phenolic configuration in some substance.

The Rôle of the Central Nervous System in Renal Hypertension. By WILLIAM DOCK, San Francisco, Cal.

When one piths the central nervous system of rabbits hypertensive because of infusion of epinephrine or renin, there is little or no fall in arterial pressure until the effect of the drug wears off. If rabbits with renal hypertension are pithed, the pressure falls swiftly to the same low levels as it does in pithed controls. The pithed rabbits, control or hypertensive, respond to epinephrine without any rise in venous pressure but with a rapid rise in arterial pressure; raising venous pressure by salt or

acacia infusion has the same effect in control as in hypertensive animals after pithing. It is concluded that there is no peripheral vasoconstrictor in the blood of rabbits with renal hypertension, and that the normal vasomotor mechanism is called into play to maintain the high arterial pressure level.

The Nature of the Afferent Arteriolar Tissue in the Mammalian Kidney, and the Changes Induced Therein by Renal Ischemia. By IRVING GRAEF and HOMER W. SMITH (introduced by Thomas Francis, Jr.), New York, N. Y.

Goormaghtigh has propounded that "myo-epithelioid" tissue in or adjacent to the afferent glomerular arteriole is endocrine in nature, and that its secretory activity may be responsible for systemic hypertension.

We have confirmed the description of European observers that, in many mammals, the afferent arteriole as it approaches the capsule may undergo a transformation from fibrillar smooth muscle cells to afibrillar or granular cells arranged in layers and has a special relationship to the *macula densa,* the intercalated portion of the distal tubule. Afibrillar cells were found in man, the dog, cat, rabbit, rat, mouse, and ferret; granular chromophilic cells in the last five species only.

We have confirmed Goormaghtigh and found that in renal ischemia hypertrophic, hyperplastic and metaplastic changes may occur in the juxta-glomerular arteriolar media leading to accumulations of "epithelioid" or "myo-epithelioid" tissue. It has been encountered in the ischemic kidney of two hypertensive human cases with unilateral renal arterial obstruction, and one case with pyelonephritis and unilateral perinephritis with marked contraction on one side.

In a surgically-removed kidney from a non-hypertensive patient 4½ months pregnant, marked hyperplasia and hypertrophy were found. There was renal arteriosclerosis as well, with incomplete narrowing of the arterial lumina. Experimentally ischemic dogs, rabbits and rats have likewise been studied.

For control material four normal human kidneys have been studied. Three were fixed immediately after electrocution. Additional cases of nephropathy, with and without hypertension, have also been studied from various species.

Variation in the appearance of the arteriolar media in normal kidneys is great enough to warrant doubt concerning the significance of hyperplastic changes when observed without evaluation of blood flow. Because of species differences the interpretation of the ischemic changes must be contingent upon a more complete study of normal kidneys, previous descriptions being based probably upon abnormal kidneys or kidneys in which focal ischemia was not excluded. The acceptance of the presumed causal rôle of changes in these cell groups in "Goldblatt Hypertension" and some hypertensive diseases must await explanation of the hyperplasia occurring in non-hypertensive animals or man.

The Effect of Changes in Arterial Pressure on the Blood Flow to the Vasodilated Forearm and Calf of Normal and Hypertensive Subjects. By ROBERT W. WILKINS and L. W. EICHNA (introduced by James Bordley, III), Baltimore, Md.

Plethysmographic measurements of blood flow to the forearm and calf during full vasodilatation of reactive hyperemia were repeatedly made in persons subjected to various procedures designed temporarily to raise or lower the arterial pressure. When these procedures failed significantly to change the pressure, the blood flow to a limb remained remarkably constant during a single experiment and from day to day. In sympathectomized limbs of all subjects a rise of arterial pressure was accompanied by an increase in blood flow, and a fall of pressure by a decrease. In normally innervated limbs of most subjects similar changes in blood flow occurred, but in some subjects severe sensory pressor stimuli caused no change or even a decrease in flow. In several hypertensive patients the pressure was reduced for relatively long periods after surgical operations (splanchnicectomy or nephrectomy). This reduction of arterial pressure was accompanied by a decrease in blood flow to the fully vasodilated limbs.

The alteration in blood flow associated with even great changes in arterial pressure, while usually marked for a given subject, often was not great enough to place the flow clearly beyond the limits of normal. This may explain the failure of other blood flow studies to reveal significant differences between small groups of normal and hypertensive subjects.

A Method for the Study of Neuromuscular Transmission in Human Beings. By A. M. HARVEY and R. L. MASLAND (introduced by George D. Gammon), Philadelphia, Pa.

A method has been devised for recording the action potential of a whole muscle in response to stimulation of the motor nerve which is suitable for studying the phenomena of neuromuscular transmission in human beings. The summated action potential from the fibers of the abductor digiti quinti led off by means of a grid lead placed on the skin over the tendon and an earthed lead over the belly of the muscle is synchronized, short in duration, and constant in amplitude. The second of the responses to two nerve volleys from 20 to 500 msec. apart is always equal to or slightly greater than the first. Also, repetitive stimulation at rates of 5 to 60 per sec. for 5 to 10 sec. shows no appreciable decline in the magnitude of successive potentials.

In patients with myasthenia gravis the second response at intervals of 20 to 500 msec. is regularly 10 to 12 per cent smaller than the first, and at rates of stimulation above 15 per sec. there is a progressive decline in successive responses. These changes become normal when prostigmin is given. Quinine methochloride, which has the typical action of curare, produces in the normal individual changes similar to those found in patients with myasthenia. Other conditions in which there is an ab-

normality of nerve or muscle function are being studied by this method.

Test for the Rapid Estimation of Vitamin B_1 Saturation. By HERBERT POLLACK and (by invitation) HENRY DOLGER, MAX ELLENBERG, and SANFORD COHEN, New York, N. Y.

Estimates as to dosage and duration of therapy of vitamin B_1 have had to be approximated by gross clinical changes. If a test were available by means of which one could estimate the degree of saturation in an individual rapidly and inexpensively, then the clinical application of vitamin B_1 therapy could be put on a rational basis.

By means of the yeast fermentation method it was found possible to estimate a B_1 activity in the urine rapidly and accurately.

For many reasons the test as finally evolved is as follows: One milligram of thiamin hydrochloride is injected intramuscularly into the patient in the fasting state. The urines are collected for four hours following the injection and the B_1 activity is determined. Altogether the test was performed on over 350 patients, many of them in duplicate and triplicate at various intervals of time. On selected groups of patients and controls the saturation test was repeated at intervals during the administration of large doses of thiamin and then subsequent to the cessation of the therapy. This was done to show the changing saturation during these test periods.

A group of 35 healthy students, physicians and instructors was chosen as controls. This group showed an excretion of over 200 gamma of vitamin B_1 in the urine for the four-hour period. The distribution curve of the excretion of the 350 patients receiving the test showed a definite break at 180 gamma for the four-hour period. From this and other analyses of the data 180 gamma excretion in four hours after the intramuscular injection of one milligram of thiamin was chosen as the lower limit of normal. One hundred and twenty-eight patients with diabetes mellitus were included in this group. They showed no deviation from the average. Two particular groups of patients were found with consistently low saturation. These were patients suffering with gastrointestinal diseases and patients in cardiac failure.

In conclusion it can be said that evidence is presented showing the practicability and application of a simple, rapid test to determine the presence of B_1 saturation.

Hyperinsulinism: Extensive Metabolic Studies Before and After Removal of Multiple Pancreatic Islet Tissue Adenomata. By JEROME W. CONN and ELIZABETH S. CONN (introduced by L. H. Newburgh), Ann Arbor, Mich.

For five months (preoperative, operative, and postoperative periods) continuous metabolic studies were made on a case of severe hyperinsulinism. Respiratory data were obtained by means of a respiration chamber. Effects of antecedent high and low carbohydrate diets upon total oxidation of a standard test dose of glucose, and upon combustion of glucose in the post-absorptive state demonstrate tremendous overcombustion of glucose when the diet is average in carbohydrate. On low carbohydrate preparation, however, glucose combustion is depressed to the same level exhibited by normals under the same conditions. Adrenalin hyperglycemia does not stimulate carbohydrate combustion as does alimentary hyperglycemia. Effects on the glucose tolerance curve of variations in the antecedent diet are qualitatively the same as in normal but quantitatively different. Studies after removal of the insulomata gave results identical with normal controls.

It is reported (Am. J. Physiol., 1940, **128**, 290) that adrenal cortical extracts render mice resistant to the hypoglycemic effect of insulin. Sodium, chloride and nitrogen balance studies were made with and without the intramuscular administration of 1500 dog units daily (30 cc. Upjohn-Cortin). Although sodium and chloride retention and increased nitrogen excretion were demonstrated, there was no appreciable effect upon the hypoglycemic levels or on the number of daily attacks.

For several weeks postoperatively a temporary period of underutilization of carbohydrate was observed with glycosuria, ketonuria and fasting blood sugar levels as high as 310 mgm. per cent. Normal tolerance returned without the aid of insulin.

A Quantitative Study of the Urinary Excretion of Hypophyseal Gonadotropin, Estrogen, and Androgen of Normal Women. By SIDNEY C. WERNER (introduced by Robert F. Loeb), New York, N. Y.

Adequate quantitative information about the excretion by the normal woman of hypophyseal gonadotropin, estrogen, and androgen is lacking. The tannic acid precipitation method (Levin-Tyndale) for hypophyseal gonadotropin determination has been found to permit quantitative recovery of estrogen and androgen from the supernatant and alcohol-acetone-ether washings of the precipitate, by acid hydrolysis and ether extraction. No emulsion forms. Estrogen and androgen are separated by normal NaOH. The assay methods of Levin-Tyndale (gonadotropin), Kahnt-Doisy (estrogen), Callow-Callow (colorimetric androgen), have been used. Every value represents 6 to 12 animals or more. The entire urinary output of 5 normal women has been assayed over 3 to 4 months in 48-hour batches, including another 3 cycles throughout the year in one case.

The normal values and pattern of hormone excretion are defined. Previous concepts concerning the hypophysis-ovary relation need revision. Independent cycles of the ovarian follicles apparently occur during a constant output of hypophyseal hormone. Usually, then, a sudden increased release of hypophyseal gonadotropin occurs at the mid-interval, associated with ovulation of the matured follicle, as suggested by the subsequent excretion of pregnandiol.* Androgen output is constant for the individual, varies between subjects.

* Pregnandiol determinations were obtained through the courtesy of Dr. E. T. Engle by the method of Browne-Venning.

The Excretion of Cortin under Conditions of Damage. By PAUL G. WEIL* (by invitation) and J. S. L. BROWNE, Montreal, Canda.

Studies on the cortin-like action of extracts of urine have been reported by Perla and Marmorston in 1931, by Grollman and Firor in 1933 and by Harrop and Thorn in 1937. In 1938 Anderson, Haymaker and Joseph showed that the blood and urine of patients with Cushing's syndrome contained cortin. In 1938 Selye and Schenker devised a method for the assay of cortin, using the immature adrenalectomized rat exposed to cold. The method is specific, rapid and one hundred times more sensitive than the ordinary survival tests.

The urine is extracted with ethylene dichloride and the residue remaining after distillation of the solvent is taken up in water and administered to the test animals by stomach tube. Using this sensitive test it has been shown that certain individuals excrete cortin in detectable amounts. Cortin can be recovered from the urine of patients after injection of either adrenal cortical extract or desoxycorticosterone acetate. No cortin was found in the urine of twelve normal individuals of both sexes of various age periods. Cortin was found in the urine of seven patients with the adrenogenital syndrome (Cushing's syndrome one, hirsutism six), of four out of six cases of hypertension, of ten patients with acute and chronic infection including one case of pneumonia, one of subacute bacterial endocarditis, two of otitis media, two of chronic osteomyelitis, one of pneumonitis, two of influenza, one of tetanus, two cases following burns, and ten cases after surgical operations. One of the patients with pneumonia excreted relatively large amounts of cortin during the height of the disease. As his condition improved cortin disappeared from the urine. Certain urines, including those of patients receiving large amounts of sulphanilamide and sulphapyridine have been found to be toxic. The action of toxic substances, such as the excretion products of the above mentioned compounds, in obscuring the cortin action of the urine is thought to be responsible for the failure to demonstrate cortin in the urine of six cases of pneumonia and four other cases of infection. The possibility of the presence of toxic substances in urine extracts must always be considered. The absence of detectable cortin activity in normal urine may represent a balance between secretion by the adrenal cortex and its utilization by the body on the assumption that cortical substances are inactivated in the course of their utilization. According to this view the appearance of cortin in the urine may represent the difference between secretion and utilization. The cortin present in the urine may not therefore reflect quantitatively the degree of increased secretion of the adrenal cortex. A lowering of renal threshold for cortin under conditions of damage cannot be excluded at present but seems unlikely.

The increased secretory activity of the adrenal medulla as part of the defense mechanism of the organism was pointed out by Cannon. An increased excretion of cortin under conditions of damage such as infections and trauma is considered to be a manifestation of the response of the organism to a damaging stimulus by an increased secretory activity of the adrenal cortex. It has been shown that the adrenal cortex of the laboratory animal hypertrophies after the animal has been exposed to a noxious stimulus. It is suggested that the increased secretion of the adrenal cortical hormone forms part of the protective mechanism of the body against damage.

*Aided by a grant from the Banting Research Foundation.

Studies on the Rôle of the Adrenal Cortex in Carbohydrate Metabolism. By GEORGE W. THORN and (by invitation) GEORGE F. KOEPF and ROGER A. LEWIS, Baltimore, Md.

The following disturbances in carbohydrate metabolism were observed in a majority of a group of 25 patients with classical signs and symptoms of Addison's disease:

1. A rise, greater than normal, in the non-protein respiratory quotient following intravenous glucose administration.
2. A marked inclination to develop hypoglycemia 3 to 4 hours after the administration of glucose orally or intravenously.
3. A decreased glycemic response to a standard dose of epinephrine.
4. An inability to maintain a normal glycemic level during a prolonged fast.

The persistence of a disturbance in carbohydrate metabolism after treatment has restored electrolyte balance, plasma volume and blood pressure to normal suggests that the adrenal cortex has a direct effect on carbohydrate metabolism. It is evident that, whereas the correction of the underlying disturbance in carbohydrate metabolism is essential for complete restoration to normal function, the carbohydrate-regulating effect of the adrenal cortex is not necessary for the maintenance of life in the absence of complications.

"Diabetes Insipidus" Induced in Normal Animals by Desoxycorticosterone Acetate. By CHARLES RAGAN, JOSEPH W. FERREBEE, P. PHYFE (by invitation) and DANA W. ATCHLEY and ROBERT F. LOEB, New York, N. Y.

In the course of experiments on the effects of desoxycorticosterone acetate in normal animals, we have observed the development of "diabetes insipidus." The severity of the diabetes insipidus has varied considerably in different animals and is definitely augmented by the administration of sodium chloride. A recent study of one of the dogs with "diabetes insipidus" is best demonstrated by means of the accompanying chart. It will be observed that the fluid intake at the beginning of the chart was about 6000 cc. a day. Fluid output is not charted because measurement of urine volume and weight indicated that the dog was in fluid balance. It will be noted that large doses of pitressin had some effect in that they raised the specific gravity and lowered the water

intake. Following the withdrawal of pitressin, fluid intake rose to a level higher than that before this substance was administered and the specific gravity of the urine fell. When fluid intake was restricted to 2500 cc. for a day, the specific gravity again rose as in the case of pitressin administration. One difference, however, is to be observed, namely, that the concentration of sodium in the serum rose sharply with fluid restriction, whereas no change occurred at the time pitressin was given. When desoxycorticosterone was discontinued the fluid intake dropped in seven days to 1500 cc., despite the fact that the daily ration of 8.5 grams of sodium chloride was continued. With this decrease in fluid intake, there was a striking increase in urine specific gravity but no increase in blood sodium level. In this respect the administration of pitressin was qualitatively like that observed upon the withdrawal of excess cortical hormone.

With the readministration of desoxycorticosterone the water intake again rose and the specific gravity of the urine fell, although not to a degree as extreme as on previous occasions. Restriction of fluid again was accompanied by a sharp increase in specific gravity and also in the sodium content of the serum. From these observations it would appear, as has been suggested by Silvette and Britton in their work with cortical extract, that pitressin and desoxycorticosterone are antagonistic in their action. It is tempting to speculate that desoxycorticosterone increases the reabsorption of sodium by the renal tubules and that this action is opposed by posterior pituitary substance. Studies on rats and further studies on dogs are in progress at the present time.

Effects of Synthetic and Natural Estrogens on Blood, Liver and Bone Marrow. By CYRIL M. MACBRYDE, DANTE CASTRODALE, ELSON B. HELWIG, OLGA BIERBAUM and JOHN S. POE (introduced by David P. Barr), St. Louis, Mo.

The advent of synthetic estrogens into therapy has raised the question whether they may be harmful. About 15 per cent of our patients treated with stilbestrol have experienced nausea and a few have vomited. Early animal experiments have suggested the possibility of changes in blood and liver resulting from stilbestrol. We have attacked this problem by simultaneous study of patients and experimental animals (dogs and rats). Fourteen patients receiving from 1.0 to 5.0 mgm. stilbestrol daily have shown no deviation from normal in repeated liver function studies or blood examinations.

Dogs receiving from 1.0 mgm. to 100 mgm. stilbestrol daily (from equivalent to 100 times the maximum human therapeutic dose) have exhibited changes ranging from simple anemia to thrombocytopenic purpura and severe anemia with a marked hypoplasia of the bone marrow. Areas of fatty degeneration of the liver are observed.

We have, however, demonstrated similar changes with comparable doses of estradiol, so that at present it seems doubtful whether the synthetic estrogens are any more toxic than those obtained from natural sources. Thrombocytopenia and anemia also resulted in rats treated with comparable doses of stilbestrol and estradiol at dosage levels corresponding to 5 to 10 times the maximum therapeutic dose.

Radiocardiograms—the Electrical Impedance Changes of the Heart in Relation to Electrocardiograms and Heart Sounds. By JAN NYBOER, SAM BAGNO, A. BARNETT and R. H. HALSEY (introduced by H. O. Mosenthal), New York, N. Y.

Using a vacuum tube method of broadcasting and detection at high radio frequency, high accuracy has been attained in reproduction of a new type of cardiogram which may be called the "radiocardiogram." The significance of these curves, although still uncertain, shows a very close relation to the mechanical volume changes of the heart. Marked variations in curve contour and stroke amplitude are produced by valvular lesions and arrhythmias such as extrasystoles, sinus arrhythmias and auricular fibrillation. These tracings have a quantitative significance and are evaluated in terms of minute-volume cardiac output. Thus comparative values of 4000 cc. per ventricle in humans, 150 cc. per ventricle in anesthetized cats, and 2.0 cc. per ventricle in frogs, have been found as the cardiac output under given conditions. Comparative changes are noted following exercise, injection of metrazol, bleeding, and during decompensation and recovery. Simultaneous electrocardiograms or heart sounds identify the relative changes in the impedance curves during the cardiac cycle.

"Radiocardiograms" are altered especially in order to observe the rate of change of electrical impedance. In other words, the probable velocity with which the blood changes during the cardiac stroke is registered. This type of curve is a differentiated cardiac electrical impedance and may be named "a differentiated radiocardiogram." The auricular and ventricular input is usually registered as a sharp valley or peak, respectively.

Equations defining the quantitative aspect of cardiac electrical impedance have been checked mathematically and practically but are withheld from this abstract.

Objective Measurement of Relative Intracranial Blood Flow in Man. By EUGENE B. FERRIS, JR. and (by invitation) MILTON ROSENBAUM, EPHRAIM ROSEMAN and NATHANIEL BROWER, Cincinnati, O.

Utilizing the principle of the venous occlusion plethysmograph, an objective method for comparative measurement of intracranial blood flow is described. The index of blood flow is obtained by recording the maximum rate of cerebrospinal fluid displacement (through a lumbar puncture needle 2 mm. inside diameter) during sudden compression of the neck veins. The outflow needle is connected to a reservoir, partly filled with Ringer's solution, which in turn is attached to a Brodie bellows for recording volume changes. By adjusting the level of fluid in the reservoir, intracranial pressure and volume can be maintained at any desired level. When a suitable outflow record is obtained, pressure on the neck is re-

leased and the displaced cerebrospinal fluid returns from the reservoir to the subarachnoid space.

By controlling sources of error, such as blockage of the outflow needle, leakage of cerebrospinal fluid, and ineffectiveness of the neck cuff in transmitting pressure to the deep neck veins, maximum outflow rates of similar magnitude have been obtained in fourteen control subjects and in four subjects on whom the experiment was repeated one to two times. The variation in control outflow rates obtained consecutively during each experiment was slight.

The transient effect of hyperventilation, CO_2 inhalation, and temporary elevation of intracranial pressure is similar to that obtained by other methods. Nicotinic acid causes a significant increase in flow. The cerebral blood flow has been significantly diminished in paresis and in cortical atrophy.

The Effects of Patency of the Ductus Arteriosus on the Circulation. By C. SIDNEY BURWELL and (by invitation) EUGENE C. EPPINGER and ROBERT E. GROSS, Boston, Mass.

Gross' operation (J. A. M. A., 1939, 112, 729) for ligation of the patent ductus arteriosus has permitted the application of the direct method of Fick to the measurement of pulmonary and peripheral blood-flow in these patients. Samples of blood were obtained from the pulmonary artery and from the aorta before and after the ligation of the ductus. Samples were drawn also from the pulmonary artery within fifteen to twenty seconds after occlusion of the ductus to establish the oxygen content of mixed venous blood leaving the periphery when the ductus was open. To test the validity of the method similar observations were made in dogs with the subclavian artery opening into the pulmonary artery.

The studies in patients showed that in the presence of a patent ductus arteriosus observed during operation:

1. Blood from the aorta enters the pulmonary artery via the ductus.
2. The amount of blood flowing through this shunt is from 45 to 75 per cent of the left ventricle output.
3. The total blood-flow through the pulmonary artery in these patients is between 8 and 19 liters per minute.
4. The blood-flow to the periphery is between 3 and 6 liters.
5. Therefore, the output of the left ventricle is 2 to 4 times that of the right, presumably because blood from two sources enters the left ventricle.

Objective Evidence of the Efficacy of Certain Drugs in the Treatment of Angina Pectoris. By JOSEPH E. F. RISEMAN and (by invitation) A. S. FREEDBERG and ERWIN SPIEGL, Boston, Mass.

Electrocardiograms taken continuously during the induction of attacks of angina pectoris by exertion show that a depression of ST 4 occurs during exertion and reaches a maximum when the patient is forced by precordial pain to stop work. This depression varied between 1 and 4 mm. in twenty-six patients studied, always occurred during attacks induced by exertion or anoxemia and was constant for each patient.

The effect of medication (nitroglycerine, octyl nitrite, theobromine sodium acetate and quinidine sulfate) on the electrocardiogram during work and on the amount of work which could be done under standardized conditions before inducing pain was studied in thirteen patients. When lactose or sodium bicarbonate (grains 5) was given four times daily for one week with an additional dose one to three hours before the test, the amount of work which could be performed and the electrocardiographic results were similar to those obtained when no medication was given. When, however, theobromine sodium acetate (grains 7½) was given, ten of the patients were able to do more work without developing pain and exercise was accomplished without inducing the characteristic anoxic electrocardiographic changes. The same results were obtained in eight patients receiving quinidine sulfate (grains 5), and in eleven who exercised two minutes after taking nitroglycerine (1 to 200 grains). Following the administration of nitroglycerine or octyl nitrite, patients were able to do much more work than after other drugs and the electrocardiographic changes were not induced by a 100 per cent increase in work; the duration of this beneficial effect, however, was not as prolonged as after theobromine sodium acetate or quinidine sulfate.

These results, which provide evidence that theobromine sodium acetate and quinidine sulfate, as well as nitroglycerine and octyl nitrite, are of value in the treatment of angina pectoris, are contrary to the clinical opinions expressed in the literature (Evans and Hoyle; Gold, Kwit, and Otto) that no drug is of value in the treatment of angina. The results are in accord with the theory that the administration of nitroglycerine or the purines results in an improved blood flow through the coronary tree.

Observations on the Effects of Intravenous Injection of Histamine in Cases of Ménière's Syndrome. By BAYARD T. HORTON and (by invitation) GUSTAVUS A. PETERS and C. HUNTER SHELDEN, Rochester, Minn.

Twenty-seven subjects, many of whom were totally incapacitated, were treated by the intravenous injection of 2.75 mgm. of histamine diphosphate dissolved in 250 cc. of physiologic saline solution. The vertigo promptly disappeared, tinnitus was relieved in a small per cent of the cases and the patients were able to return to work.

Special studies were made to determine the bodily responses to the administration of the drug. These studies included erythrocyte counts, leukocyte counts, differential counts, and determinations of the basal metabolic rates, the blood sugar, the concentration of individual fats and chlorides in the plasma, the concentration of potassium and protein in the serum, the albumin-globulin ratio, and the carbon dioxide combining power of the plasma, respectively, before and after the intravenous injection of histamine. Electrocardiograms were made, the surface temperatures were determined and samples

of gastric contents were analyzed, respectively, before, during, and after administration of the drug. All subjects were in a basal state, under controlled environmental conditions. The most striking observations were the marked rise, in many instances, in the concentrations of the fatty acids in the plasma, in cases where the fatty acids were normal, the potassium in the serum and the blood sugar, the decrease of the concentration of cholesterol in the plasma and the decrease in the hematocrit values. Inversion of the T wave in lead III in the electrocardiogram and occasional extrasystoles were observed. The response of the gastric acids was always maximal, even though histamine was frequently administered so slowly that it did not accelerate the heart rate. The basal metabolism was not affected during slow rates of administration but was increased during rapid administration of the drug. No untoward effects were obtained in approximately 400 intravenous injections.

Infectious Feline Agranulocytosis. Kodachrome Moving Picture Demonstration of the Circulation of the Omentum as Affected by Serum from a Cat With This Disease. By JOHN S. LAWRENCE and (by invitation) MARGARET B. STRINGFELLOW, RICHARD J. ACKART, FRANCIS W. BISHOP, and IRVING ARIEL, Rochester, N. Y.

The intravenous injection into normal cats of serum obtained from cats at the height of infectious feline agranulocytosis is followed by leukopenia and pronounced neutropenia in the peripheral blood. Observations of the omental circulation following the intravenous injection of "agranulocytic" serum have been made in an attempt to determine whether the peripheral leukopenia could be explained in the same way as with hydrophile colloids, *i.e.*, by passage of the white blood cells to the marginal areas with sticking of the cells in large numbers to the endothelial wall. In no instance has there been found increased accumulation of white blood cells in the marginal areas such as has been seen repeatedly following the intravenous injection of 10 per cent gelatin or typhoid vaccine. The results with the serum have varied from practically no change to sudden and prolonged diminution or absence of white blood cells in the para-capillaries of the omentum. In one instance the visible white blood cells disappeared from the omental circulation for a period of 40 minutes. No correlation has been found between the level of the white blood cell count following the injection of "agranulocytic" serum and the number of white blood cells visible in the omental vessels. Since no accumulation of these cells has been noted in the omental vessels, this cannot be accepted as the explanation for the leukopenia. However, deposition of cells in other areas has not been excluded. Other observations in our laboratory indicate that peripheral destruction of white blood cells may occur at the height of the disease in infectious feline agranulocytosis. Of course, it is well recognized that the changes in the bone marrow are of major importance with reference to the leukopenia that occurs at the height of the disease but it is also felt that peripheral destruction may be an additional factor.

Familial Non-Hemolytic Jaundice with Indirect Van den Bergh Reaction. By WILLIAM DAMESHEK and (by invitation) KARL SINGER, Boston, Mass.

Two families with an unusual type of chronic jaundice were studied. The hereditary nature of the disorder was established in 3 generations. Although the bilirubin was of the "indirect" type suggesting a hemolytic process, the absence of splenomegaly, spherocytosis, reticulocytosis, increased erythrocyte fragility, and of a hyperactive bone-marrow was opposed to the diagnosis of familial hemolytic icterus. This condition was furthermore ruled out by the normal or somewhat low values for daily fecal urobilinogen output. The hereditary nature of the disorder and its long duration without symptoms or signs of progressive hepatic disease indicated a simple disturbance in function. A significant abnormality was the greatly delayed excretion of injected bilirubin from the blood, indicating (in the absence of other abnormal tests for liver function) a disturbance in the permeability of the hepatic cells to the excretion of bilirubin. In congenital hemolytic jaundice with approximately the same degree of icterus the bilirubin excretion test was normal. Striking analogies were present between our human cases and the hereditary jaundice of rats recently described by Malloy and Lowenstein. Our studies demonstrated further that familial jaundice is not always hemolytic in type and that an indirect van den Bergh reaction is not necessarily indicative of a hemolytic process.

Treatment of Experimental Canine Black-tongue and Clinical Pellagra with Coramine. By DAVID T. SMITH and (by invitation) JULIAN M. RUFFIN, GEORGE MARGOLIS and LESTER H. MARGOLIS, Durham, N. C.

Severe cases of pellagra respond as readily to treatment with coramine (pyridine-B-carboxylic acid diethylamide) as to nicotinic acid. The doses employed by us (3 cc. daily) and by other investigators (2 to 20 cc. daily) were rather large and were chosen empirically without previous animal experimentation.

The experimental method was standardized by treating 45 cases of acute black-tongue with daily doses of nicotinic acid which ranged from 0.1 mgm. to 10 mgm. per kilogram of body weight. Daily doses of 0.5 mgm. per kilogram gave the maximum results and no additional improvement resulted from doses 20 times as large.

Coramine was administered parenterally to 22 dogs with acute black-tongue in daily doses of 1.45 to 14.5 mgm. per kilogram. Daily doses of 7.25 mgm. per kilogram were uniformly successful, and doubling the dose resulted in no additional improvement.

Coramine was administered orally to 20 dogs with acute black-tongue. Daily doses of 2.9 mgm. cured 7 out of 8 animals and doses of 7.25 mgm. were uniformly satisfactory.

The minimum dose giving the maximum response may be defined as 7.25 mgm. daily per kilogram of body weight.

Patients with acute pellagra should receive 2 to 3 times the dog curative dose or 3 to 5 cc. of coramine daily.

The Pathogenesis of Azotemia in Hemorrhage from the Upper Gastro-Intestinal Tract. By JOHN B. JOHNSON (introduced by Samuel H. Bassett), Rochester, N. Y.

Fifteen cases of gastric and duodenal hemorrhage have been investigated in an effort to study the mechanism of this azotemia. Renal function was studied by frequent measurement of the urea and creatinine clearances. In most instances the initial observations of kidney function were begun within a few hours after admission.

No direct correlation between the amount of hemorrhage and azotemia was found. Every case which showed a blood urea nitrogen above 28 mgm. per cent had a definite reduction in renal function. In some cases this reduction was permanent, in others temporary due to shock. None of the cases with normal renal function showed an elevation of blood urea nitrogen above 28 mgm. per cent, even when the hemorrhage was extensive. No changes were observed in the creatinine, CO_2 combining power, and blood chlorides.

The conditions of hemorrhage, except for anemia and shock, were simulated in selected cases by the administration of large quantities of human blood by stomach tube. Nitrogen balance studies in these cases revealed that 40 to 60 per cent of the protein given as blood was recovered as nitrogen in the urine. The blood urea nitrogen did not rise significantly above physiological levels except in the cases which showed distinct permanent reduction in kidney function.

Physiological Adjustments of Normal Subjects to Sudden Loss of Blood. By EUGENE A. STEAD, JR. (introduced by Marshall N. Fulton), Boston, Mass.

Seven hundred and sixty to twelve hundred and twenty cc. of blood were removed rapidly by venesection from normal professional donors in the horizontal position. Five of the six subjects developed collapse when from 15.5 to 19.7 per cent of the total blood volume was removed. As the blood was being removed there was a slight narrowing of the pulse pressure and an increase in heart rate of 14 to 30 beats per minute. The hands and feet became cooler and there was slight sweating of the forehead. During this time the subjects had no cerebral symptoms; the blood flow to the brain being adequate, the carotid sinus and aortic pressor areas caused peripheral vasoconstriction and a rise in heart rate.

The onset of the collapse was sudden. The blood pressure fell sharply to 50 mm. of Hg or below. At the height of the collapse the subjects showed signs of both sympathetic and parasympathetic overactivity. The heart rate was very slow, ranging between 36 and 40 beats per minute. The subjects developed nausea, weakness, ashen gray pallor, blurred vision and profuse sweating. One subject became unconscious.

Immediately after hemorrhage there was a rapid small increase in plasma volume as protein-poor fluid entered the blood stream. This caused a slight fall in the serum protein concentration. The plasma volume continued to increase for 72 hours, but the protein concentration showed no further fall, indicating that protein and fluid were being added to the blood stream at the same time. The fall in hematocrit paralleled the increase in plasma volume.

These observations are important because they show that (*1*) when dilution is complete on the third to fourth day following venesection, about ¼ of the serum protein is protein which has been added to the blood since the hemorrhage; (*2*) there is no readily available store of non-circulating red blood cells which is added to the blood stream in times of emergency; (*3*) the peripheral hematocrit reflects fairly accurately the direction and extent of the changes in the plasma volume.

READ BY TITLE

Assay of Adrenocorticotropic Hormone in Cases of Cushing's Syndrome. By KARL E. PASCHKIS (introduced by Hobart A. Reimann), Philadelphia, Pa.

The syndrome associated with basophilic adenoma of the anterior pituitary, bearing Cushing's name, is clinically nearly identical with certain tumors of the adrenal cortex. It has been assumed that in Cushing's syndrome the pituitary acts by stimulating the adrenal cortex through its adrenocorticotropic hormone. Serum extracts were assayed for their adrenocorticotropic activity and were found active in cases of Cushing's syndrome. This finding supports the theory that the basophilic adenoma of the pituitary stimulates the adrenal cortex. In comparison with cases of pituitary basophilism, cases of hypertension and of adrenal cortical tumor were examined. The results were negative.

March Hemoglobinuria: Studies of the Mechanism and Clinical Characteristics. By D. ROURKE GILLIGAN (by invitation) and HERRMAN L. BLUMGART, Boston, Mass.

Hemoglobinuria produced by physical exertion, so-called "march hemoglobinuria," occurs uncommonly. The pathologic physiology of the attacks has not been clearly defined.

Three cases of march hemoglobinuria have been studied by us. The subjects were young males. Brisk short walks in one subject, and running in the other two cases induced attacks. Attacks were asymptomatic. Physical examination revealed no abnormalities except icteric sclerae in two of the subjects, and intermittently palpable spleen and liver in one of these. The urine was completely normal in all cases between attacks. The diagnosis was clearly differentiated from other types of paroxysmal hemoglobinuria.

Hematological findings were completely normal. Hemoglobin was present in the plasma at levels of 40 to 70 mgm. per 100 cc. in each attack of hemoglobinuria. It was calculated that the cells from 7 to 12 cc. of blood

were destroyed during an attack. Less than 10 per cent of the released hemoglobin appeared in the urine. Albuminuria was present at the time of hemoglobinuria. The plasma bilirubin increased considerably after attacks in the two patients with slight jaundice and hyperbilirubinemia.

In the case in which walking produced attacks, the body position during the exercise, rather than the degree of exertion, was shown to be the precipitating factor. Thus, when a moderately kyphotic posture was induced by a plaster cast no hemoglobinuria resulted from amounts of walking which regularly produced attacks in the normal upright posture. Further, prolonged exercise on the bicycle ergometer with an oxygen consumption greater than that during walking also failed to produce an attack. These findings suggest that interference with blood flow in the abdominal organs during exercise may be important in the production of the hemolysis.

The constant bilirubinemia in two cases was not clearly attributable to blood destruction since attacks of hemoglobinuria were infrequent and there was no anemia or reticulocytosis.

In our experience this condition occurs with sufficient frequency, especially in athletes, so that its presence should be considered in any case in which a red urine is voided.

A Further Investigation of the Urorosein Reaction of Pellagra Urines. By J. A. LAYNE (by invitation) and C. J. WATSON, Minneapolis, Minn.

The color reaction described by Ellinger and Dojmi was employed by Beckh, Ellinger, and Spies as a basis for the quantitative estimation of porphyrin in the urine. These investigators reported marked increases of porphyrin in a series of pellagra urines. Watson observed subsequently that the color reaction was due to urorosein rather than porphyrin. This was confirmed by Meiklejohn and Kark. In the present investigation, additional evidence has been obtained (*1*) that the color reaction is not due to porphyrin; (*2*) that the chromogen is indolacetic acid, which does not, however, give the urorosein reaction except after primary oxidation with nitrite; (*3*) that the chromogen is often present even in the normal urine, but fails to give a spontaneous reaction in the absence of nitrite or of other similar oxidizing substances. The latter have been noted, but not identified, in pathological urines, particularly from individuals presenting evidence of nicotinic acid deficiency to a greater or lesser extent.

Although the urorosein reaction is commonly positive in pellagra urines, it has not been possible to correlate its presence and disappearance with the deficiency and the administration, respectively, of nicotinic acid. The reaction has often been noted to disappear spontaneously prior to administration of nicotinic acid, and further, to reappear even long after adequate amounts have caused regression of all signs of deficiency. Positive spontaneous urorosein reactions (without addition of nitrite) have been noted at one time or another in each of ten cases of nicotinic acid deficiency studied thus far. It may be emphasized that in none of those was the amount of porphyrin sufficient to be productive of color with the Ellinger-Dojmi reaction. This fact could be ascertained readily by preliminary removal of porphyrin from the ether extract of the urine, with 5 per cent HCl. The urorosein color was then developed by extraction from the ether with 25 per cent HCl according to the Ellinger-Dojmi procedure. The actual amounts of porphyrin present were not as great as are often encountered in various diseases, notably pernicious anemia, lead poisoning, and cirrhosis of the liver. There is, therefore, no reason to suppose, as has been suggested, that the light sensitivity in pellagra is related to porphyrin.

The toluene preservatives of pellagra urines, also of urines from certain other patients suffering from malnutrition of one cause or another, often develop a pink or even deep red color, due in many instances at least to indirubin. The present investigation has sought to determine whether the occurrence of this substance was in any way correlated with the presence of indolacetic acid, indican, or both. No definite correlation has been found to exist. The possibility is not excluded, however, that given the proper conditions, indolacetic acid and indoxyl may unite to form indirubin. Certain observations, in fact, suggest that this does occur.

Blood Plasma Volume Changes Following the Administration of Diuretics. By GEORGE M. DECHERD, JR., and D. B. CALVIN (by invitation) and GEORGE HERRMANN, Galveston, Tex.

Patients with congestive heart failure and edema were selected and put at rest in bed under standard conditions for 3 days. The blood plasma volume was determined by the method of Gregerson, Gibson and Stead, as modified for clinical use by Gibson and Evelyn, using the blue dye T1824. After this control determination one of the three usual types of diuretic drugs, salyrgan, aminophyllin or digoxon, was injected and blood samples were taken at frequent intervals during the ensuing 12 hours. Correlation of the plasma volume levels with the urinary output suggests that the mechanism of the diuretic effect is different for each drug.

Salyrgan, intravenously, produced plasma volume changes which support our previously held view that the chief site of action of mercurials is on the renal tubular epithelium. There was a decrease in plasma volume which parallels the diuresis. In one instance in which no diuresis followed salyrgan administration there was a moderate increase in plasma volume, suggesting a possible effect on fluid mobilization from the tissue.

When aminophyllin is injected intravenously, the present studies indicate that, in addition to the acceleration of glomerular filtration previously described, there is also evident a definite effect elsewhere. This is manifested by a conspicuous rise in plasma volume beginning within 30 minutes after aminophyllin injection. This is abated at the height of the diuretic flow, and disappears as

diuresis continues, finally resulting in a sharp drop in blood plasma volume.

After the administration of digoxin there is a slight rise in plasma volume which persists until diuresis is well established; when diuresis occurs the plasma volume drops. The plasma volume seems to be affected by passage of fluid from the tissues, as well as by fluid loss through the kidneys, as would be anticipated when the drug used acts primarily on the myocardium and improves the circulation.

With each of the drugs used, as diuresis progresses there is a mobilization of tissue fluids and electrolytes, with changes in the serum proteins similar to those demonstrated by Calvin in experimental hydremia in the dog.

*Heart Size and Experimental Atheromatosis in the Rabbit.** By L. N. KATZ and (by invitation) A. SANDERS, R. S. MEGIBOW, S. CARLEN and J. RANSOHOFF, Chicago, Ill.

The relationship of cardiac hypertrophy to arteriosclerosis and coronary sclerosis is still controversial. This relationship was studied experimentally. Atheromatosis of the aorta and subendothelial lipoidosis of the coronary arteries were induced in 16 rabbits by feeding a high fat and cholesterin diet for three to four months. These rabbits constituted experimental series 'A.' Six rabbits, although on a similar diet for a similar duration of time, developed no gross or microscopic evidence of atheromatosis and these animals constituted control experimental series 'B.' Eighteen untreated rabbits served as controls, constituting control series 'C.' Body weights and ages in all three groups were the same. In series 'C,' heart weights varied from 1.9 to 5.8 grams, and only two hearts weighed more than 5 grams. The average cardiac weight in this group was 3.8 grams. Heart weights varied from 2.1 to 6.6 grams in series 'B' and the average cardiac weight was 3.9 grams. Of the 16 rabbits constituting experimental series 'A,' there were 12 which had hearts weighing more than 5 grams, and the average heart weight was 6.3 grams. Pulse wave contours and blood pressure readings were taken in 4 atheromatous rabbits by the direct Hamilton technique, just prior to sacrifice. These were no different from similar determinations made in 7 normal untreated rabbits. Microscopy revealed the presence of partial to complete occlusion of many of the smaller coronary arteries due to marked subendothelial lipoidosis, areas of fatty degeneration, and early and old myocardial infarcts. Apparently, then, marked atheromatosis of the coronary arteries in the rabbit produces cardiac hypertrophy.

The Colorimetric Assay of Weakly Phenolic Ketones (Estrone) in Extracts of Human Urine. By N. B. TALBOT, E. MACLACHLAN and F. KARUSH (by invitation) and A. M. BUTLER, Boston, Mass.

Though biological methods for the determination of estrogenic hormones have the advantage of proving the presence of physiologically active material, they are relatively inaccurate and time consuming. The chemical methods of assaying human urine are, so far as we are aware, applicable only to urine of pregnant women. Any improvement in chemical assay overcoming this limitation and permitting the observation of change in endocrine function would, therefore, be an improvement over existing methods of assay.

The present paper reports a procedure for the determination of the weekly phenolic ketone (estrone) content of human urines which contain as little as 5 or 6 micrograms in the 24-hour output. The urine is hydrolyzed with acid and extracted with ether. The purification procedure of Cohen and Marrion has been modified to include several additional washings with 0.1 N alkali and to include a reducing agent (sodium hydrosulfite) which facilitates the removal of non-estrogenic substances from the extract. The "estrone" fraction thus obtained is further purified by the use of Girard's reagent T which separates ketonic from non-ketonic substances. The ketonic fraction thus obtained should theoretically contain only substances which are weakly phenolic and at the same time ketonic. Thus far estrone is the only example of that type of compound which has been isolated from extracts of human urine. The assay depends upon the formation of a colored compound when estrone is coupled with diazotized dianisidine. This coupling takes place at the phenolic hydroxyl position. No color is obtained, therefore, with non-phenolic ketones such as the neutral 17-ketosteroids (androgens). The extinction wavelength curve of the color developed from solutions of crystalline estrone and pregnancy urine extracts is identical. The data obtained show that:

1. Crystalline estrone in amounts ranging from 2.5 to 30 gamma per sample may be determined by the colorimetric procedure with an accuracy of 10 per cent.
2. The recovery of crystalline estrone in pure solution through the entire purification procedure averages 67 per cent (range 62 to 81 per cent).
3. The recovery of crystalline estrone added to the crude ether extract of hydrolyzed children's urine originally containing no estrone averages 65 per cent (range 57 to 79 per cent).
4. The range of 24-hour excretion of "estrone" for immature children was 0 to 4 gamma.
5. The 24-hour output of "estrone" by normal cyclic women and women in the 4th to 7th month of pregnancy averaged 25 and 400 gamma, respectively.

Thus the data obtained apparently correspond with the physiological status of the individuals studied.

Hypersensitivity to Light: Studies on an Unusual Case Treated Successfully with Histamine. By RICHARD B. CAPPS and (by invitation) RICHARD H. YOUNG, Chicago, Ill.

Hypersensitivity to light with the production of wheals is a very unusual condition. Such cases as can be found in the literature have been inadequately studied and in-

* Aided by the A. D. Nast Fund for Cardiac Research.

effectively treated. This report concerns an extreme example of this condition with studies of the mechanism and the effect of treatment with histamine. As far as we know, similar observations have not been previously made.

The patient, a 34-year-old blond male, was so sensitive to light that as little as 1/8 of an erythema dose of a carbon arc lamp produced whealing. Fainting occurred with excessive exposure. The effect of light of different wave-lengths was investigated. No porphyrin was present in the urine. An increased histamine content of the blood and an increase in the gastric acidity were demonstrated following whealing. Skin biopsies were obtained before and after exposure.

Accurate studies of the skin sensitivity were made possible by observing the appearance time of wheals with different times of exposure to a standard light. Histaminase and the repeated administration of histamine were both found to abolish the reaction of whealing.

Attempts to Produce Pernicious Anemia Experimentally. By MAXWELL M. WINTROBE and (by invitation) HERMANN LISCO, JOSEPH L. MILLER, JR. and LAWRENCE R. KOLB, Baltimore, Md.

Pigs weaned at an early age (3 weeks) were fed a diet consisting of casein (25.8 per cent), sucrose (56.9 per cent), lard (10.8 per cent), cod liver oil (1.3 per cent) and a salt mixture, supplemented with brewers' yeast (3 grams per kilogram of body weight).

When they became accustomed to this artificial diet and seemed to be in a good nutritive state, the quantity of yeast given some of the animals was gradually reduced and thiamin, riboflavin, nicotinic acid and filtrate factor were given instead, separately and in various combinations. Comparable animals receiving the above synthetic vitamins and no yeast were given desiccated whole liver or an anti-pernicious anemia liver extract. Still others received wheat germ oil or liver in addition to yeast.

Macrocytic anemia occurred in a few animals deprived of yeast but receiving thiamin, riboflavin and nicotinic acid, and in all such animals ataxia and degeneration of the sensory neuron, including the posterior funiculi of the spinal cord, developed. Yeast gave only partial protection against this degeneration but desiccated whole liver or yeast plus wheat germ oil were fully protective.

Assays of the antianemic potency of the livers of ataxic and nonataxic animals have shown distinctly greater potency in the latter.

The Clotting Action of Stock and Detoxified Fer-de-Lance Venom. By GEORGE L. KAUER, JR. (by invitation) and PAUL REZNIKOFF, New York, N. Y.

Eagle has shown that snake venoms act as enzymes in promoting the clotting of blood. This study was undertaken to determine the effect of fer-de-lance venom from which the neurotoxin was removed, and to compare its action with a "stock" fer-de-lance venom.

The detoxified venom was first used three months after its preparation, and the same sample was used throughout the seven-month period of experimentation.

Detoxified venom given intravenously to rabbits in doses of 0.1 cc. of a 1–800 solution to 0.3 cc. of a 1–100 solution caused an increase in the clotting time which lasted three to six hours, varying with the dosage. Preliminary observations indicate that blood fibrinogen is lowest when the clotting time is longest. When given intramuscularly to rabbits in doses of 0.5 to 1.0 cc. of a 1–100 solution, a decrease in the clotting time occurred one to three hours after injection following a temporary increase.

Both stock and detoxified venom clotted oxalated blood much more quickly than heparinized blood. Pure fibrinogen solution was clotted as rapidly by 0.1 cc. of 1–100 detoxified venom as by 0.1 cc. "pure" thrombin. The effect of heparin on this reaction is being studied.

Clinical Significance of Urinary Androgens. By HARRY B. FRIEDGOOD and JOHN K. WOLFE (introduced by Soma Weiss), Boston, Mass.

Previous studies have disclosed that the range of total daily androgen excretion for normal and virilistic females overlaps, although the latter tend to have higher levels. Excessively high values occur in virilism due to corticoadrenal tumor and occasionally in virilism without tumor. Estimation of the *total* urinary androgens is not clarifying the nature of the pathological physiology of virilism; nor is it useful, except in a limited way, in the differential diagnosis of these cases. These considerations led to a study of the chemical structure of the urinary androgens and the relative proportions in which they are excreted in two cases of virilism due to tumor and one case of adreno-genital syndrome without tumor.

Two crystalline compounds have been isolated and positively identified chemically, *viz.* dehydroisoandrosterone (I) and Δ 3,5-androstadiene-17-one (II). (I), which has been isolated in all cases, accounts for 45 to 50 per cent of androgenic activity in one tumor case, 13 per cent in another, and 1 to 2 per cent in the adreno-genital syndrome. (II), which was found in the first tumor case, and is being sought in the others, represents the first isolation of this androgen from female urine. The remaining keto-steroids, still unidentified, are being subjected to a similar systematic study.

The Peripheral Blood Flow in Hyperthyroidism. By HAROLD J. STEWART and (by invitation) WILLIS F. EVANS, New York, N. Y.

Measurements of the peripheral blood flow in cc. per sq. m. per minute have been made in patients suffering from Graves' disease. In addition, the basal metabolic rate, velocity of blood flow (arm-to-tongue method (decholin)), pulse rate, and blood pressure were recorded in each of three phases studied: namely, before iodine, again during iodine therapy, and finally after thyroidectomy. Eighteen patients have been studied. In the measurement of the peripheral blood flow we made use of the Hardy-Soderstrom radiometer and the methods described

by Hardy, Daniel, and Soderstrom. All measurements were made in the morning while the patients were in a basal metabolic state; the room temperature did not vary more than 0.5° C. in any single experiment; the subjects were nude, being covered only by a sheet. Seventeen patients were women and one a man. The ages ranged from 18 years to 56 years. In the eight patients upon whom these studies have been completed, it was found that the peripheral blood flow was high (average 213 cc. per M^2 per minute) in the phase "before iodine" when the basal metabolic rate was elevated. After the institution of iodine therapy, decrease in peripheral blood flow (average 139 cc. per M^2 per minute) and in basal metabolic rate occurred. After thyroidectomy, a further decrease in blood flow (average 78 cc. per M^2 per minute) and in basal metabolic rate was recorded. The relationship between basal metabolic rate and peripheral blood flow was linear in that, when all the observations were pooled, it was found that as the basal metabolic rate decreased, the peripheral blood flow decreased. Definite but not striking increase in circulation time occurred, approaching the normal after thyroidectomy. Pulse rate and blood pressure usually followed the basal metabolic rate and peripheral blood flow. The skin in most cases showed an increased average skin temperature before therapy and decreased with iodine and thyroidectomy. No significant fluctuations in rectal temperature were observed. There are certain observations indicating that the minute volume output of the heart is increased in Graves' disease, and now from these observations it appears that the peripheral blood flow is also increased.

Renal Enlargement in Rats Produced by Testosterone Proprionate. By JOHN B. LUDDEN and ERICH KRUEGER (by invitation) and IRVING S. WRIGHT, New York, N. Y.

Selye reported renal enlargement in *adult female mice* and rats after testosterone proprionate. The present study of the effect of testosterone proprionate on *immature* male, *mature* male and *female* rats demonstrates similar action in each group. The histological picture varied from that of Selye.

Studies were made on *immature* male rats (12.5 mgm. testosterone proprionate daily for 14 days), *mature* male rats (10 mgm. testosterone proprionate daily for 21 days) and *mature* female rats 10 mgm. testosterone proprionate daily for 21 days). Controls were given sesame oil.

Average weight of kidneys of treated *immature* male group was 831 mgm. per 100 grams of body weight compared with 691 mgm. in controls. Kidneys of treated *mature* male group had average weight of 993 mgm. per 100 grams of body weight compared with 697 mgm. for controls. In mature female group average kidney weight was 933 mgm. per 100 grams of body weight compared with 755 mgm. in controls. In mature groups differences were especially clearcut, there being no overlapping of kidney weights of treated rats by those of control rats.

Histological study of kidneys revealed generalized enlargement in all groups, but no other clear evidence of deviation from normal morphology. This observation contrasts with findings reported by Selye, namely, definite hypertrophy of parietal lamina of Bowman's capsule.

The Rôle of Anemia in Water Retention. By MAURICE B. STRAUSS and (by invitation) HERBERT J. FOX, Boston, Mass.

Since Addison first noted the occurrence of edema in the anemia now bearing his name, it has been recognized that water retention is of common occurrence in various types of anemia. This phenomenon has been ascribed to "cardiac weakness." However, venous pressure determinations have failed to reveal abnormal levels. Although some patients with anemia may have lowered plasma protein levels, no correlation of the two factors was observed by Keefer and Myers nor by us in 32 pairs of observations. When sodium salts were administered to these 32 patients, water retention occurred in all, the degree of retention varying directly with the severity of the anemia. No significant correlation between the amount of water retention and the colloid osmotic pressure of the plasma proteins was observed. It is concluded that anemia *per se* is conducive to water retention and edema formation.

Electrocardiographic Changes During Intravenous Therapy of Pneumonia (Preliminary Report). By DAVID D. RUTSTEIN, K. JEFFERSON THOMSON, DANIEL M. TOLMACH and ROBERT J. FLOODY (introduced by L. Whittington Gorham), Albany, N. Y.

As part of a study of the circulation of pneumonia patients, electrocardiographic observations in relation to intravenous therapy were made.

Electrocardiograms of pneumonia patients were taken prior to intravenous therapy. During intravenous administrations, chest lead IV F (electrode position constant) was observed in a "cardioscope." Tracings were recorded at about the middle of each injection, two minutes following its completion, and whenever changes appeared during administration. These consisted of variations in direction, configuration, and voltage of T_4 and P_4.

In 59 pneumonia patients, 112 injections of horse or rabbit serum (49 horse and 63 rabbit) were studied. The electrocardiographic variations following rabbit serum were similar to those following horse serum. The electrocardiograms in 19 (32.2 per cent) of these patients changed during or after at least one injection. Twenty-three (20.5 per cent) of the 112 administrations were accompanied by a variation: 16 in T_4 and 7 in P_4.

A similar study was conducted on 24 pneumonia patients who received 32 injections of sodium sulfapyridine or sodium sulfathiazole (26 sodium sulfapyridine and 6 sodium sulfathiazole). Five (20.8 per cent) of these injections in 5 (15.6 per cent) of the patients, were associated with a change: 3 in T_4 and 2 in P_4. Six patients had nausea or vomiting during the intravenous administration of one of these drugs. Only 2 of these had electrocardiographic changes during the occurrence of

these symptoms: one had inversion of P_4 and the other a disappearance of P_4 associated with a slowing of the rate.

Electrocardiographic changes indistinguishable from acute myocardial infarction were observed in 3 patients. One received Type I antipneumococcus horse serum, another Type VIII antipneumococcus rabbit serum, and the third sodium sulfathiazole.

Varying Relations Between Inulin, Creatinine and Urea Clearances in Children with the Nephrotic Syndrome. By LEE E. FARR and (by invitation) PALMER H. FUTCHER and KENDALL EMERSON, JR., New York, N. Y.

In approximately one-fifth of the children under five years of age admitted to this clinic with the nephrotic syndrome, the urea clearance was increased to above 140 per cent of normal. With recovery from the disease, the urea clearance dropped to normal levels. We have seen this type but once in an adult. In the remaining four-fifths of the nephrotic children under five years of age and in the great majority of our nephrotic patients over this age, the urea clearance was normal or subnormal on the patient's first admission. The present studies were carried out to determine if, in these two groups of patients, the renal clearance of two non-urea substances was affected in the same manner as urea.

Inulin, exogenous and endogenous creatinine, and urea clearances were determined simultaneously in several high clearance nephrotic children with urea clearances 140 to 200 per cent of normal, and in several low clearance nephrotic children with urea clearances below 20 per cent of normal. The duration of disease was similar in comparative patients in each of the groups.

In patients with high urea clearances, the inulin clearance was found to be increased above the normal ranges to about the same degree as the urea clearance. On the other hand, the endogenous creatinine clearance was substantially below the inulin clearance.

In patients with low urea clearances, all three clearances tended to approximate closely the same absolute value.

The significance of the above observations is discussed.

Studies on Migraine: The Contrast of Vascular Mechanisms in Headache and Pre-Headache Phenomena. By G. A. SCHUMACHER and A. M. CAHAN (by invitation) and H. G. WOLFF, New York, N. Y.

Headache

It has been shown that migraine headache results from the dilatation and stretch of cranial arteries. To ascertain further the rôle of the cerebral arteries in migraine headache the following was done: During severe headache in 5 subjects, lumbar puncture was performed. By means of a manometric system attached to the lumbar needle, the cerebrospinal fluid pressure was progressively increased to approximately 800 millimeters of water. Such increase in pressure, sufficient to abolish histamine headache, did not diminish the intensity of the headache. It is inferred that the headache in migraine does not arise primarily from the cerebral arteries, but chiefly from the dilatation and stretch of the branches of the external carotid artery.

Pre-headache phenomena—scotomata

Perimetric studies of pre-headache scotomata were correlated with systemic arterial pressures during the action of amyl nitrite. (*1*) After small amounts of this agent, the scotomata diminished and disappeared within 10 seconds after the facial flush, to remain absent for 2 to 4 minutes. During visual restoration there was little change in the systemic arterial pressure. (*2*) After the inhalation of larger amounts of amyl nitrite, the scotomata again promptly disappeared shortly after the flush, to be soon followed, however, by confluent scotomata which merged to produce, except for central vision, transient amaurosis. This was associated with disorientation and pronounced fall in blood pressure. Normal visual fields again followed and then the scotomata reappeared. It is inferred that these pre-headache phenomena result from cerebral vasoconstriction which is succeeded by the aforementioned vasodilatation and headache.

Determination of the Transfusion Requirement in Anemia. By JOHN G. GIBSON, 2ND (introduced by Henry A. Christian), Boston, Mass.

Every clinician has wanted to know how much blood must be given to an anemic patient to raise the hematocrit to the desired level. In the past, this information could be obtained only by actual determination of the blood volume. The transfusion requirement can now be quickly computed from the patient's hematocrit and predicted normal total red blood cell volume (obtained from a nomogram).

In chronic anemia there is a direct relationship between the percentage of reduction from normal in total red cell volume (deficit) and the hematocrit. Thus, at hematocrit levels of 10, 20, 30, and 35, total red cell volume is reduced by approximately 75, 50, 30 and 15 per cent, respectively. The product of the difference in percentage deficits corresponding to the original and desired hematocrit level (obtained from a nomogram) and the normal total red cell volume, divided by the average hematocrit of transfusion blood (about 40), gives the amount of whole blood needed to attain the desired hematocrit level. Excess plasma given by transfusion is quickly disposed of.

Normal total red cell volume varies greatly with sex and physical measurements, ranging from 1200 cc. in small females to 2860 cc. in large males. In anemic patients with normal total red cell volumes of these amounts, the minimum quantity of whole blood required to raise the hematocrit from 20 to 30 is from 500 cc. to 1500 cc.

The computation is not valid in acute hemorrhage before dilution has taken place (2 to 4 days) or in shock, in which there may be hemoconcentration.

Application of Clearance Method to Determination of Unilateral Renal Blood Flow in Man. By HERBERT CHASIS, JULES REDISH and ALBERT ERDMANN, JR. (introduced by William S. Tillett), New York, N. Y.

In view of numerous reports indicating that unilateral renal disease may be a frequent etiological factor in essential hypertension, a more accurate method of appraising unilateral renal function is required. To this end the clearance method has been applied to the unilateral measurement of renal blood flow, filtration rate, etc., in a limited group of patients with normal renal function, with demonstrated unilateral renal disease, and with essential hypertension. It has been demonstrated that accurate simultaneous collection of right and left ureteral urine is possible if necessary precautions are taken to observe and prevent leakage around the catheters. The total renal blood flow determined in this manner is comparable to the figure obtained by the usual total clearance method. In those patients with essential hypertension who have been examined thus far, the renal blood flow was found to be equal in both kidneys, though the filtration fraction is characteristically increased above normal. In the patients with unilateral uropathy the blood flow was found to be decreased in the diseased kidney. In two patients who had operative procedures designed to increase renal blood flow (renal omentopexy in one and nephropexy for ureteral kink in the other), renal blood flow was found to be lower in the operated kidney two years later.

The method is now being applied to the measurement of the tubular excretory mass (D-Tm), *i.e.,* the evaluation of the total functional renal mass.

Effect of the Application of Tourniquets on the Hemodynamics of the Circulation. By RICHARD V. EBERT (introduced by James P. O'Hare), Boston, Mass.

Many clinicians believe that pooling of blood in the extremities by means of tourniquets is as effective as phlebotomy in the treatment of acute left ventricular failure. The purpose of this study was to determine whether the amount of blood pooled in the extremities by this means was equal to that removed by the usual phlebotomy. The blood volume was determined in 5 subjects under the following conditions: (*1*) with the extremities free, (*2*) after occlusion of the arterial circulation to both legs and one arm by cuffs inflated to a pressure of 250 mm. of Hg, (*3*) after venous congestion of the three extremities by inflating the cuffs to diastolic pressure for 7 to 10 minutes, followed by occlusion of the arterial circulation. By subtracting the result obtained in Experiment 2 from that obtained in Experiment 1, the volume of blood normally contained in the three extremities was calculated. By subtracting the result obtained in Experiment 3 from that obtained in Experiment 2, the volume of blood which was removed from the head, trunk and arm by venous congestion of the remaining three extremities was calculated.

In 5 normal subjects in the recumbent position the average volume of blood contained in the three extremities was 900 cc., or 16 per cent of the total blood volume. An average of 740 cc. of blood was removed from the head and trunk by congesting the extremities. Therefore, tourniquets effectively applied pool more blood in the extremities than is removed from the body by the average venesection and are a rational therapeutic measure.

The sudden removal of an average of 15 per cent of the volume of blood circulating in the head and trunk (740 cc.) by tourniquets produced circulatory collapse in 4 of 7 normal subjects tested. This agrees with the observation that the rapid removal of 15 to 20 per cent of the blood volume in man by venesection is accompanied by the symptoms of shock.

Proteus and Pyocyaneus Infections: a Review of Six Cases of Bacteremia with Immunologic Studies in One. By GUSTAVE J. DAMMIN (introduced by Clifford L. Derick), Boston, Mass.

The mortality rate in Proteus and Pyocyaneus bacteremias which result from dissemination from a primary focus is high. When this focus is the kidney, the mortality rate is about 60 per cent. In 5 of the 6 cases in this series, the kidney was the primary focus. Recovery occurred in but one of these cases.

From the recovered case, *B. pyocyaneus* (*Pseudomonas aeruginosa*) and *Proteus mirabilis* were isolated from the blood, urine, stool and osteomyelitic sinus. The patient entered in peripheral vascular collapse with bronchopneumonia and right kidney blocked by calculus. Nephrostomy and subsequent nephrectomy were performed. Otherwise treatment was symptomatic. By agglutination, mouse protection and bactericidal tests, a high degree of immunity was demonstrable. The agglutinin titers for these organisms from all the sources varied: for *B. pyocyaneus* between 1:80 and 1:10,000 and for *Proteus mirabilis* between 1:2560 and 1:80,000. White mice were protected against more than 2 MLD of both organisms. Bactericidal antibodies for *B. pyocyaneus* were present in higher titer than for *Proteus mirabilis,* showing a bactericidal action 1000 times greater than the control.

A positive Weil-Felix reaction appeared during the three-months' course of investigation. By agglutinin absorption tests, this strain of *B. Pyocyaneus* and Proteus X19 were demonstrated to contain a common antigen.

The Effects of Ingestion of Large Amounts of Fluid Upon the Course of Circulating Blood Volume. By EMANUEL GINSBURG (by invitation) and SAMUEL H. PROGER, Boston, Mass.

Reports concerning the immediate effects of ingestion of fluids upon the circulating blood volume are conflicting. Accordingly, the problem was reinvestigated, the course of the blood volume being followed for 3 hours after drinking 1000 cc. of water or 1 per cent saline. The improved method for determining plasma volume by means of the "Evans Blue" dye was used. Blood pressures were also followed. Nine individuals without car-

diovascular disease, most of them schizophrenic, served as subjects. There were four experiments with water, and seven with 1 per cent saline. Of ten patients with cardiovascular disease, eight received salt solution and two received water.

In the group without cardiovascular lesions there was a 9 per cent drop of both circulating plasma and total blood volumes 15 minutes following the ingestion of 1000 cc. of saline. In three of four patients in the same group there were no changes in 15 minutes after the ingestion of 1000 cc. of water. In this entire group the circulating blood after 1½ hours had not increased above the preingestive values.

The course of the blood volume in patients with cardiovascular disease was parallel to that in the preceding group, except that there was no difference between the effects of salt and water 15 minutes after ingestion.

The arterial blood pressures 15 minutes following ingestion were elevated in 50 per cent of all cases comprising the two groups, and unchanged in the others. During the remainder of the experiments, there were no changes from the preingestive values.

Patients' Attitudes and Behavior in Ward Round Teaching. By JOHN ROMANO (introduced by William P. Murphy), Boston, Mass,

Bedside teaching is an established procedure in medical education. However, patients' reactions to this procedure have received little attention. In order to gain objective data, an investigation was undertaken (*1*) to discover if the experience is traumatic, (*2*) to understand the patients' reactions to their illnesses, (*3*) to study the patients during presentation, which is an experimentally induced anxiety situation, (*4*) to learn how the procedure may be utilized as psychotherapy.

Accordingly, under uniform conditions, 84 unselected patients were studied before, during and after Saturday morning rounds. Three to 5 patients were presented to the resident and visiting medical staff and to 40 to 60 students and visiting physicians. Methods of examination before, during and after presentation included psychiatric study; determination of pulse, respiration, blood pressure; spontaneous discussion by the patient of his reactions. The patients were classified as having (*1*) little or no anxiety associated with their physical disease, (*2*) considerable anxiety with their physical disease, (*3*) predominantly neurotic symptoms with no physical disease, (*4*) confusion due to various factors.

No severe psychological trauma was observed. In the few instances in which patients were tense or anxious, the reactions were mild and in no way resembled panic reactions.

Considerable information was obtained concerning the emotional significance of the illness to the patients. Anxiety was experienced by less than one-fourth of the patients in the period preceding presentation; 14 patients exhibited objective evidence of tension during presentation; 12 were embarrassed by the public recitation of the history; 6, by the examination. There were no essential changes in pulse, respiration, blood pressure.

While the entire procedure of the ward rounds may and should be utilized as psychotherapy, the discussion period has the greatest potential value. Most patients preferred to remain for discussion. Many patients requested that the essential conclusions of the conference, particularly as they related to their illness, recovery, and return to work, be communicated to them in simple understandable language.

Intravenous Injection of Magnesium Sulfate in Subjects With Hypertensive and Renal Disease. By ALEXANDER W. WINKLER and (by invitation) HEBBEL E. HOFF and PAUL K. SMITH, New Haven, Conn.

The response of patients with cardiovascular and renal disease to intravenous injection of magnesium sulfate differs in certain respects from that of normal subjects. Normally, injection of small amounts of magnesium sulfate evokes intense cutaneous vasodilatation accompanied by marked fall of blood pressure. In hypertensive subjects cutaneous vasodilatation was regularly observed, but simultaneous fall in blood pressure was frequently slight or altogether absent.

Injected magnesium is normally excreted rapidly and almost completely in the urine, while in subjects with impaired renal function urinary excretion is much delayed. With advanced renal insufficiency the concentration of magnesium in the serum may remain elevated for several days, since little is excreted by the gut.

Therapeutic injection of 500 cc. of 2 per cent solution raises the serum concentration to about 7 m.Eq. per liter, which is insufficient to produce demonstrable change in the nervous system except relief of headache. Another injection within forty-eight hours raises the concentration to about 12 m.Eq. per liter because of the persistent elevation caused by the first injection. At this higher level drowsiness and depression of tendon reflexes appear. Respiratory depression occurs only after disappearance of tendon reflexes. Thus these reflexes are a guide during injection.

A New Hypothesis of the Production of the T-wave in the Electrocardiogram Based on Electro-kinetic Phenomena. By J. ROSCOE MILLER and ROY F. DENT (introduced by N. C. Gilbert), Chicago, Ill.

Perfusion experiments on the dead heart showed that a potential was developed between the epicardium and endocardium. With a pressure of 40 cm. of mercury an amount of current in excess of one half millivolt was produced. This indicated that the intramural streaming potentials incident to cardiac contraction were sufficient to account for the T-wave in the electrocardiogram. Consequently, an attempt was made to reproduce the T-wave by forcible constriction of the dead heart. Experimental animals were killed by means of intravenous injection of magnesium sulfate. This lowered the irritability of the myocardium so that a short time after the chest was opened there was no response to stimulation. Manual constriction of the heart produced a T-wave

similar to that seen in the unanesthetized animal during normal cardiac contraction. The contour of the wave could be regulated by the amount of pressure exerted and the length of time it was continued. These facts are significant in that they indicate that the T-wave is a product of cardiac contraction and contradict the current explanation based on the theory of repolarization.

A Study of the T-Wave of the Electrocardiogram in Left Bundle Branch Block. By WILLIAM A. SODEMAN, New Orleans, La.

T_1 is typically inverted in left bundle branch block, but at times is "atypical" (isoelectric, diphasic, or upright). To determine the significance of such changes, tracings were selected showing normal conduction and bundle branch block in the same patient. With the aid of a planimeter, determinations of the areas of the QRS complex and T-wave in microvolt seconds were made for both types of conduction. Comparison of the summation of the QRS and T values with both types of conduction confirmed the observations of Wilson and further indicated that the "atypical" T-waves in bundle branch block could be predicted and were the expected findings upon the basis of changes in the QRS area. With block negative T-waves became more negative, less negative, and even positive, upon the basis of changes in the QRS alone. Previously positive T-waves gained in negativity depending upon the changes in QRS area. The results indicate that (*1*) T-wave changes resultant from left bundle branch block bear a definite relation to the QRS and T areas in normal conduction, (*2*) "atypical" T-wave changes (upright, diphasic) in Lead I do not necessarily indicate further myocardial changes, and (*3*) the "typical" (inverted) T-wave may be secondary to QRS changes, may result from local variations in the excitatory process resulting from disease, or both.

Culture of Human Marrow. Studies of the Relative Effectiveness of Neoarsphenamine, Mapharsen, Sulfanilamide, Sulfapyridine, Sulfathiazol, and Sulfamethylthiazol on Infections with Streptococcus Viridans (Alpha Hemolytic Streptococcus). By EDWIN E. OSGOOD and (by invitation) INEZ E. BROWNLEE and JULIA JOSKI, Portland, Ore.

Marrow cultures were infected with streptococcus viridans, and equal portions were placed in each of several vials to each of which, except the control, was added the desired concentration of the drug to be tested. Pour plate colony counts and stained smears were made at intervals. Neoarsphenamine in a concentration of 1–150,000 was effective against more strains than any other drug tested, but it had to be present for six to forty-eight hours in this concentration. Sulfathiazol in a concentration of 1–10,000 was effective against many strains including those against which neoarsphenamine was ineffective, but was ineffective against some strains against which neoarsphenamine was effective. Sulfamethylthiazol and sulfapyridine were effective against most of the strains which were sterilized by sulfathiazol, but because of their lower solubility would probably not be as effective clinically. Sulfanilamide was ineffective against the strains tested, and mapharsen in a concentration of 1–1,500,000 was effective against some strains but not as effective as neoarsphenamine in a concentration of 1–150,000.

A suggested plan of treatment for subacute bacterial endocarditis based on these studies and the clinical results to date are presented with lantern slides which illustrate these results.

Results of Treatment of Diabetes Insipidus in Man and in Animals with Pellets of Desiccated Posterior Pituitary Gland and with Pitressin in Oil. By JAMES A. GREENE and (by invitation) L. E. JANUARY, Iowa City, Ia.

Methods to produce slow absorption of hormones are desirable in certain endocrine deficiencies. Diabetes insipidus is such a disease. Five cats with experimentally produced diabetes insipidus and two patients have been treated by implantation of pellets of desiccated posterior pituitary gland. Three such cats and three patients have been treated with injections of pitressin in oil.

The diabetes insipidus has been controlled by such therapy in the animals and in the patients. Certain difficulties encountered with pellet therapy are discussed. The use of pitressin in oil indicates that it is of definite value in the control of this disease.

The Effect of Undernutrition on the Ovary of the Guinea Pig. By D. J. STEPHENS and (by invitation) WILLARD ALLEN, Rochester, N. Y.

In a previous communication it has been shown that undernutrition in the guinea pig results in thyroid atrophy with flattening of the acinar epithelium and accumulation of colloid. The thyroids of such animals were unusually responsive to stimulation by the thyrotropic factor of the anterior hypophysis. The ovaries of the undernourished animals also showed evidences of atrophy and retrogression. Underfeeding sufficient to result in a loss in weight of 25 to 30 per cent in a period of two weeks resulted in reduction of ovarian weight and in marked retrogressive changes. There was virtual disappearance of follicles in the majority of the animals. The interstitial cells of the ovaries of the undernourished animals were small and their nuclei showed the "cartwheel" formation of chromatin which has been described in hypophyseal insufficiency. Refeeding resulted in increase in body and ovarian weight and a return of ovarian histology toward normal. The administration of small amounts of an anterior pituitary extract resulted in marked hypertrophy and hyperplasia of the interstitial tissue and increase in ovarian weight.

Evidence is presented which suggests that the retrogressive changes occurring in thyroid and ovary in undernutrition may be due to failure of the anterior pituitary to continue to produce thyrotropic and gonadotropic substances in amounts sufficient to maintain thyroid and ovarian structure and function.

Studies on the Nicotinic Acid Content of Blood and Urine. By E. WHITE PATTON and W. R. SUTTON (by invitation) and JOHN B. YOUMANS, Nashville, Tenn.

A study has been made of the nicotinic acid content of blood and urine, utilizing the cyanogen bromide-aniline reaction as a basis for the chemical determinations. Values obtained without initial hydrolysis have been compared with those obtained after mild and strong hydrolysis.

In normal subjects the range of nicotinic acid concentration has been found to be 0.30 to 0.50 mgm. per cent in the blood and 3.0 to 5.0 mgm. are excreted in twenty-four hours in the urine. Subjects with known nicotinic acid deficiency have exhibited a slightly lower blood level and a definitely lowered urinary excretion of nicotinic acid. The variation in the blood level in these subjects has not been consistent.

Varying degrees of alkaline hydrolysis of the blood yield results which are very similar to those obtained without initial hydrolysis. In urines with a normal or low nicotinic acid content, varying degrees of hydrolysis resulted in a distinct increase over the value obtained without initial hydrolysis. This increase was not noted when urines with a high concentration of nicotinic acid were similarly treated.

Oral administration of 150 to 300 mgm. of nicotinic acid or nicotinic acid amide causes a variable and transitory rise in the blood level within one hour. When daily doses of this magnitude were taken orally, the blood level rose to approximately twice its previous level. In deficient subjects there seems to be some lag in this blood level elevation after repeated daily doses of nicotinic acid. Within three hours approximately 20 per cent of the ingested dose of nicotinic acid may be accounted for in the urine of normal subjects, whereas only about 3 per cent of a similar dose of nicotinic acid amide may be recovered in a similar time. In each instance the increase in urinary excretion subsequent to oral administration is transitory and terminates within three hours after ingestion.

Erythrocyte Resistance in Congenital Hemolytic Jaundice and in Experimentally Produced Jaundice. By RICHARD T. BEEBE and (by invitation) ABRAHAM FALK, ALBERT M. YUNICH and EDWARD P. HANLEY, Albany, N. Y.

In the course of some investigations on the fragility of erythrocytes in disease we were impressed by the striking increase in resistance of the red blood cells in patients with obstructive jaundice. We were able to bring about this condition in dogs by ligating the bile ducts and showed that there was a direct relationship between the degree of jaundice and the fragility of the cells. We were unable to demonstrate increased resistance of erythrocytes when jaundice was produced in rabbits by injecting bile salts and bile pigment.

Red blood cell resistance is also increased in chronic secondary and primary anemias without jaundice, leading us to feel that bile pigment is not the important factor in causing the increased resistance of red cells.

We hoped, on the basis of this and other observations, to be able to bring about an increase in the resistance of cells in hemolytic jaundice by the administration of some factor in bile, but as yet have been unsuccessful.

A Comparison of Certain Vascular Responses of Normal and Hypertensive Rabbits. By C. K. FRIEDLAND and F. KAPP (by invitation) and E. M. LANDIS, Philadelphia, Pa. and Charlottesville, Va.

It has been shown previously in normal rabbits (Landis, Montgomery and Sparkman, J. Clin. Invest., 1938, 17, 189) that when tyramine, epinephrine, guanidine and pitressin are injected in doses sufficient to elevate blood pressure they also diminish blood flow to the ear, as measured by fall of skin temperature. In contrast, heated extracts of rabbits' kidneys elevate blood pressure conspicuously without diminishing auricular blood flow.

In the present observations the vascular responses of hypertensive rabbits were studied by the technique used previously for studies on normal rabbits. Hypertension was produced by applying to both renal arteries silver clips channeled to a depth of 0.5 to 0.6 mm. The auricular vessels of these hypertensive rabbits dilated when body temperature was elevated to between 40 and 40.5° C., as was the case with normal rabbits. The amplitude of arterial pulsation in the ear was greater than in normal rabbits but skin temperature rose to the same point in both groups during maximal dilatation. Epinephrine and tyramine raised blood pressure and diminished peripheral blood flow in hypertensive and normal animals but with conspicuous differences in sensitivity. Rabbit kidney extracts raised blood pressure of the hypertensive rabbits in spite of the higher resting pressure prior to injection, but the skin temperature of the ear did not change. It appears that the temporary pressor response to kidney extract is merely superimposed upon the existing hypertension.

Penetration of Clot by Sulfanilamide, Sulfapyridine, Sulfathiazole and Sulfamethylthiazole. By JAMES M. FAULKNER and (by invitation) CHARLES N. DUNCAN, Boston, Mass.

Solutions of sulfanilamide, sulfapyridine, sulfathiazole and sulfamethylthiazole were prepared in normal saline and in human blood serum in concentrations varying from 10 to 24 mgm. per 100 cc. In these solutions human blood clots were suspended for periods of 24 to 240 hours, at 37.5° C. At the end of the period the clot was removed and washed with distilled water and chemical determinations were made of the amount of drug present in the clot and in the surrounding solution. It was found that there was no appreciable penetration of the clot by any of the compounds. On the other hand, when whole blood containing any of the above compounds was allowed to clot, the drug was distributed approximately evenly between the clot and the serum. If any inference

is to be drawn from these observations relative to the chemotherapy of subacute bacterial endocarditis, it is that, even if the drug is effective when in contact with the causative organism, rapid eradication of the infection is not to be expected. However, it seems possible that, if treatment is continued over a long enough period of time, preexisting thrombus may become organized and all new thrombus laid down will be impregnated with the drug, thus gradually bringing about a less and less favorable medium for growth of the infecting organism.

The Action of Dihydrotachysterol (A. T. 10) on the Concentration of Serum Sodium, Protein and Calcium. By JOHN H. TALBOTT and (by invitation) WALTER F. LEVER, Boston, Mass.

Metabolic studies on more than 50 patients suffering from pemphigus have been performed during the past 5 years. In most patients a decreased concentration of serum sodium, protein and calcium accompanied the cutaneous lesions. These findings lend weight to the argument that the pathogenesis of symptoms in pemphigus is associated with a disturbance of the acid-base equilibrium in the body.

In searching for some measures to restore the disordered equilibrium, A. T. 10 was considered because of its serum calcium raising effect. This was achieved according to expectations in each of 12 patients to whom it was given. Other effects not anticipated included an increase in concentration of serum sodium and an increase in concentration of serum protein. With the doses recommended, the average increase in serum calcium was 2.3 m.eq. per liter (4.6 mgm. per 100 cc.), the average increase in serum sodium was 5.6 m.eq. per liter, and the average increase in serum protein was 2.5 grams per 100 cc. Clinical improvement followed chemical restoration.

It is hoped that these properties of A. T. 10 may be utilized in the treatment of other conditions such as elevation of serum protein in patients with hypoproteinemia.

Comparison of the Action of Choline and Lipocaic in the Prevention of Cholesterol Atherosclerosis in the Rabbit. By K. R. ANDREWS (by invitation) and G. O. BROUN, St. Louis, Mo.

In 1937, Huber, Casey and Broun showed that the pancreatic extract lipocaic prepared according to the method of Dragstedt, Van Prohaska and Harms was effective in preventing atherosclerosis in rabbits fed a diet rich in cholesterol.

Steiner in 1938 showed that choline in a daily dosage of 500 mgm. also had the effect of preventing cholesterol atherosclerosis in the rabbit.

All lipocaic which we have so far prepared contains at least some choline. The present study compares the preventive action in cholesterol atherosclerosis of choline in dosages of 500 mgm., 75 mgm., 40 mgm., and 10 mgm. per day with daily dosage of lipocaic of similar choline content.

The results indicate that choline exerts some protective action in dosages much lower than those used by Steiner. We have found some variation in potency of different preparations of lipocaic. One preparation fed in rather large bulk to secure a high choline intake gave very poor protection. Other preparations of much lower choline content gave good protection.

The results to date have indicated that the potency of lipocaic preparations may in large part be attributed to the choline content, but do not exclude the possibility that some other substance may also be operative.

Further Studies on the in Vitro *and* in Vivo *Dissolution of Calcium Phosphate Urinary Calculi.* By FULLER ALBRIGHT and (by invitation) HIRSH SULKOWITCH, Boston, Mass.

In 1939 we reported that sodium citrate citric acid solutions have a marked ability to dissolve calcium phosphate calculi. The present study is concerned with an analysis of the properties of solutions which influence their effectiveness for this purpose.

It was found that rabbits' teeth were sufficiently uniform in structure so that their loss in specific gravity on exposure to a solution could be used as a "measuring stick."

The following observations were made: (*1*) Weakly dissociated acids buffering between pH 4.0 to 4.8 (*i.e.* pK 5.0 to 5.8) are the most effective. (*2*) At a given pH, the rate of solubility parallels the amount of undissociated acid (*i.e.* the $\frac{\text{acid}}{\text{salt}}$ ratio). (*3*) In equimolar solutions, dicarboxylic acids with pK'_1 approaching pK'_2 are more efficient than monocarboxylic acids. (*4*) When the $\frac{\text{acid}}{\text{salt}}$ ratio is kept constant, the rate of solubility in the pH range 3.0 to 4.8 is approximately constant and relates itself to the phosphoric acid titration curve. (*5*) The following organic acids were studied and are listed in the order of their efficiency: citric, phthalic, succinic, laevulinic, beta-hydroxybutyric, acetic, malonic, propionic, gluconic, lactic and pyruvic.

The usefulness of an acid clinically will depend on its ability to dissolve calcium phosphate stones without causing irritation. Several acids have been found which are almost as efficient as citric and less irritating.

Studies on the Mechanism of Hemolysis in Preserved Human Blood. By ELMER L. DEGOWIN and (by invitation JOHN E. HARRIS and JOY BELL, Iowa City, Ia.

Studies on the manner in which dextrose inhibits hemolysis are useful in devising new methods of preserving blood. Experimental data are presented to support the following conclusions. Isosmotic concentrations of dextrose and sodium citrate solutions are not isotonic for erythrocytes immediately after collection of the blood. Furthermore, there is a slowly progressive swelling of the red corpuscles during storage in the refrigerator over a period of 30 days. The amount of cell swelling during storage is not directly correlated with the amount of

hemolysis. Dextrose solutions do not inhibit hemolysis by supplementing the sugar lost by glycolysis. Within certain limits, dextrose inhibits hemolysis by serving as a non-electrolyte diluent of plasma rather than by any specific action of the sugar. Studies with sucrose solutions confirm this. The swelling of the cells in dextrose account for the increased fragility in hypotonic saline solutions; this swelling is, to some extent, reversible.

During storage, the plasma sodium diffuses into the cells as the potassium goes out. The addition of substances known to be enzyme poisons throws some light on the nature of the hemolytic process.

Iodine Components of the Blood. Circulating Thyroglobulin in Normal Persons and in Persons with Thyroid Disease. By J. LERMAN, Boston, Mass.

Rabbits injected with human thyroglobulin by various routes, particularly according to the method of Dienes (J. Immunol., 1928, 15, 141), produced antibodies in high concentration. By means of precipitin reactions such antiserum could detect minute amounts of thyroglobulin in solution, namely 0.08 to 0.15 mgm. per 100 cc. or ¼ to ½ gamma per cent of thyroglobulin iodine. No detectable amounts of thyroglobulin were discovered in the blood of numerous normal patients, 2 myxedema patients, 15 thyrotoxic patients before iodinization and 2 thyrotoxic patients after iodinization. Similarly, no thyroglobulin was detected in the urine of 3 hyperthyroid patients.

It is therefore concluded that the excess iodine usually present in the blood of hyperthyroid patients is not due to circulating thyroglobulin.

Blood obtained directly from the thyroid veins at operation was similarly tested for thyroglobulin. Ten of the twelve samples obtained at the beginning of operation were negative; two samples obtained at the end of hemithyroidectomy but from the unoperated side were also negative. On the other hand, seven of the eight thyroid vein samples obtained during or at the end of the second stage of subtotal thyroidectomy showed appreciable amounts of thyroglobulin (0.2 to 13.0 mgm. per 100 cc.). It disappeared from the circulation within 12 to 36 hours after operation.

The presence or absence, or the amount of thyroglobulin in the blood during and after operation, did not correlate with the severity of postoperative reaction.

These results suggest that the presence of thyroglobulin in the blood is due to the extrusion of colloid into the circulation by trauma, and that thyroglobulin does not ordinarily leave the follicles as such. This deduction is consistent with observations of Williams (Am. J. Anat., 1937, 62, 1) on the release of colloid from living thyroid follicles.

Studies on Hemoglobin Regeneration in Patients with Vitamin C Deficiency. By EUGENE L. LOZNER (introduced by George R. Minot), Boston, Mass.

Observations on regeneration of hemoglobin were made in five patients with moderate anemia and vitamin C deficiency as indicated by total absence of reduced ascorbic acid from the blood. These patients were maintained on a diet containing only traces of vitamin C and B complex. Three had clinical scurvy, one pellagra, and one "idiopathic" hypochromic anemia. In two patients the degree of anemia was increased by removal of 1600 cc. of blood by venesection. In four of the five patients regeneration of hemoglobin took place spontaneously or in response to iron therapy alone. In one patient, a case of clinical scurvy, iron therapy was ineffective but hemoglobin regeneration apparently resulted from the administration of 400 mgm. of ascorbic acid daily. It is concluded that hemoglobin regeneration may occur in the absence of reduced ascorbic acid from the blood by chemical test. It is, however, not implied that absence of ascorbic acid from the blood necessarily indicates the total absence of available ascorbic acid.

The Cardiac Failure in Thiamin Deficient Pigeons. By ROY LAVER SWANK and OTTO BESSEY (introduced by Samuel A. Levine), Boston, Mass.

If pigeons are slowly and uniformly depleted of their thiamin on a partially thiamin deficient diet, and starvation prevented by tube feeding, they will develop dyspnea in 3 to 6 weeks, and postmortem examination will reveal hydropericardium, pulmonary edema and congestion, congestion of the liver and (or) dependent edema. The myocardia of many of these will show focal necrosis with inflammatory cell infiltration; others will appear normal. Thiamin produces rapid recovery in all but the most advanced cases. Electrocardiographic studies reveal two types of abnormality, one consisting of changes in the QRS complex in leads one and two, and the other of changes in the T wave in leads two and three. The pathological electrocardiograms are accompanied by a marked increase in the cardiac rate. When thiamin is given, the electrocardiograms and cardiac rate return to normal quickly. A decrease in the cardiac rate occurred only during starvation. It is concluded that a chronic deficiency of thiamin without starvation will produce cardiac failure in the pigeon, that this is preceded and accompanied by pathological electrocardiograms and tachycardia, that starvation alone or during thiamin deficiency produces bradycardia, and that necrosis of the myocardium with inflammatory cell infiltration is a frequent although late finding in these cases.

The Cholesterol Content of the Thoracic Aorta and of the Renal Arteries in Human Necropsy Material: Correlation with Clinical Findings and Vascular Pathology. By MAURICE BRUGER and MAURICE R. CHASSIN (introduced by Carl H. Greene), New York, N. Y.

On material obtained from 37 consecutive necropsies, the thoracic aorta and both renal arteries were examined for cholesterol content. The results were correlated with antemortem clinical findings and with vascular pathology. It was observed that: (*1*) The renal arteries of patients who had normal blood pressures during life contained less than 0.9 per cent cholesterol, those of patients with arterial hypertension from 1.0 to 1.9 per cent cholesterol. (*2*) In subjects who had normal blood pressures, the

ratio of aortic cholesterol to renal artery cholesterol was found to increase with age (0.4 in the 1st decade to 3.6 in the 6th decade). This progressive increase in the ratio was disturbed in patients who had hypertension by the increased renal artery cholesterol. (*3*) The concentration of cholesterol in the renal arteries varied directly with that in the aorta only when the cholesterol content of the latter exceeded 3.0 per cent. With variations in aortic cholesterol from 0.2 to 3.0 per cent, low values for renal artery cholesterol were obtained. (*4*) The degree of renal arteriolar and of coronary artery sclerosis varied directly with the concentration of cholesterol in the renal arteries and in the aorta, respectively.

Mechanism of Hemolysis in Certain Anemias: Significance of Increased Hypotonic Fragility and of Erythrostasis. By THOMAS HALE HAM* *and* WILLIAM B. CASTLE, Boston, Mass.

When erythrostasis and erythro-concentration, normally occurring in the spleen, were imitated *in vitro* by the sterile incubation at body temperature of whole defibrinated mammalian blood, the red blood cells showed progressive increase in volume, in "sphericity" and an increase in hypotonic fragility to such a degree that hemolysis eventually occurred in the serum. These changes were apparently related to metabolic processes and not to hemolytic agents, such as lysolecithin.

Splenomegaly, presumably with increased intravascular stasis, was produced in dogs by prolonged nembutal anesthesia. Blood samples from the splenic vein showed hemoconcentration, variable increase in hypotonic fragility and hemoglobinemia. Concanavalin A of Sumner and Howell, injected intravenously into dogs and rabbits, produced extreme intravascular agglutination, erythrostasis in peripheral organs and an acute hemolytic anemia which was characterized by a striking increase in "spherocytes," in hypotonic fragility and by hemoglobinemia. Concanavalin A produced no significant hemolysis or change in erythrocyte fragility *in vitro*.

Thus a mechanism is described by which a normal degree of erythrostasis occurring in the spleen or other organs may cause increased destruction of blood in diseases characterized by increased fragility of erythrocytes, such as congenital hemolytic jaundice, icterus neonatorum and the acute hemolytic anemias caused by arsine and sulfanilamide. Similarly, an abnormal degree of erythrostasis should produce increased blood destruction in intravascular agglutination in hemolytic transfusion reactions, in hemolytic anemias associated with autoagglutination, in sickle cell anemia, infarcts, and "hypersplenic" anemia.

The Plasma Potassium Rise Accompanying the Paroxysm of Acute Malaria Infections. By R. L. ZWEMER and E. A. H. SIMS (by invitation) and L. T. COGGESHALL, New York, N. Y.

During malaria infections the release of merozoites from the red cells seems to liberate an unidentified toxic substance into the blood, which is believed to be responsible for the paroxysm and fever occurring at this time. If potassium were released from the parasitized erythrocytes at the time of sporulation, it might serve as a toxic substance. Determinations have been made on the variations in plasma potassium level during the course of experimental malaria infections in monkeys and paretics. There was always a sharp rise in the plasma potassium, but the amount of the increase varied with the strain of parasite used. The sharpness of the rise depended upon the rapidity of the sporulation time. With rapid sporulation it was increasingly difficult to obtain samples at the maximum elevation as its duration was shorter.

Repeated determinations at frequent intervals showed that increments of over 50 per cent may be found. In patients the peak potassium values accompanied chills, preceded the peak temperature, and fell before the drop in temperature.

The potassium release from red cells and its inadequate regulation by the body may be a toxic factor, but it is definitely an accompanying phenomenon of the malaria chill.

Studies on the Effect of Various Pituitary Hormones and Non-Specific Substances Upon the Blood in Hypophysectomized Rats. By OVID O. MEYER and (by invitation) ETHEL W. THEWLIS and HAROLD P. RUSCH, Madison, Wis.

Before this society we reported that hypophysectomy in rats was succeeded by reticulocytopenia and anemia. Exposure of hypophysectomized rats to reduced pressure in a chamber was attended by failure of production of reticulocytosis, polycythemia and bone marrow hyperplasia which normal animals demonstrated. It was further shown that the administration of growth hormone produced marked and prolonged reticulocytosis but no increase in erythrocytes or hemoglobin. The results necessitated further study to establish or exclude the existence of a pituitary hormone with a hemopoietic function. Several workers have concluded that such a hormone does exist but their evidence is not convincing.

It has now been further demonstrated that hypophysectomized rats respond with profound reticulocytosis to the parenteral administration of thyroxin, thyreotropic hormone and adrenotropic hormone. In none of these instances has it been possible to control the post-hypophysectomy anemia. Furthermore, the injection of the sodium salt of cevitamic acid (Roche) pH 6.3 to 6.5 or 5 per cent sodium bicarbonate solution is usually attended by slight but significant reticulocytosis.

It is concluded that the reticulocytosis occurring in hypophysectomized rats following the injection of pituitary hormones is non-specific since thyroxin and other substances stimulate their formation. To date, however, no single substance has been found efficacious in producing increases in the hemoglobin or erythrocytes. It is possible that the reticulocytopenia and anemia following hypophysectomy are due to general metabolic derangements. The simplicity of reticulocyte stimulation

* This investigation was aided in part by a grant from the Penrose Fund of the American Philosophical Society.

may be due to their lability in rats, whereas a greater stability of hemoglobin and erythrocyte production may require a more specific stimulus for correction of the defects.

The results tend to indicate the lack of a specific hemopoietic hormone in the anterior hypophysis with a direct action upon the bone marrow.

The Cephalin-Cholesterol Flocculation Test As An Aid in the Diagnosis of Hepatic Disorders. By FREDERICK J. POHLE and JOHN K. STEWART (introduced by William S. Middleton), Madison, Wis.

Recent investigations by Hanger (J. Clin. Invest., 1939, 18, 261) indicate that emulsions prepared from sheep brain cephalin and cholesterol are flocculated by serum from patients with hepatic disorders. It was suggested that hepatogenous jaundice could be differentiated from obstructive jaundice by this serological reaction.

In the present study the cephalin-cholesterol flocculation test was performed on serum obtained from 352 normal individuals and 195 patients with suspected intrinsic liver disease. The results were compared with other tests including the icterus index, quantitative determination of the plasma prothrombin, hippuric acid synthesis test, fractionation of the serum proteins and studies on the urobilinogen excretion. Liver tissue obtained from 32 patients at operation or autopsy was examined histologically.

The cephalin-cholesterol flocculation test was negative in all except one of the 352 normal individuals studied. Eighty-eight of the 195 patients showed a flocculation reaction and in each instance clinical or laboratory studies or both confirmed the presence of damage to the liver parenchyma. In 2 patients the test was negative when other evidence indicated that hepatic involvement was present. The degree of flocculation paralleled the severity of the liver disturbance and in patients with hepatitis or cirrhosis of the liver repeated tests proved to be of prognostic significance.

The data indicate that the flocculation test is a more sensitive and accurate index of intrinsic liver disease than any of the so-called liver function tests. In the present study the flocculation test was of little or no value in differentiating obstructive from hepatogenous jaundice. The test was frequently positive in patients with proven biliary obstruction since secondary disturbances in the hepatic parenchyma were also present.

Experimental Production During Rebreathing of Sighing Respiration and Symptoms Resembling Those in Anxiety Attacks in Patients with Anxiety Neurosis. By STANLEY COBB and (by invitation) MANDEL E. COHEN, Boston, Mass.

Respiratory and circulatory studies have been made in 100 patients with anxiety neurosis. Anxiety neurosis is a disorder featuring attacks of choking, palpitations, trembling and fear. There is general irritability, avoidance of crowds and "sexual maladjustment."

It was noted, as others have previously stated, that there is a high incidence of sighing respiration (60 per cent) in these cases as compared with control subjects (10 per cent).

In testing the response of the patients (50 cases) to CO_2 and rebreathing (12 minutes), it was found that the number of sighs was greatly increased. This did not occur as frequently or to as great an extent in the control group. If sighing was not normally present, it did not usually appear as a response to CO_2.

A study was made of patients' feelings (25 cases). During the 12-minute period of rebreathing most of these stated that they experienced feelings and sensations resembling or identical with their *anxiety attacks.* In some cases the patient exhibited observable differences in behavior during rebreathing such as tearing off mouthpiece, clutching at throat, writhing and wringing hands.

Studies Pertaining to the Metabolism of Synovial Fluid Mucin. By MARIAN W. ROPES and WILLIAM v.B. ROBERTSON (by invitation) and WALTER BAUER, Boston, Mass.

Synovial fluid mucin is an easily dissociable protein-polysaccharide complex of remarkably constant composition and characteristics. Physically and enzymatically it is similar to the mucin of subcutaneous tissue. Therefore, the metabolism of mucin is important in the physiology not only of joints but also of connective tissue in general.

The modes of formation and destruction of mucin are not definitely known. Evidence to date indicates that it is formed by synovial tissue cells and carried into the joint by the plasma dialysate which forms the synovial fluid.

The difficulty in removal of globulins, which are smaller molecules than mucin, from normal joints, and the altered characteristics of mucin in pathological effusions, suggest that mucin is broken down prior to removal. Additional evidence has been obtained from studies of the glucosamine content of normal fluid and pathological effusions before and after precipitation of mucin.

Our studies have disclosed three types of agents which may play a rôle in the destruction of mucin and its polysaccharide—bacterial enzymes, phosphatase and ascorbic acid-peroxide.

Mucinase, an enzyme obtained from filtered cultures of Cl. perfringens and various other bacteria, depolymerizes mucin and partially hydrolyzes the polysaccharide. Attempts to demonstrate the presence of mucinase in normal joint fluid or in pathological effusions in which mucin had been partially destroyed have been unsuccessful.

Phosphatase also causes breakdown of synovial fluid mucin. The marked and unexplained variations in the concentration of phosphatase in joint fluid suggest that it may be one factor in the metabolism of mucin.

More pertinent physiologically is the destruction of mucin by vitamin C. We have shown that ascorbic acid-peroxide, an oxidation product intermediate between ascorbic acid and dehydroascorbic acid, causes depoly-

merization of mucin or its polysaccharide. Here, as in the case of the destruction of mucin in joint disease, glucosamine is not liberated. The action of ascorbic acid-peroxide is not limited to mucins of mesothelial origin but depolymerizes also epithelial mucins, starch, pectin, chondroitin sulfuric acid from cartilage and capsular polysaccharides of pneumococcus.

The possibility that ascorbic acid plays a rôle in the metabolism of mucin is supported by the abnormalities of vitamin C metabolism in rheumatoid arthritis. It has been shown that the level of vitamin C in the blood is reduced, and often can be raised to normal only by the administration of massive doses of ascorbic acid. Metabolic experiments in this laboratory indicate that a large part of the ingested ascorbic acid does not remain in the reduced form in patients with rheumatoid arthritis. We have, however, found no difference in the power of normal and rheumatoid serum or synovial fluid to oxidize ascorbic acid.

The depolymerizing activity of ascorbic acid-peroxide on synovial fluid and other connective tissue mucins, the abnormalities of vitamin C metabolism in rheumatoid arthritis and the marked involvement of mucin-containing tissues in this disease suggest that ascorbic acid plays a rôle in the mechanism of tissue changes in rheumatoid arthritis but in no way indicate an etiological relationship.

The Bactericidal Property of Blood in Gonococcal Infections. By HOWARD C. COGGESHALL, HELEN B. ARNOLD and L. DIENES (introduced by Charles L. Short), Boston, Mass.

Various investigators have used the bactericidal property of blood to measure immunological response. Recently, it has been employed in gonococcal infections, but the results are not conclusive because of the lack of control data. For evaluation of this test we selected 44 cases with uncomplicated and complicated gonococcal infections (11 acute urethritis, 9 prostatitis, 10 salpingitis, 2 epididymitis and 12 arthritis). Fifty-three tests were made on these cases and were controlled by 150 tests on 43 normals. Gonococcal complement fixation was determined on all bloods.

The method was similar to that employed by Todd, Ward, Robertson and Keefer. Most tests were made with a strain isolated from an acute case of urethritis. However, a total of 13 strains isolated from other sources was tested.

Blood obtained from controls exerted in most instances a marked bactericidal effect which varied from 0 to 1,000,000 organisms killed, the median being 10,000. Uncomplicated cases of gonorrhea showed the same range and distribution of blood bactericidal activity. However, complicated cases showed a slight increase in the average bactericidal titer, the median being 100,000. Results from any given case were not significant because of the wide variations observed in both normal and infected cases.

Comparison of 13 strains of gonococci showed definite variations in resistance to the bactericidal activity of blood. Strains resistant to normal blood tended to be equally resistant to blood obtained from the patients studied. Since the bactericidal property of blood from patients with gonorrhea or one of its complications is not increased strongly and regularly, even after the gonococcal fixation test becomes positive and does not differ significantly from that of controls, it would seem that this test in its present form is not an adequate measure of the immunological response to gonococcal infections.

The Passage of Thiocyanate and Glucose from the Blood Stream into the Joint Spaces. By J. WALLACE ZELLER and E. G. L. BYWATERS (introduced by Granville A. Bennett), Boston, Mass.

In order to obtain further information concerning the physiology of articular structures, the permeability of the synovial tissues to the crystalloids, NaCNS, and glucose was studied in normal calves. Thiocyanate was detectable in the synovial fluid nine minutes after intravenous injection. Fairly constant serum CNS levels were reached within one hour, but the time required for attaining equilibrium between the serum and the synovial fluid varied from one to six hours. At equilibrium the CNS in serum averaged 9 per cent higher than in synovial fluid. The CNS content of aqueous humor was about one-third that of synovial fluid, and only traces were present in the cistern fluid. The CNS concentrations in these three body fluids and in the serum roughly paralleled the protein concentrations. A similar relationship between CNS and protein concentrations of serum and transudates has been observed in patients with edema. Our results confirm the suggestion that some of the CNS is held in the serum in a non-diffusible state.

Glucose entered the joint space more slowly, appearing about twenty minutes after intravenous injection. The blood sugar returned to the pre-injection level in approximately two hours. When the blood sugar was falling, the rate of utilization of glucose by the articular tissues and the rate of diffusion from the joint space into the synovial capillaries were not sufficiently rapid to keep the synovial fluid sugar level at or below that of the serum. Similar relationships between blood and pleural transudates in diabetic patients with cardiac failure have been described.

The experiments show that substances of small molecular size diffuse readily into the joint spaces. With respect to CNS and glucose, the equilibrium between serum and normal synovial fluid resembles the equilibrium between serum and transudates in patients with edema. This similarity offers further indication that synovial fluid is tissue fluid.

The Treatment of Hypogonadism. By W. O. THOMPSON and (by invitation) N. J. HECKEL and S. G. TAYLOR, III, Chicago, Ill.

The following aspects of the treatment of hypogonadism are of special interest:

1. *Factors limiting response to glandular treatment.* The response to treatment is determined by the stimulat-

ing agent and the capacity of the organs stimulated to respond. Striking growth of the genitalia, other secondary sexual characteristics, and the skeleton may be induced by some gonadotropic materials and sex hormones, but the response appears to be modified greatly by the age at which the stimulus is applied. For example, at any age from birth to puberty the penis may be made to grow to adult proportions (but not larger) by administration of the gonadotropic material from the urine of pregnant women. After puberty striking growth may be induced only if the penis is very small, but the growth never appears to equal the normal. The growth of body hair roughly parallels that of the penis. A similar state of affairs obtains in the treatment of young boys and of adults of the eunuch and eunuchoid types with male sex hormone (testosterone propionate). The response of the genitalia and other secondary sexual characteristics in the female with primary hypogonadism to treatment with estrogenic materials, including stilboestrol, bears a similar relationship to the age of the patient.

There appears to be an optimum time for induction of genital growth and the changes associated with it and this time is apparently the period during which they normally occur.

2. *Hormonal factors influencing the growth of the prostate in man.* The following observations in man support the hypothesis that the growth of the prostate is dependent upon the production of male sex hormone:

(*a*) In young boys showing marked genital growth during the administration of gonadotropic principles or male sex hormone, and in adult eunuch and eunuchoid individuals showing similar changes during the administration of male sex hormone, the prostate which is commonly not palpable before treatment may assume the proportions seen in the normal adult.

(*b*) The prostate regresses in size when such treatment is omitted.

(*c*) The prostate normally enlarges at the time of puberty in association with a marked increase in the production of male sex hormone.

These observations would appear to contraindicate the treatment of benign prostatic hypertrophy with testosterone propionate.

In elderly men with waning sexual function, who experience marked improvement during the administration of testosterone propionate, the size of the prostate should be checked frequently.

The Destruction of Thiamin by Unacidified Bile and Pancreatic Juice. A Possible Explanation of the Cord Changes in Pernicious Anemia. By HENRY FIELD, JR. and (by invitation) WILLIAM D. ROBINSON and DANIEL MELNICK, Ann Arbor, Mich.

Degenerative changes in the spinal cord, more or less simulating those of pernicious anemia, have been observed in beriberi, pellagra and experimental deficiencies of vitamins A, B, and some unidentified factor in the B_2 complex. A deficiency in intake of these vitamins in pernicious anemia has not been demonstrated but a deficiency might be conditioned by the pathological physiology of the disease.

We have found that patients receiving intensive alkali therapy for peptic ulcer and those with achlorhydria have subnormal urinary excretions of thiamin. There is no significant destruction of thiamin when it is incubated with achlorhydric gastric juice. As much as 56 per cent of thiamin is destroyed when it is incubated with human bile or pancreatic juice at their natural pH. A relatively small destruction occurs when thiamin is incubated with bile or pancreatic juice adjusted to the pH commonly found in the intestinal tract.

The patient with achlorhydria will develop a thiamin deficiency unless he takes in more of it than will protect a normal individual. A chronic, variable thiamin deficiency over many years may explain the cord changes of pernicious anemia. It is possible that the abnormal physiology of this disease may effect the utilization of other vitamins.

Chloride Excretion in Experimental Diabetes Insipidus. By E. HENRY KEUTMANN and ROWLAND T. BELLOWS (introduced by S. L. Warren), Rochester, N. Y.

Chloride and water excretions were studied in dogs with diabetes insipidus. The disease was produced by cauterization of the supra-optic nuclei. The rate of glomerular filtration was calculated by means of creatinine clearances.

The response to the intravenous injection of various concentrations of salt solution was studied. Before operation the maximum ratio of $\frac{\text{Cl. in urine}}{\text{Cl. in serum}}$ obtained when 5 per cent sodium chloride solution was injected was 2.36. After operation the maximum of this ratio obtained with identical procedure was 0.59. The clearance of chloride was also reduced.

Similar differences before and after operation were found when less concentrated salt solutions were used.

When pitressin was administered to animals with diabetes insipidus, there was an immediate and marked increase of the ratio $\frac{\text{Cl. in urine}}{\text{Cl. in serum}}$ and an immediate increase in the clearance of chloride.

After operation the rate of glomerular filtration decreased. When pitressin was administered, there was no immediate increase of glomerular filtration while the chloride concentration and excretion increased. It is thought that the changes in chloride excretion can best be explained by increased reabsorption of chloride after the production of diabetes insipidus.

Observations on Resistance of Pneumococci to Sulfapyridine and Sulfathiazole. By FRANCIS C. LOWELL and ELIAS STRAUSS (by invitation) and MAXWELL FINLAND, Boston, Mass.

The susceptibility of different strains of pneumococci to the action of these drugs was found to exhibit considerable variations. These variations in susceptibility

were observed in different laboratory strains, in strains isolated from different patients and in strains obtained from the same patient at different times in the course of treatment.

Susceptible strains were made resistant by various *in vitro* procedures. Different strains varied in the ease with which they acquired resistance.

When strains that were originally susceptible to the action of both sulfapyridine and sulfathiazole were made resistant to the action of either one of these chemicals they also acquired resistance to the other.

The Positive Conditional Salivary Reflexes in Psychoneurotic Patients. By GEORGE F. SUTHERLAND (by invitation), JACOB E. FINESINGER and (by invitation) FRANCIS MCGUIRE, Boston, Mass.

This study deals with variations found in the positive salivary reflex in eighteen psychoneurotic patients.

1. The magnitude of the response varied from day to day, even from combination to combination.
2. The greatest response usually occurred in the second combination of the day.
3. A metronome stimulus elicited greater response than did a 100-watt light stimulus.
4. A correlation existed between the emotional state, as determined by an interview, and the reflex status. Some patients developed progressive inhibitory states characterized by (*1*) a diminution in response, (*2*) equalization of response to auditory and visual stimuli, (*3*) paradoxical reaction, (*4*) ultra-paradoxical reaction, and (*5*) temporary inhibition of the reflex.

The Occurrence of Methemoglobinemia During Therapy with Sulfapyridine, Sulfathiazole, and Sulfamethylthiazole: Formation of Methemoglobin in Vitro. By CHARLES L. FOX, JR. and BRUCE HOGG (by invitation) and REUBEN OTTENBERG, New York, N. Y.

The blood of patients receiving sulfanilamide has been shown to contain methemoglobin and an additional pigment. Patients receiving sulfapyridine, sulfathiazole, and sulfamethylthiazole do not appear as deeply cyanotic as patients receiving sulfanilamide. Like sulfanilamide, these three drugs do not produce methemoglobin *in vitro*. Photo-oxidized sulfanilamide has, however, been shown to produce methemoglobin *in vitro*. In seeking to explain the mechanism of anti-bacterial action of these drugs, it seemed important to ascertain whether methemoglobinemia accompanies therapy and, if possible, to reproduce this *in vitro*.

Curves drawn by the Hardy recording spectrophotometer, and the change in optical density at λ 630 mμ after addition of cyanide, clearly demonstrated methemoglobinemia during therapy with these three drugs.

In vitro, no methemoglobin was formed by any of the drugs. After oxidation of these drugs by irradiation with ultraviolet light, the resulting faintly yellow solutions all produced methemoglobin.

Complete absorption curves were also obtained on mixtures of hemoglobin and solutions of the photo-oxidized drugs. As in the case of sulfanilamide, analysis of these curves and those of patients' blood demonstrated, in addition to the methemoglobin produced, a third unidentified pigment with maximum absorption in the red end of the spectrum.

The data show that therapy with these drugs is accompanied by methemoglobinemia. The *in vitro* formation of methemoglobin only by oxidized forms of these drugs suggests that the methemoglobinemia occurring during therapy results from oxidation of the drugs used.

Studies of Homogentisic Acid Production in a Case of Alkaptonuria. By J. MURRAY STEELE and (by invitation) KONRAD DOBRINER and MORTON GALDSTON, New York, N. Y.

The study concerns the effect of feeding various amounts of protein and certain vitamins and of injecting *d*- and *l*-phenylalanine upon homogentisic acid production in a 56-year-old man.

On a protein diet averaging 130 grams daily he excreted 7.8 grams of homogentisic acid in 24 hours; on a 60 gram diet, 3.6 grams; and on a 30 gram diet, 1.8 grams of homogentisic acid. On the high protein diet neither daily injections of crude liver extract nor campolon had any effect within a period of 6 days. Nicotinic acid, thiamine chloride, riboflavin and other vitamin studies are under way. Nicotinic acid in 1 gram doses daily is without effect upon the homogentisic acid excretion.

After 7 days' observation on the low protein diet, 4 grams of *d*-phenylalanine were injected intravenously. During this 24-hour period the homogentisic acid excreted rose from an average of 1.8 to 3.4 grams, and the urinary carboxyl carbon from 47.4 to 129.3 mgm. Four days later 4 grams of *l*-phenylalanine were injected and the homogentisic acid excreted rose from 1.8 grams to 5.6 grams while the urinary carboxyl carbon did not rise significantly. Of the *d*-phenylalanine injected only 40 per cent was converted into homogentisic acid; while of the *l*-phenylalanine, 95 per cent was converted. If the rise in urinary carboxyl carbon is calculated as phenylalanine, then of the *d*-phenylalanine injected, 28 per cent was excreted as amino acid, while of the *l*-phenylalanine, there was none or only a trace.

Pregnancy in Relation to Rheumatic Fever and Rheumatic Heart Disease. By BERNARD J. WALSH (by invitation) and EDWARD F. BLAND and T. DUCKETT JONES, Boston, Mass.

The continued follow-up of a large number of patients who have received care at the House of the Good Samaritan because of rheumatic fever has provided data pertaining to pregnancy and its influence on this group. These data are of particular interest because they include observations made for considerable periods both before and after pregnancy.

The material consists of 264 births occurring in 153 women, or 1.7 living children per patient. An additional 34 births took place prior to the seventh month of pregnancy. The mean age for the group at their initial

pregnancy was 21½ years. Rheumatic heart disease was present in 60 per cent.

In only 13 instances (5 per cent of the total live births) did events occur in relation to pregnancy that might be considered as evidence of active rheumatic fever. These events may be divided into three groups:

1. Frank rheumatic fever with joint pain and swelling; 4 patients.
2. Development of congestive failure during the eighth and ninth months of pregnancy; 5 instances in 4 patients.
3. The development of congestive failure after pregnancy; 4 patients.

In ascribing the congestive failure that appeared in those of Groups 2 and 3 to rheumatic fever, we affirm our belief that the occurrence of congestive failure in adolescent or young adult patients with rheumatic heart disease is by and large an indication of active rheumatic fever. However, cardiac failure becoming manifest during the last trimester of pregnancy renders this likely rôle of active rheumatic fever a more uncertain one. Conversely, the development of congestive failure in the postpartum period, a time when blood volume, blood flow, and the cardiac output have returned to normal, makes active rheumatic fever a likely causative agent in the production of the congestive failure.

Excepting the cases previously mentioned, there has been no detectable progress in cardiac disease that could be related to pregnancy.