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READ BEFORE THE SCIENTIFIC SESSION

PRESIDENTIAL ADDRESS

BIOLOGICAL BEACHHEADS

BY THOMAS FRANCIS, JR.

In the past year a group of nations of divergent ideologies, through coordinated and exhausting effort, has succeeded in applying control measures to a disease which had been increasing in scope and virulence so as to reach epidemic proportions in the world politic. A few experienced political epidemiologists had recognized the danger early and pointed out the threat, but the majority relied upon our isolation and quarantine regulations to meet it. Various placebos were tried. It was not, however, until an open focus appeared on our own flank that we really rose to action. The emergency demanded highly concentrated authority, enormous expenditures and the drafting of men from all activities into one great effort. By amazing combinations of land, sea and air power, beachheads were established and a *cordon sanitaire* formed. From these points the further advances were made which finally disrupted the essential reservoirs to a point of ineffectiveness, and the epidemic subsided.

Like all other epidemic diseases, however, it survives in foci to which must be applied all conceivable specific and environmental control measures in order to prevent a resurgence. This is the foremost problem of the day and, unless effectively approached, reduces our other hopes for advancement to sheer vapor.

No people can pass through such experiences without receiving a deep imprint upon its philosophy. The influence extends beyond the social and political fields, hence, it is not surprising that the patterns which were developed under military exigencies should be proposed as those which would function effectively in the establishment of biological beachheads.

The trends are seen in the current discussions of national legislation in support of research. One group has urged action similar to the methods used in the atomic bomb research project. It apparently visualizes a higher echelon of master minds which plans, organizes and directs—busily splitting its mental 235 in an effort to set up a chain reaction in the low grade cerebral pitchblende of a large body of workers. Research workers are human tools—the important thing is to know what job they are good for and how to use them. The impression is promoted that the mass attack will settle problems of disease quickly and finally. Another proposal accepts the desirability of increased funds for scientific endeavor from federal appropriations to be distributed by a body of scientists with a minimum of governmental direction—but nonetheless an organization administered through the federal government.

There is general agreement that it is highly desirable to encourage more men of ability to enter the different fields of scientific investigation. Moreover, if these men can develop sufficient common interest to study certain problems with different disciplines and different points of view, to share experiences and trade ideas, it is clearly advantageous. The past five years have furnished numerous examples of men giving up their individual preferences to join in a coordinated effort designed to test a lead or to give their abilities to continued, tedious studies, even though disagreeing with the major plan. Furthermore, in most problems a stage is reached where it is profitable and strategic to concentrate upon an organized study which can test under controlled conditions the validity and applicability of experimental observations. This quantitative approach would seem to be most useful when the stage of application is reached. But whether the concept of coordinated study can be expanded indefinitely is open to considerable doubt.

Disease is a complex biological problem and while much has been learned concerning certain mechanisms at play and the reagents involved, I believe it is fair to say that the intimate details of but few of them are really known. Nor, with possibly a few exceptions, is it clear how a clinical case of disease actually begins. While we have reached the atomic age in the physical sciences, biologically we are still in the molecular stage. Experimental work is primarily qualitative in its approach. It constitutes the advance intelligence, the scientific G–2, seeking to gather data on which biological beachheads can be established. It requires judgment in evaluating and correlating small bits of information and in deciding which areas are most vulnerable to attack. It must not allow rumor in the form of uncontrolled observations, or premature interpretation to be mistaken for fact. "The experimental method," said Claude Bernard, "is the scientific method which proclaims freedom of mind and of thought." It does not submit to authority, but draws from within itself an impersonal authority which dominates science. Original thinking and observation do not derive from conformity with accepted opinion.

How best can a national research foundation serve to promote these ends and at the same time preserve spontaneity and freedom of action? Certainly, not through another atomic bomb project. Perhaps the greatest reservations concerning the desirability of a national agency lie in skepticism as to the spirit in which it will function. Administrative principles of a large organization tend to be founded on orthodoxy. There should be as little display of central authority and direction as

can possibly be got along with. Care should be taken to avoid the setting up of favored programs of research to the exclusion or disadvantage of other less prominent fields of activity; this procedure could lead to lobbying and pressure groups who would work to promote special interests. Moreover, programs incline inevitably to seek the application. One might, with a certain sincerity, suggest the motto "A pogrom on programs." The current tendency to give support only to well defined projects should be minimized, and encouragement given both to extended work in a broad field which offers many opportunities, and to dabbling in a narrow field where the next move is obscure. Gilding of the lily should not become the major scientific objective; the simplicity of observation should not give way to the glamorous phrase; the seat of influence must not replace the work bench in determining the direction of investigation. A national foundation must be free of political domination by either the professional or the scientific politician. If undertaken it must be inaugurated on a sufficiently sympathetic basis that it shall not have to justify itself in terms of the first few years' results, nor concern itself too greatly with detailed evaluations of the progress which is being made. The concept which flows through the Bush report of general research funds largely administered through university channels to meet their own needs, and to take advantage of their own resources, seems of all the most desirable, because it returns the opportunity and the responsibility for initiation and support of research to its proper place. Moreover, it would probably result in a great reduction in incidence of that occupational disease of the experimentalist, a divergent strabismus developed from trying to keep one eye on his work and the other on the source of funds.

There is a need to increase the positions and the environments in which men can work continuously upon problems in which they themselves are interested. The current system contrives to drive men from research since the positions to which they can advance furnish frustration rather than fruition of their research interests. The generation of ideas and new information should constitute sufficient warrant for their support without detailed pleading before a dispensing board.

There is a need to promote the investigation of disease as a broad problem in biology. Too often the preclinical years of the medical curriculum are urged to emphasize clinical application rather than biological implications. Greater latitude for thought and work in these latter channels will undoubtedly extend the boundaries of clinical investigation.

There is little doubt that if more men who could be interested in the investigation of disease problems were found, given the opportunity to develop, provided facilities and *time*—for thought and work, afforded reasonable incomes and opportunity to advance, all in an atmosphere of scientific freedom, progress in medicine might well be more rapid. This is the manner in which increased funds can be most effectively employed.

In the original formation of a federal organization for the support of scientific research, which now seems imminent, it will be the responsibility of members of this and other research societies to see that the personnel and the philosophy upon which they act are truly representative of the best scientific thought. Otherwise it is we, not they, who will have lost the beachhead. Failure will not only be harmful to *research,* but will destroy a great opportunity science has had to project the honesty and objectivity of the scientific outlook into a world of social confusions and warped emotions.

A Comparison Between Infectious Hepatitis and Serum Jaundice in Experimentally Infected Human Volunteers. By W. PAUL HAVENS, JR., New Haven, Conn.

Although the exact relationship between *infectious hepatitis* and *homologous serum jaundice* is not understood, experiments in the transmission of these two conditions to human volunteers have revealed certain information which assists in making a distinction between them.

The causative viruses of both diseases are filtrable, resistant to a temperature of 56° C. for 30 minutes, and may be transmitted to human volunteers in serial passage, producing a clinical disease in man which resembles catarrhal jaundice.

In contrast to these similarities are certain differences which include route of infection, length of incubation period, and period of infectivity.

Our strain of *infectious hepatitis* virus produces disease in human volunteers following parenteral inoculation or ingestion, with incubation periods ranging from 15 to 34 days. Virus is demonstrable in both blood and stool during the acute phase but not in the incubation or convalescent periods. Homologous immunity is present in these patients.

Our strain of *homologous serum jaundice* is infectious when inoculated parenterally with incubation periods ranging from 56 to 134 days. It is demonstrable in the blood of inoculated subjects one-third and three-fourths way through the long incubation period and during the acute phase of disease, but not 1 month after onset. Apparently it is not present in the stool of patients, nor is it infectious when ingested. Patients convalescent 6 months from infection with this strain are not immune to experimental infection with our strain of *infectious hepatitis* virus.

A Study of the Urinary Coproporphyrin in Hepatitis and Cirrhosis. By C. J. WATSON, Minneapolis, Minn.

In this study the total coproporphyrin in the 24-hour urine was determined in 154 cases. This series included 60 cases of infectious hepatitis; 45 cases of cirrhosis of the liver of various types; 17 cases of jaundice due to extrahepatic biliary obstruction; 1 case of carbon tetrachloride poisoning with jaundice; 1 case of jaundice due to sulfanilamide. The relative percentage of the type 1 and 3 coproporphyrin isomers was determined by means of differential precipitation of the esters in 30 per cent acetone, as described by Schwartz, Hawkinson, and Watson. Normal human urine has been found to contain from 65 to 90 per cent of the type 1 isomer. The normal range for the total coproporphyrin in 24 hours

is from 30 to 100 gamma, most often from 40 to 80 gamma.

The present study permits the following conclusions:

1. The urinary coproporphyrin is commonly elevated in acute hepatitis. The elevated values persist well into the defervescent period and in many instances, for some time after other liver function tests have returned to normal or near normal range. The increase in all instances thus far studied has been due to an increase in the type 1 isomer. One possible exception has been encountered in a case of sporadic jaundice in an individual who was a moderate alcoholic and who had been exposed to other chemicals. In this case, 90 per cent of the coproporphyrin in the urine was the type 3 isomer. In the case of jaundice due to carbon tetrachloride poisoning and to sulfanilamide, the increase of coproporphyrin was the type 3 isomer.

2. The total coproporphyrin of the urine is often increased in cases of cirrhosis of the liver, markedly elevated values being noted in some cases. Elevations of the same magnitude are commonly encountered in jaundice due to extrahepatic biliary obstruction. Thus, the determination of the total coproporphyrin has but slight value in the differential diagnosis of jaundice. Of chief interest, however, is the finding that in the majority of cases of cirrhosis in alcoholics, the elevated coproporphyrin value is due to increase of the type 3 isomer while in the remainder, including the cases following infectious hepatitis, the increase has always been of the type 1 isomer.

The Mechanisms of the Liver and Kidney Injury Produced by Toxic Substances. I. Some Effects of Pyridine and Their Prevention by Methionine. By JAMES H. BAXTER (introduced by Tinsley R. Harrison), Dallas, Texas.

Experimental liver and kidney injury including cirrhosis have been produced in two general ways: by administration of toxic substances and by feeding diets deficient in lipotropic substances. This investigation deals with the relationship between the processes which follow.

When pyridine was added to an otherwise adequate diet and fed to young rats, weight gain ceased and death occurred in about a week. Livers and kidneys showed extensive degenerative changes. Animals surviving for longer periods developed cirrhosis.

The addition of methionine to the diet prevented these effects to a considerable extent.

Pyridine was used in these experiments because it is methylated in the animal body (at least in dog and man), probably at the expense of lipotropic substances which act as methyl donors.

There is also evidence that a number of other hepatoxic and nephrotoxic substances may be methylated in the body, and still others may act by interfering with the action of lipotropic substances, perhaps by inhibition of enzyme systems.

Action of pyridine through other mechanisms which are influenced by certain substances containing sulfhydryl groups may be at least partially responsible for the effects observed.

If the liver and kidney damage produced by pyridine (and perhaps these other substances) prove to be due to this exhaustion of lipotropic factors, thus producing the same effect as a deficient intake of lipotropic substances, then, at least in some cases, "toxic" cirrhosis and "deficiency" cirrhosis may be fundamentally related.*

The effects of feeding methyl pyridinium hydroxide have been compared with the effects of feeding pyridine in stoichiometric amounts. If the toxic effects of pyridine are due to its methylation with exhaustion of lipotropic substances, then methyl pyridinium hydroxide which is formed by the methylation of pyridine would not be expected to produce these effects. Young rats continued to grow (though at a somewhat slower rate than normal) without apparent illness and without demonstrable lesions at autopsy, when given diets containing methyl pyridinium chloride equivalent on a stoichiometric basis to twice the concentration of pyridine necessary to produce death with extensive degenerative changes in the livers and kidneys.

Attempts to isolate methyl pyridinium hydroxide from the urine of rats fed pyridine are in progress, but so far have not been accomplished with certainty.

It should be emphasized that it is not intended to suggest that all the toxic effects of pyridine are due to the mechanism described, but only the liver and kidney injury and possible injury to certain other organs that have not been extensively studied. It is interesting that while pyridine produces depression of the nervous system and anesthesia, methyl pyridinium hydroxide in large doses is a convulsant. It is also interesting that when given intraperitoneally in mice, the M. L. D. of methyl pyridinium chloride is about 0.22 mgm. per gram, while the M. L. D. of pyridine is about 1.2 mgm. per gram or about eight times as much on a stoichiometric basis, despite the fact that the chronic toxicity of pyridine on oral administration is much greater than that of the methyl derivative.

Other toxic substances that might act through a similar mechanism will be investigated. Preliminary experiments indicate that cystine affords considerable protection against pyridine, but less than methionine. Choline alone has little or no protective effect, but choline plus cystine is more effective than cystine alone, and even more effective than methionine. Thioglycollate is ineffective while thiouracil gives marked protection.

The Coagulation Properties of Normal and Hemophilic Whole Blood, Plasma, and Plasma Protein Fractions. By JESSICA H. LEWIS (by invitation), GEORGE R. MINOT, J. P. SOULIER (by invitation), H. J. TAGNON, C. S. DAVIDSON, and F. H. L. TAYLOR (by invitation), Boston, Mass.

Normal and hemophilic whole blood, plasma and plasma protein fractions were studied *in vitro* and *in vivo*. The

*Explanatory Note: These studies are being extended in collaboration with Dr. Morton F. Mason.

prothrombin and fibrinogen content were found to be the same. The protease activity after treatment with chloroform, as measured by the nonprotein nitrogen production from a casein substrate and by lysis of a fibrin clot, was found to be similar in both hemophilic and normal plasma and globulin fractions. The electrophoretic pattern of hemophilic plasma did not differ measurably from normal plasma.

Shortening of the coagulation time of blood from patients with hemophilia was produced *in vitro* by the addition of small amounts of normal blood, plasma and certain globulin fractions; notably Fractions I, II + III, and IV_1 of Cohn. Fractions IV, 3 + 4 and V (albumin) had no effect. Globulin fractions prepared in a similar fashion from pooled hemophilic plasma had no *in vitro* shortening effect upon the coagulation time of hemophilic blood.

Transfusions of normal blood, plasma or Fraction I markedly shortened the coagulation time of hemophilic patients. Transfusions of similar amounts of hemophilic whole blood, plasma or Fraction I, derived from pooled hemophilic plasma, did not shorten the clotting time in hemophilia.

Thus, the difference in coagulation properties between hemophilic and normal blood was found not in the prothrombin, fibrinogen or protease activity, but in the fact that globulin derivatives of normal plasma have antihemophilic activity, while those derivatives from hemophilic plasma have no such activity.

Role of Synthetic Folic Acid in Blood Maturation. By Tom D. Spies, Birmingham, Ala.

Our studies have shown that synthetic folic acid has a profound effect on the bone marrow of persons with Addisonian pernicious anemia, sprue, and related anemias. These investigations have been conducted in selected persons after complete history, physical examination, peripheral blood and bone marrow studies.

In selecting the cases, the following criteria were used: (*1*) The patient must have a macrocytic anemia with red blood cell counts of 2.5 million or less and a color index of over 1. (*2*) He must be untreated, or he must not have been treated recently enough to interfere in any way with our evaluation of the effect of folic acid. (*3*) He must not have any complicating disease which might be lethal during the course of the study. (*4*) The bone marrow must contain megaloblasts and have the typical erythroblastic arrest seen in macrocytic anemia. A fifth criterion used for the selection of any patient in Cuba, where we were studying sprue, was that he must have "fatty stools" and weight loss.

After the subjects were selected, they were placed on a control diet free of meat, meat products, fish, and poultry, and baseline determinations of blood values were made. Without any other alteration of the baseline conditions, synthetic folic acid was given either parenterally or orally in amounts ranging from 1 mgm. per day to 500 mgm. per day. Great clinical improvement usually begins around the third or fourth day, and this is corroborated by laboratory studies. The person feels stronger and develops an appetite, and the reticulocytes increase in the peripheral blood and in the bone marrow. Within two weeks the white blood cells, the red blood cells, and the platelets all increase in the peripheral blood, and the bone marrow tends to revert to normal. These findings, the dosages, the best methods of administration, and the mechanisms concerned will be discussed in detail.

Further Observations on the Anti-Pernicious Anemia Effect of Synthetic L. Casei Factor. By Carl V. Moore and (by invitation) Olga S. Bierbaum, St. Louis, Mo.

The following observations have been made on the therapeutic effectiveness and mode of action of synthetic *L. casei* factor in Addisonian pernicious anemia.

1. Maximal or near-maximal reticulocyte responses have been obtained with daily doses as small as 1 mgm. given parenterally, and 3 mgms. given orally. These quantities do not regularly produce comparable responses, however, and there apparently is significant variation in minimal effective dose to which different patients will react.

2. *L. casei* factor can be absorbed from the rectum. When 100 mgm. were given daily as a retention enema to one patient, a nearly maximal reticulocytosis resulted.

3. Simultaneous administration of normal human gastric juice did not enhance the anti-anemic effectiveness of *L. casei* factor in one subject. This supports published evidence that the vitamin does not possess extrinsic factor activity.

4. Hematologic and clinical remissions, initially induced by *L. casei* factor, have been maintained for 6 months in 3 patients by the weekly injection of 140 mgm. of the synthetic material.

5. Hematologic and clinical remissions have been maintained for 6 months in 25 subjects, who formerly had been treated with liver extracts, by parenteral administration of 25 to 75 mgm., *L. casei* factor.

6. Manifestations of combined system disease have become worse in only one patient, and in this instance the change followed the development of cellulitis.

Studies on the Effect of Methyl Bis (β chloroethyl) amine hydrochloride on Diseases of the Hemopoietic System.* By Leon O. Jacobson and (by invitation) Charles L. Spurr, E. S. Guzman Barron, Taylor R. Smith, Clarence Lushbaugh and George F. Dick, Chicago, Ill.

The therapeutic efficacy of intravenous injections of methyl bis (β chloroethyl) amine hydrochloride (Dema) in the treatment of certain diseases of the hemopoietic system has been studied. The diseases each of which

* Abbreviated to "Dema" for purposes of brevity.

were confirmed by biopsy or sternal aspiration include:

Diagnosis	*Number of patients*
Hodgkin's Disease	25
Lymphosarcoma	6
Sympathicoblastoma	2
Multiple myeloma	2
Myelogenous leukemia	
Acute	1
Chronic	6
Polycythemia rubra vera	3
Lymphatic leukemia	
Acute	1
Chronic	7

The dose of Dema used in this series of cases was 0.1 mgm. per kilogram of body weight and was given in courses of 1 to 7 daily injections. Ten mgm. of Dema were dissolved in 10 ml. of 0.9 per cent NaCl immediately before use and the calculated amount injected directly through the rubber tubing of a Fenwal intravenous medication set which was already delivering normal saline to the subject at a relatively rapid rate.

A delayed but extremely serious toxic manifestation is the lymphopenia, neutropenia and thrombocytopenia which develops and reaches a maximum within the first three weeks. The changes occurring in the peripheral blood are paralleled in the bone marrow. Sternal punctures indicate that an extreme degree of destruction may occur. Recovery, however, is complete after varying intervals.

The period of observation of the patients after single or repeated courses of Dema varies from 1 to 28 months. In all cases so treated except for the cases of acute leukemia, multiple myeloma and one case of lymphosarcoma, definite clinical remissions of the disease process involved were produced varying in duration from 1 to 8 months. The most encouraging results have been seen in Hodgkin's disease; symptoms were quickly alleviated and evidence of lymphadenopathy, splenomegaly and hepatomegaly regresses remarkably. Roentgenographic evidence of mediastinal enlargement and involvement of the parenchyma and hilum of the lung showed similar regression. Repeated courses of treatment with Dema have produced further remissions.

Superiority of this type of treatment over that of X-ray therapy is *not claimed* but cases with apparent X-ray resistance have responded favorably. Dema or a related compound may prove to be a useful adjunct to X-ray therapy.

The Treatment of Arsenic and Mercury Poisoning with BAL (2,3-dimercaptopropanol). By JOHN A. LUETSCHER, JR., and WARFIELD T. LONGCOPE, Baltimore, Md.

Thirty cases of arsenical intoxication have been treated with BAL. Dermatitis has been the commonest form of intoxication, and has responded to the inunction or injection of BAL. A few cases of hepatitis and of blood dyscrasias have been treated with less obvious benefit. No deaths occurred among these patients. The urinary excretion of arsenic has been followed in 17 patients receiving BAL. An increased excretion of arsenic regularly followed BAL treatment of arsenical dermatitis, and reappeared on repeated courses of treatment. The increase of urinary arsenic coincided with the appearance in the urine of a substance with chemical characteristics resembling BAL. The arsenic excretion in hepatitis was not regularly affected by injections of BAL.

Forty-one cases of mercury poisoning have been treated with BAL. Two patients, treated 5 and 14 hours after poisoning, died. No deaths have occurred when BAL was given within 4 hours of ingestion of mercury, regardless of the amount of poison. In a control series, a dose of less than 1 gram of mercuric chloride caused no deaths, but there were 27 deaths among 86 patients who took 1 gram or more. There have been no deaths in a comparable group of 25 patients who took 1 gram or more of mercuric chloride but who were treated with full doses of BAL within 4 hours.

Combined Quinine-Plasmochin Treatment of Vivax Malaria: Effect of Relapse Rate. By HARRY MOST, CHARLES A. KANE, IRVING M. LONDON, and EDMUND F. SCHROEDER (by invitation), and PAUL H. LAVIETES, Swannanoa, N. C.

Quinine sulphate 1.0 gram and plasmochin naphthoate 0.02 gram simultaneously at 8-hour intervals for one day followed by quinine grams 0.65 and plasmochin naphthoate 0.02 simultaneously at 8-hour intervals for the next 13 consecutive days were administered to 72 white patients with acute attacks of vivax malaria of Pacific origin who were followed for at least 120 days after treatment.

The clinical relapse rate and total failure rate during 120 days observation was 4 per cent and 11.1 per cent respectively, following the above course of treatment. This is in sharp contrast to clinical relapse rates of 75 to 85 per cent and total failure rates of 85 to 90 per cent based on similar observations after treatment of more than 500 patients for acute attacks of vivax malaria of Pacific origin with quinine, quinacrine or other antimalarial drugs.

Combined quinine-plasmochine treatment resulted in apparent cure in 90 per cent of patients as judged by the occurrence of clinical relapse or appearance of parasites without fever or symptoms during a period of 120 days after treatment. Using the same criteria only 10 to 15 per cent of cures follow treatment with quinine, quinacrine or other antimalarial drugs currently in use.

No conspicuous or serious toxic manifestations were observed in 100 white patients who received combined quinine-plasmochin therapy for 14 consecutive days.

A Study of the Prophylactic Effect of Several 8-Amino Quinolines Including Plasmochin for South Pacific (Chesson) Vivax Malaria. By ALF S. ALVING and (by invitation) LILLIAN EICHELBERGER, BRANCH CRAIGE, JR., RALPH JONES, JR., THEODORE N. PULLMAN, and C. MERRILL WHORTON, Chicago, Ill.

James, in 1931, demonstrated that plasmochin in doses of 80 mgm. a day for 3 days, followed by 60 mgm. a day

for 5 days, starting the day before sporozoite inoculation, protected volunteers against *Plasmodium vivax* (Rumanian) infections. Feldman, *et al,* obtained only partial prophylaxis in *Plasmodium vivax* (McCoy) infections on the same regime.

In order to ascertain (*1*) whether plasmochin is an effective prophylactic drug against South Pacific (Chesson) strain of *Plasmodium vivax,* and (*2*) whether the prophylactic effect of plasmochin is a unique property of that drug or is shared by related compounds, four 8-amino quinolines, including plasmochin, were similarly tested on inmate volunteers at Stateville Penitentiary. Plasmochin was administered in daily doses of 90 mgm. (free base). The other drugs, SN-1452, SN-11,191, SN-13,276, were given at or near the maximum tolerated dose. Of 11 volunteers, 6 have been protected against infection by plasmochin, SN-1452, or SN-11,191 for 13 months. SN-13,276 has protected 9 out of 10 volunteers treated, the longest period of observation being 5 months. Several of the patients who were not protected were later cured by drugs not ordinarily curative in vivax infections.

Cure of Subacute Bacterial Endocarditis with Penicillin. By ARTHUR J. GEIGER and FRANCIS G. BLAKE, New Haven, Conn.

Of 20 patients treated in the past 2 years with penicillin in massive doses, cure was achieved in 19. One relapse and one re-infection were encountered in the ultimately cured cases. The underlying heart disease was congenital in 2, and rheumatic in the others. The patients ranged from 3 to 65 years in age, and none of the 17 survivors are invalids.

The penicillin resistances of the *Streptococcus viridans* ranged from 0.01 to 0.05 units per ml., and no increase in resistance developed in cases requiring more than one course of therapy.

Four methods of administration were tested: (*1*) fractionated intramuscular injections, (*2*) continuous intramuscular infusion, (*3*) continuous intravenous infusion, and (*4*) one or 2 daily intramuscular deposits of penicillin in oil and beeswax. Serum penicillin concentrations attained with each mode of treatment indicated the superiority of the continuous intravenous and the intramuscular depot (in oil and beeswax) methods for maintaining sustained penicillin effects.

Penicillin administered in the cured cases ranged from 3,900,000 to 102,000,000 units given for 3 weeks to 16 months.

In one cured case, which died 9 months later of another disease, the fibrocalcific and abacterial lesion of the previous endocarditis proved anatomically that the infection had been eradicated.

The Relationship of Serological Types of Group A Hemolytic Streptococci to Toxin Production and Antibody Response. By LOWELL A. RANTZ, San Francisco, Calif., WESLEY W. SPINK, Minneapolis, Minn., and (by invitation) PAUL J. BOISVERT.

A large number of Group A hemolytic streptococcal respiratory infections in young men were studied. The etiological agents were classified into types by the precipitin technique of Lancefield.

When Dick positive individuals were infected by streptococci of types 17, 19, and 30, the acute illness was usually associated with a skin rash and skin sensitivity to the erythrogenic toxin was lost during convalescence. These phenomena were absent when the infectious agent was a strain of any other type except 3. In the latter instance the Dick test was usually reversed in the absence of demonstrable rash.

Close correlation has been discovered to exist between the amount of fibrinolysin formed by strains of several types *in vitro* and their ability to stimulate the production of antifibrinolysin in infected human beings.

The quantitative estimation of streptolysin production *in vitro* has been technically unsatisfactory but the magnitude of the antistreptolysin response is much greater following infection by certain types than by others.

These observations establish the fact that certain strains or types of Group A streptococci differed from one another in a constant manner in regard to important biological properties and in their effect on the human host.

Experimental Transmission of Minor Respiratory Illness to Human Volunteers. By THEODORE J. ABERNETHY, Ft. Bragg, N. C.

Attempts were made to induce respiratory disease in human volunteers by means of filtered secretions obtained from two single donors (OL and NE), both of whom had acute febrile respiratory illnesses without pneumonia. Immunity to re-inoculation with homologous and heterologous filtrate was also tested. Thirty-eight volunteers, kept in strict isolation before and after inoculation, comprised the study group.

Two clinically distinguishable types of minor illness, with different incubation periods, were induced. Thirteen of 19 volunteers receiving "OL" filtrate developed illnesses after 1 to 2 days; the principal clinical features were sneezing, nasal obstruction, coryza, and cough. Fourteen of 19 persons inoculated with "NE" filtrate became ill after an incubation period of approximately 5 to 6 days; sore throat was the outstanding feature and nasal symptoms were minimal. Partial immunity to the re-inoculation of homologous filtrate was found in the group which received "NE" inoculum; none was found in the subjects given "OL" filtrate. Cross immunity was not demonstrated with either filtrate. Atypical pneumonia was not induced. Controls inoculated with their own filtered respiratory tract secretions remained free of symptoms.

The results indicate that at least two filtrable agents, presumably viruses, can induce minor respiratory illness in man.

Studies of the Incidence and Pathogenicity of Pleuropneumonia-like Organisms in Humans. By LOUIS DIENES and WILLIAM E. SMITH (introduced by MARIAN W. ROPES), Boston, Mass.

Pleuropneumonia organisms are important pathogens in animals, producing chronic diseases usually with in-

volvement of joints. Pathogenicity in humans is suggested by the present studies.

Organisms of the pleuropneumonia group (L organisms) were first cultured from the human genitourinary tract in 1937. Their incidence in the female genitourinary tract is relatively high, 58 out of 244, (26 per cent). In males, the incidence is only 6 out of 71 (8 per cent) and L organisms have been found in only 24 patients. In females, these organisms have been found predominating or in pure culture in acute inflammatory and suppurative processes of the genito-urinary tract. In males, all of the 24 patients with positive cultures had prostatitis. The organisms were obtained in pure culture in 5 cases and disappeared after the prostatitis subsided in 3 cases. There was a severe cystitis in one patient and in one a periurethral abscess from which pure cultures of L organisms were obtained.

A relation of L organisms to an infectious type of arthritis is suggested by the fact that 12 of the 24 male patients had acute joint involvement at the time the prostatic cultures were positive. Four presented the characteristics of Reiter's disease with urethritis, arthritis and purulent conjunctivitis. In one of these cases L organisms were cultured from the prostate during 2 attacks 1½ years apart. The second of these attacks followed a prostatic massage, the secretion from which was negative for L organisms. Two weeks later, urethral discharge showed an abundant growth of L organisms in pure culture. In 2 patients L organisms were cultured from synovial fluid. Acute joint involvement was rare in women, being observed in only 4. The husband of one had a positive prostatic culture, and both developed acute arthritis within a few weeks after marriage.

Sulfonamides and penicillin did not affect the genitourinary or joint symptoms. The results of treatment with streptomycin were sufficiently suggestive to warrant further trial.

These observations suggest that pleuropneumonia-like organisms have pathogenic activity in the male and female genitourinary tracts, and may be related to an acute infectious type of arthritis.

The Site of Origin of "Blackout" in Aviators. By E. H. LAMBERT (introduced by C. F. Code), Rochester, Minn.

Blackout is a temporary loss of vision without loss of consciousness which aviators experience when subjected to centrifugal force in aircraft or on a human centrifuge. In the investigations to be reported, temporary loss of vision was produced at 1 g. (gravity) by application of air pressure to the eyeball. When the effective systolic arterial pressure at the eye (systolic pressure at head level minus the pressure applied to the eye) was 49 to 30 mm. Hg vision was dimmed; peripheral vision was lost at 32 to 20 and vision was completely lost at 21 to 0. These visual changes had the same latent period, progress of development and level of effective blood pressure as the visual changes produced by centrifugal force. Application of 20 to 30 mm. Hg pressure to the eyeball when the subject is exposed to centrifugal force lowers the threshold of force at which visual changes occur by 1 g. Suction of 30 to 40 mm. Hg applied to the eyeball prevents the occurrence of blackout when the man is exposed to centrifugal force. These experiments allow the conclusion that blackout is of retinal origin.

Some Effect of Injected Cytochrome C on Myocardial and Cerebral Anoxia in Man. By SAMUEL PROGER and (by invitation) DEMETRE DEKANEAS, Boston, Mass.

1. The effects of anoxia on the electrocardiogram can be prevented by the injection of cytochrome C.

2. Injected cytochrome C has an equivocal effect in prolonging exercise tolerance in patients with angina pectoris. It has no noticeable immediate effect on myocardial infarction.

3. Subjects seem to tolerate anoxia more easily when they have been previously injected with cytochrome C.

4. The effects of anoxia on the electroencephalogram can be largely prevented by the intravenous injection of cytochrome C.

5. The effects of anoxia in impairing visual discrimination can be overcome by the intravenous injection of cytochrome C.

6. The effects of anoxia in slowing the cerebral functions required for code transliteration can be overcome by the injection of cytochrome C.

Acclimatization to Intermittent Anoxia. By WRIGHT ADAMS, Chicago, Ill.

Alveolar carbon dioxide and oxygen tensions have been measured in fifteen male subjects during sixteen series of exposure to a simulated altitude of 10,000 feet above sea level in a decompression chamber. The subjects spent five hours daily for six days of each week for six consecutive weeks in this mildly anoxic condition. The alveolar samples were taken more than three hours after a meal and after more than three hours of continuous exposure to simulated altitude.

The carbon dixide tension, after an initial reduction, showed a definite tendency to drop progressively during the first weeks of intermittent exposure. The mean tension during the preliminary control period was 40.0 mm. Hg. During the first week of exposure it was 36.9 mm., during the second and third weeks it was 35.8 mm., and during the last three weeks 35.1 mm. There was considerable individual variation in both the initial reduction and the progressive decrease with prolonged exposure.

The oxygen tension, after an initial reduction, tended to increase during the course of intermittent exposure. The increase was greatest in those subjects who showed the greatest progressive decrease of carbon dioxide tension, but the oxygen values were more variable from day to day.

Acclimatization to Humid Heat: A Function of Adrenal Cortical Activity. By JEROME W. CONN and (by invitation) MARGARET W. JOHNSTON and LAWRENCE H. LOUIS, Ann Arbor, Mich.

Our studies indicate that the process of acclimatization to heat is characterized metabolically by (*1*) negative

nitrogen balance, independent of the composition of the diet, and (*2*) sharply falling concentrations of sodium and chloride in sweat and urine. Similar findings have been observed in normal animals treated with large doses of adrenal cortical extract.

If, during acclimatization, the negative N balance represents a secondary expression of increased adrenal cortical activity, the primary stimulus for which the need is to conserve salt, the administration of desoxycorticosterone acetate (D.C.A.) should serve as a useful tool in dissecting the mechanism since (*1*) it could remove the pressure on the adrenals for the production of a substance capable of retarding body losses of salt, and (*2*) *per se,* it has no significant effect upon protein metabolism.

D.C.A. was administered to men (*1*) unacclimatized to heat and living in a temperate climate, (*2*) undergoing acclimatization to heat, and (*3*) fully acclimatized to heat. Results:

1. It always diminishes markedly the concentration of sodium and chloride in sweat and urine, the most persistent effect being upon sweat.

2. During acclimatization (with an existent negative N balance) it results in a sharp approach to nitrogen equilibrium.

3. *Upon cessation of D.C.A.* a very marked rise in the concentration of sweat salt always occurs. The process of acclimatization is temporarily impeded, and in fully acclimatized men acclimatization is temporarily lost.

Conclusions: 1. Increased adrenal cortical function is importantly involved in the process of acclimatization to heat.

2. Correction by exogenous D.C.A. of the negative N balance characteristic of the process of acclimatization indicates that production of endogenous adrenal cortical substance (which affects both electrolyte and nitrogen metabolism) has been diminished; and that the original stimulus to the adrenals (under these conditions) represents the need to conserve body salt.

3. Temporary loss of acclimatization and loss of the ability to produce sweat dilute in sodium chloride upon withdrawal of D.C.A. suggests that it requires several days for the adrenal cortices to again reach a high degree of functional activity, after having been put at relative functional rest by a few days of aid from an exogenous source (D.C.A.).

Oxygen Content of Pulmonary "Capillary" Blood in Unanesthetized Human Beings. By L. DEXTER, C. S. BURWELL, and (by invitation) F. W. HAYNES, and R. E. SEIBEL, Boston, Mass.

The venous catheter technique of Cournand and Ranges (1941) has been used in the present study. A 9F venous catheter, 100 cm. long, with a single hole directly on the tip, has been introduced through the median basilic vein into the right auricle, right ventricle, and pulmonary artery, usually the right branch. The catheter has then been pushed as far as possible into a small branch of the pulmonary artery and wedged so as to obstruct this branch. Dog experiments have indicated no deleterious effects physiologically or pathologically from this procedure providing the catheter does not plug the pulmonary arterial branch for more than one hour. With the catheter in place, blood samples have been withdrawn under oil and their oxygen content and saturation compared with those of blood withdrawn from the femoral artery. In a series of normal individuals, the oxygen saturation of blood obtained from the pulmonary artery by this method has been found to be 95 to 98 per cent, corresponding closely to the oxygen saturation of the femoral arterial samples. Samples from other parts of the pulmonary artery have uniformly been less oxygenated as would be expected of mixed venous blood. That the blood so obtained represents blood which has flowed from pulmonary capillaries and possibly pulmonary veins in a retrograde fashion from the pulmonary bed distal to the tip of the catheter rather than from systemic arteries emptying into the pulmonary artery is borne out by the fact that in a group of cyanotic patients with congenital heart disease and a right-to-left shunt, blood from the femoral artery has had varying degrees of oxygen unsaturation, while blood obtained from the distal portion of the pulmonary artery as described has been almost fully saturated with oxygen.

This procedure appears of value in differentiating cyanosis of pulmonary origin from that due to a venous shunt, and in determining the oxygen content of blood entering the left auricle.

Demonstration that the Human Right Ventricle Obeys Starling's Law during Physiological Changes in Respiration. By HENRY D. LAUSON, ANDRE COURNAND, and RICHARD A. BLOOMFIELD (introduced by Dickinson W. Richards, Jr.), New York, N. Y.

Although Starling's law of the heart is widely accepted, its operation in man still requires further proof.

Simultaneous right ventricular and intrapleural pressures were recorded during quiet and forced respiration in three recumbent tuberculous patients, with recent pneumothorax, whose circulation was considered essentially normal. Pressures in successive cardiac cycles were measured (*a*) exactly at the end of diastole, and (*b*) at the peak of the following systole. The concurrent intrapleural pressures were subtracted to give the "net initial" and "net systolic" pressures, which are related to the degree of stretch of the filled ventricle, and to the degree of response to that stretch, respectively.

Analysis of several hundred cardiac cycles revealed (*a*) an inverse correlation between the intrapleural pressure and the two net ventricular pressures; and (*b*) a direct linear relationship between the net initial pressure and the net systolic pressure of the same beat. For example, a net initial pressure of 2 mm. Hg was followed by a net systolic pressure of 22 mm. Hg during expiration, while during inspiration the former increased to 8 mm. Hg and the latter increased to 36 mm. Hg.

The results constitute a direct demonstration of the essential features of Starling's law in man under physiological conditions.

The Role of the Kidney in Chronic Heart Failure: Evidence of a Forward Failure Hypothesis of Edema Formation. By A. J. MERRILL (introduced by E. A. Stead, Jr.), Atlanta, Ga.

The cause of edema in chronic cardiac failure has never been established. Everyone agrees that the fluid intake must exceed the fluid output and that the edema fluid accumulates because of failure of the kidney to excrete the excess salt and water. The question of why the salt and water is retained has not been answered. The proponents of the backward failure theory believe either that it is forced into the tissues by a high venous pressure or that it is retained by the kidney because of the adverse effect of a high venous pressure on kidney function. The observations recorded here are not in agreement with this concept, but point to a marked decrease in renal blood flow from forward failure as the primary mechanism leading to edema formation.

Patients with chronic failure who formed edema at rest were studied. The renal blood flow was uniformly reduced to one-third to one-fifth of normal. The filtration rate was reduced to one-half to one-third of normal. Thus the amount of sodium presented to the tubules was greatly reduced and tubular reabsorption of the sodium was nearly complete, though the absolute amount absorbed was less than in the normal.

The reduction in renal blood flow to this extreme level was unrelated to the level of the venous pressure. It could be correlated with the level of the cardiac output.

The kidney at rest normally received from one-fourth to one-fifth of the cardiac output. This large blood flow is not necessary to maintain the life of the renal cells. It seems to be important in the normal metabolic functions of the kidney and in urine formation. When the cardiac output becomes inadequate for the needs of the body, vasoconstriction in the kidneys allows shunting of blood elsewhere without permanent injury to the kidneys. It is believed that this fall in renal blood flow is the primary cause of edema in patients who have chronic failure and who become edematous at rest.

Metabolic Changes in Young People with Coronary Heart Disease. By JACOB LERMAN and PAUL D. WHITE, Boston, Mass.

This study was stimulated by 2 types of observations: (*1*) the clinical study of young persons with coronary heart disease by Glendy, White and Levine; (*2*) though myxedematous patients with angina often get worse on thyroid, they may, if thyroid is administered cautiously, actually improve or get rid of their angina. This led to observing the effect of thyroid in coronary disease and the rôle of metabolic disturbances in its pathogenesis. It was deemed advisable to limit the study to young people (40 years and under).

We have data on 28 patients, 25 of them being males. The most striking finding has been the relative frequency of low metabolic rates and of high cholesterol levels in the blood. Adequate BMR levels, ranging between plus 3 and minus 36, were obtained in 27, and in 21 they were under minus 10. The blood cholesterol ranged between 179 and 480 mgm. per cent, the majority (22 out of 28) being over 250 mgm. per cent. Blood sugar and serum protein values were within normal limits. There were no stigmata of endocrine disturbance in any case.

On thyroid, the BMR levels tended to rise and the blood chlesterol to fall. Although it is too early to determine the effectiveness of thyroid, results thus far indicate that in all cases with angina but 2, the administration of thyroid in small dosage was associated with diminution or disappearance of pain; in cases without angina, it did not precipitate angina or any other untoward symptom.

Tissue Circulation. Pulmonary Ventilation as Measured by Gas Exchange with a Note Regarding Decompression Sickness and Polycythemia Vera. By H. B. JONES (by invitation) and J. H. LAWRENCE and J. G. HAMILTON, Berkeley, Calif.

During the inhalation of pure oxygen the nitrogen is washed out of the lungs and removed from the tissues. The nitrogen elimination can be determined by analysis of inert gas residues in expired gases. The data can be fractionated into portions coming from lung gases and various body tissues. The lung components give a measure of pulmonary ventilation efficiency. Eleven of twelve polycythemias studied showed a reduction of portions of their pulmonary exchange. Such an effect was only noted in two subjects of a normal series of forty-three.

As determined by radioactive inert gases and nitrogen exchange, the rate of nitrogen elimination from the body tissues has been found to be a measure of the perfusion of blood through the tissues. The body can be divided into two to four groups of tissues on a basis of volume of tissue and blood supply from gas exchange measurements. The tissue vascularity in the twelve polycythemia patients studied was within the normal range.

The gas exchange rate can be shown to be a precise indicator of prediction of decompression sickness and degree of protection from decompression sickness by nitrogen elimination during oxygen inhalation, for group measurements.

The Effects in Man of Blockade of the Autonomic Ganglia by Tetraethyl Ammonium Bromide. By RICHARD H. LYONS and (by invitation) GORDON K. MOE, ROSALIE B. NELIGH, SIBLEY W. HOOBLER, KENNETH N. CAMPBELL, ROBERT L. BERRY, and B. R. RENNICK, Ann Arbor, Mich.

The parenteral administration of tetraethyl ammonium bromide in animals produces blockade of autonomic ganglia as judged by ganglionic paralysis of the nictitating membrane, functional denervation of the heart, and a decrease in blood pressure with increase in peripheral blood flow.

The effects of this drug in man indicate that it may be useful in several ways. It produces a vasodilatation in the extremities, as measured by changes in skin tempera-

ture, of the same degree as that found under spinal anesthesia or sympathectomy. There is striking relief of pain in vasospastic peripheral vascular disease and in causalgic states. It produces a significant decrease in both systolic and diastolic pressure in many patients with hypertension. Symptoms of hypertensive encephalopathy and of dyspnea with hypertensive heart failure have been temporarily relieved in the few cases so treated. The decrease in diastolic pressure with test doses of the drug tends to approximate the diastolic pressure found two weeks after splanchnic section in hypertensive patients.

Other evidence of blockade of the autonomic ganglia resulting from the drug is the development of severe postural hypotension in hypertensive patients as well as in normal subjects, loss of sweating, cessation of gastrointestinal motility, increase in heart rate, decrease in venous pressure, dry mouth, mydriasis with loss of accommodation and ptosis.

The cardiac output as measured by the ballistocardiogram is increased about 20 per cent in normal and hypertensive subjects. The renal blood flow remained fairly constant in spite of the drop in blood pressure though there was a decrease in filtration rate proportionate to the fall in blood pressure.

The drug is rapidly excreted by the kidneys when given either intravenously or intramuscularly so that some of the effects are usually of relatively short duration.

The Effects of Bed Rest and Immobilization upon some Aspects of Calcium Metabolism and Circulation in Normal Men: Their Modification by the Use of the Oscillating Bed. By JOHN E. DEITRICK and G. DONALD WHEDON (introduced by Ephraim Shorr), New York, N. Y.

Four normal men were studied on a metabolism ward during control (6 to 8 weeks) bed rest (6 to 7 weeks), and recovery (4 to 6 weeks) periods. Immobilization was standardized by plaster casts from umbilicus to toes. Diets were constant.

Total calcium losses ranged from 8.95 to 23.9 grams, maximum daily loss reached at the fifth to sixth week. Urinary calcium excretion during bed rest more than doubled in all four men. Despite this, no compensatory mechanism for increasing calcium solubility in the urine was demonstrated. pH of urine rose slightly. Citric acid excretion and urine volumes remained relatively constant.

Deterioration of postural circulatory mechanisms was the principal effect upon the circulation produced by bed rest. Subjects showed an increased tendency to faint on tilting to 65°. Experiments suggest that the most important factor in this deterioration is a decrease in venous return of blood from the legs.

Oscillating Bed: The experiment was repeated on two of the original subjects under identical conditions except for the use of a motor-driven oscillating bed eight hours a day during immobilization. Total calcium losses were reduced by 50 to 70 per cent from that occurring in the fixed bed. Urinary calcium increased only one-third to one-half as much. The oscillating bed tended to prevent the deterioration of circulatory control in the upright position.

Studies on Chronic Thyrotoxic Myopathy. By GEORGE W. THORN, and (by invitation) HOWARD A. EDER, Boston, Mass.

In addition to the generalized weakness accompanying thyrotoxicosis, several forms of myopathy have been reported. In some patients the muscular weakness and atrophy are profound and often out of proportion to the degree of thyrotoxicosis. This syndrome has been termed chronic thyrotoxic myopathy. During the past two years we have studied five such patients. The disease is characterized by symmetrical muscular weakness and atrophy which involves the muscles of the shoulder and pelvic girdle particularly. All patients showed a striking disturbance in creatine metabolism and elevated basal metabolic rates ranging from plus 33 to plus 60 per cent. One patient died before adequate treatment could be instituted. Four patients have shown striking and continued improvement following treatment of thyrotoxicosis by iodine plus subtotal thyroidectomy or thiouracil. Possible mechanisms whereby certain patients with thyrotoxicosis develop profound muscular atrophy is described.

Two patients with myasthenia gravis complicated by thyrotoxicosis have also been studied. Striking improvement in the myasthenia gravis was observed following treatment of the *thyrotoxicosis.* The remarkable improvement which may occur in the clinical condition of patients suffering from myopathy complicated by thyrotoxicosis indicates the importance of establishing the diagnosis and instituting appropriate therapy.

Evidence that Chorionic Gonadotrophic Hormone Stimulates Human Leydig-Cell Function and Maturation; and that Purified Follicle-Stimulating Hormone Stimulates Spermatogenesis. By CARL G. HELLER and WARREN O. NELSON (introduced by Edwin E. Osgood), Portland, Ore. and Iowa City, Iowa.

Biopsies of the testes of twenty adult prepuberal eunuchoids proved that they had Leydig-cells which were undeveloped and seminiferous tubules which failed to carry on active spermatogenesis. Assays of urinary gonadotrophins revealed depression of follicle-stimulating hormone (F. S. H.) and interstitial-cell-stimulating hormone (I. C. S. H.).

Administration of chorionic gonadotrophins, 750 I. U. twice daily intramuscularly, promptly resulted in stimulating the production of androgenic hormones, as judged by the development of the secondary sex characteristics. Estrogen and 17-ketosteroid excretion rose concomitantly adding further evidence of androgenic stimulation. Testicular biopsies taken 3 to 6 months later revealed that the interstitial cells of Leydig had developed normally and were in a secretory state. Thus one can conclude that the chorionic gonadotrophins specifically stimulate the morphological maturation of the interstital cells of Leydig and apparently stimulate them to secrete androgen.

The seminiferous tubules increased in size but spermatogenesis was not initiated. Therefore a purified follicle-stimulating hormone (F. S. H.) (prepared by enzymatic digestion by Dr. Hartford McShan of the University of Wisconsin) was injected daily for several months to a number of the patients, while continuing the chorionic gonadotrophic therapy. This resulted in active spermatogenesis as revealed by examination of seminal fluid and testicular biopsies.

Measurement of an Insulin Antagonist in the Serum of an Insulin Resistant Patient by the Blood Sugar Curve Method in Mice. By FRANCIS C. LOWELL, Boston, Mass.

Serum from a patient resistant to insulin had previously been shown to prevent hypoglycemic convulsions in mice injected with insulin due, apparently, to the presence in the serum of an antibody for insulin. The use of the blood sugar curve method in mice injected with mixtures of serum and insulin has made possible the demonstration of insulin neutralization with much smaller amounts of serum than heretofore. This has permitted repeated tests on a single blood specimen and the insulin-neutralizing activity could be measured with a certain amount of accuracy. Serum from the patients and from normal individuals were studied. A total of 25 tests were done, 6 animals were used in each and three blood sugar determinations, at 30 minute intervals, were made in each animal.

In addition to the clear-cut demonstration of insulin-neutralization by the patient's serum, the results indicated that more than 1,000 units of insulin, given in a short period of time, would have been required to control the patient's resistance to insulin.

It is concluded that an immune mechanism such as that which probably was present in the patient studied, will readily explain the extreme degree of insulin resistance which is occasionally encountered.

READ BY TITLE

The Thyrotropic Hormone: Its Inactivation by Elemental Iodine and Its Reactivation by Thiouracil and other Goiter Producing Compounds. By ALEXANDER ALBERT (by invitation) and RULON W. RAWSON, Boston, Mass.

The addition of elemental iodine to a solution of thyrotropic hormone precipitates the hormone as a brown iodoprotein complex which has no thyrotropic activity as measured by thyroid weight, loss of thyroid iodine and thyroid mean acinar cell height in the day-old cockerel. A direct relationship has been demonstrated between the amount of iodine added and the degree of inactivation of hormone. Mixing thyrotropic hormone with iodine as potassium iodide does not cause any loss of hormonal activity. The inactivation is not due to the involuting action of iodine on the thyroid.

The brown precipitate dissolves when treated with reducing agents, *i.e., thiouracil,* potassium thiocyanate, amino mercapto thiadiazole and phenylaminomethyl mercaptothiazoline, ascorbic acid and sodium thiosulfate. Precipitates treated with the first four agents, which are goitrogenic, recover in varying degrees their original thyroid stimulating activity. The latter two reducing agents which are not goitrogenic did not materially reactivate the hormone. The goitrogenic agents in the amounts used to reactivate the hormone produced no change in the thyroid when administered alone, but augmented the thyroid stimulating effect when mixed with active hormone.

The Reaction of Hemophilic Blood to the Clot Promoting Factor in Normal Plasma and a Method for Its Quantitative Measurement. By BENJAMIN ALEXANDER and GRETA LANDWEHR (introduced by H. L. Blumgart), Boston, Mass.

A method has been devised for the quantitative measurement of the reaction of hemophilic blood to the clot promoting effect of normal plasma. This method is of value in estimating the coagulation defect found in this disease.

Minute amounts (0.00005 cc.) of normal plasma hastened the coagulation of hemophilic blood *in vitro,* and .002 cc. lowered the clotting time to normal. A logarithmic plot of added plasma against the coagulation time was linear in two hemophiliacs. The curves had different slopes. In one patient the effect could be represented by the equation:

$$0.29\text{–}2.7 \log (\text{clotting time}_{\text{min.}}) = \log \text{normal plasma}_{\text{cc.}}$$

This effect was reproducible and accurately predictable over 5 months' observation.

Fresh or freshly processed frozen plasma from different individuals had the same potency.

The infusion of 150–200 cc. of fresh or freshly processed plasma lowers the clotting time of the blood of two hemophiliacs to normal; coagulation remains normal for about 24 hours, and thereafter slowly returns to its previous level within 3 to 4 days. Two cases treated 3 times weekly with this amount of plasma over 5 months have never failed to respond. The coagulation times were maintained at decidedly lower levels.

By this approach, control of the abnormal coagulation in hemophilia is feasible.

Penicillin Aerosol with Negative Pressure in the Treatment of Sinusitis. By COLTER RULE and BETTINA GARTHWAITE (introduced by Alvan L. Barach), New York, N. Y.

When oxygen is passed through a nebulizer containing a solution of 40,000 to 50,000 units per ml., the nebulin (or aerosol) produced may be delivered to the nasal and oral pharynx as well as to the bronchial and alveolar surface. A valve has been constructed by which intermittent suction develops a negative pressure (45 to 60 mm. Hg) in the antrum. After treatment penicillin has been recovered from antral washings. Acute and chronic cases of sinusi-

tis have been treated with clearing of symptoms and radiological evidence of disease.

Lantern slides will be used to show the effect of this procedure on purulent sinusitis and also illustrative cases of chronic bronchitis and bronchiectasis in which inhalation of penicillin aerosol was used.

Nitrite Protection against Cyanide Poisoning. By ALLAN D. BASS (by invitation) and WILLIAM T. SALTER, New Haven, Conn.

It was demonstrated by Chen, Rose and Clowes that nitrites, with thiosulfate, afford a definite protection against injected cyanide. The mechanism involves the formation of methemoglobin in the circulating erythrocytes. This work has been extended to hydrocyanic acid in gaseous form. A nomogram has been constructed to show the limiting concentrations and time intervals in terms of blood methemoglobin concentration.

Dogs, maximally protected, show no obvious symptoms for over an hour in an atmosphere so concentrated in cyanide that the control (unprotected) animal succumbs within two minutes. When protected dogs finally lose consciousness, they recover much more rapidly when rescued than do unprotected animals. Indeed, the latter frequently fail to recover.

This "antidote" is one of the few known which have a rational mechanistic basis after systemic absorption. Certain applications to civilian hazards are possible within the limitations imposed by methemoglobinemia and hypotension.

This work was released with the approval of the OSRD Committee on Medical Research, under whose auspices the observations were made.

A Critique of Physical Fitness Tests. By WILLIAM B. BEAN and (by invitation) C. R. PARK and D. M. BELL, Ft. Knox, Ky.

The Army needed tests to assess soldiers' fitness for active duty; to evaluate convalescence, to compare different units and to measure the effects of training. Since there was no general agreement on the meaning of the term fitness, or the role of physique, physiologic state and psychologic factors, several types of performance test were employed extensively. The Harvard Fatigue Laboratory Step Test, the Army Air Forces Test and the Army Ground Forces Test were run 6 times in 8 weeks by approximately 700 soldiers during controlled training in a field trial of combat rations. All tests suffered from failure to control motivation, from defective scoring systems and from the influence of learning on scores. There was poor agreement between different tests. No test considered the post-exercise state and only one evaluated physiologic cost. In the group studies no correlation occurred between individual scores and incidence of minor clinical and biochemical abnormalities. It was concluded that there is no abstract state of fitness—its definition must include a particular task and tests to measure it should resemble that task. On the basis of wartime experience a program of fundamental research is needed to define fitness better and devise more satisfactory tests.

Studies on Immunity to Bacterial Pyrogens. By PAUL B. BEESON, Atlanta, Ga.

The present work is part of an investigation of the mechanism by which patients undergoing typhoid vaccine fever therapy develop a marked tolerance to this pyrogenic stimulus. Rabbits were given daily injections of the same dose of vaccine, and were found to exhibit a progressive diminution in febrile response during the first 6 to 10 injections, after which they reacted to each injection with low-grade fever of approximately the same extent. Rabbits which were given increasing quantities of bacterial vaccine were able to withstand intravenous inoculation of large doses of vaccine with only slight fever. The same doses caused hyperpyrexia and death in normal control animals. Animals rendered immune to the effects of typhoid vaccine were tested with vaccines of heterologous bacterial species (*Ps. aeruginosa* and *S. marcescens*), and were found to be similarly immune to them. The same type of immunity was induced with purified typhoid bacterial pyrogen, a carbohydrate substance.

A striking effect was produced in pyrogen-immune animals by reticulo-endothelial blockade, using either Thorotrast or trypan blue. This completely abolished the immunity, so that the animals responded to the injection of the same dose of vaccine with prolonged, high fevers.

The immunity to bacterial pyrogens has several peculiar features. It is maximal on the day following the last injection of pyrogen and disappears completely in from 1 to 3 weeks. There is apparently no relationship to the production of specific antibodies, since the immunity applies to heterologous bacterial species and since it can be provoked by the purified pyrogen, which is not antigenic. Furthermore, the immunity cannot be passively transferred with serum. Elevation of body temperature plays no part in the development of the immunity, since prevention of fever by administration of amidopyrin during the period of training did not interfere with the development of immunity. Also, animals given a series of mechanically-induced fevers did not develop immunity to bacterial pyrogens. In view of the effect of reticulo-endothelial blockade, it would appear that the development of immunity to bacterial pyrogens involves an alteration in the functional activity of the reticulo-endothelial system.

The Folic Acid Content of Leukocytes: Observations on Normal Subjects and Persons with Leukemia. By FRANK H. BETHELL and (by invitation) MARION E. SWENDSEID, Ann Arbor, Mich.

Folic acid has been shown to be an essential factor for normal hematopoiesis in several species of animals, and the recent observations of Spies and others indicate that this substance may be required for orderly erythropoiesis in humans. In earlier studies, on the rat, it has been shown that a deficiency of folic acid is followed by arrested maturation of the precursors of all of the formed elements of the blood, resulting in progressive leukopenia, anemia

and thrombocytopenia. These observations suggest that altered metabolism of folic acid may play a role in hematopoietic disorders characterized by excessive or disorderly proliferation of blood cells or their precursors. Accordingly, determinations have been made of the content of folic acid in the leukocytes of healthy subjects and in those of persons with acute and chronic forms of leukemia.

In twelve normal subjects the content of folic acid varied from 40 to 180 micrograms per cubic centimeter of packed white cells with an average value of 80. In six cases of chronic lymphogenous leukemia the range of value was 70 to 160 micrograms, with a mean of 108. In seven cases of chronic myelogenous leukemia a range was obtained of 75 to 220 micrograms, with a mean of 146. In persons with chronic leukemia the highest folic acid values were found in association with the greatest percentages of relatively immature white cell elements. Determinations made after irradiation therapy in four cases of chronic leukemia demonstrated a decrease in leukocyte folic acid content which coincided with a reduction in the percentage of the more immature cellular elements.

In seven cases of acute leukemia, six of myeloblastic and one of leukosarcoma, the range of values for folic acid was from 250 to 800 micrograms per cubic centimeter of white cells with an average of 460. This value is five times that of the mean folic acid content of the leukocytes of normal subjects. Whether excessively large amounts of folic acid are required by the younger and more rapidly growing leukemic cells or whether the high content of the substance in such cells represents a failure of utilization or metabolic dysfunction is not answered by these observations. However, it may be concluded that, in leukemia, a direct relationship exists between the amount of folic acid contained in the white cells of the peripheral blood and the degree of immaturity of the cells.

Foreign Body Emboli to the Heart and Lungs. By EDWARD F. BLAND, Boston, Mass.

In connection with a comprehensive survey of wounds of the heart in the Mediterranean Theater, four unusual cases were encountered in which large shell fragments migrated centrally by way of the blood stream: in three instances to the lungs, and in one to the right ventricle. Each patient presented features of special interest:

Case 1. Autopsy revealed penetration of the inferior vena cava and a large 10.5 gm. metal slug (2.5 × 1.0 × 1.0 cm.) in the chamber of the right ventricle. Death on the 13th day was due to multiple pulmonary emboli.

Case 2. Autopsy revealed penetration of the inferior vena cava and an embolic shell fragment (1.5 × 0.6 × 0.4 cm.) in inferior branch of the left pulmonary artery. Death on the 14th day resulted from intraperitoneal hemorrhage.

Case 3. Thoracotomy 6 weeks after a cervical wound revealed a metallic shell fragment in the inferior branch of the right pulmonary artery. It was not removed and recovery has been complete.

Case 4. X-ray showed a large metal fragment in the left hilar region; not found on surgical exploration. Post-operative X-ray showed the foreign body now in the right hilar region; surgical exploration revealed the fragment impacted in the right main pulmonary artery. It was not removed. Recovery has been complete with only slight dyspnea on considerable effort.

It is noteworthy that in the three instances where lodgement occurred in a large pulmonary artery neither pulmonary infarction nor significant symptoms ensued. A shift of the large metal fragment from the left main pulmonary trunk to the right main trunk in Case 4 is remarkable.

Increased Protein Content of the Cerebrospinal Fluid in Rheumatoid Spondylitis. By EDWARD W. BOLAND and NATHAN E. HEADLEY (by invitation) and PHILIP S. HENCH, Rochester, Minn.

Fifty soldiers were studied, 33 with rheumatoid spondylitis alone, 17 with rheumatoid spondylitis and arthritis of peripheral joints. The total protein content of spinal fluid from the lumbar region was increased (between 46 and 105 mgm. per 100 ml.) in 42 per cent of the 50 cases. It is increased sometimes in rheumatoid arthritis of peripheral joints, more often in rheumatoid spondylitis alone, most often in rheumatoid arthritis of both spine and peripheral joints. The increase was related to the severity of the disease, but not to its duration or spinal spread. Colloidal gold reactions were generally normal.

The increase in spinal fluid protein in rheumatoid spondylitis is of about the same order as that in most cases of ruptured intervertebral disks. If the protein in any given case is increased notably above 100 mgm. per 100 ml., some cause other than spondylitis should be sought, even though spondylitis is present.

In peripheral rheumatoid arthritis excess protein may invade the subarachnoid space via the choroid plexus sometimes from increased plasma proteins, sometimes from an increased permeability of the choroid plexus when plasma proteins are normal. In rheumatoid spondylitis the same may occur but additional protein may enter the lumbar subarachnoid space via spinal perivascular and perineural spaces.

Studies of Hepatic Blood Flow in Man. By STANLEY E. BRADLEY (introduced by Chester S. Keefer), Boston, Mass.

The effects of increased intra-abdominal pressure and of drugs upon the hepatic blood flow in man were studied by means of a method previously described, which is based upon the hepatic clearance of Bromsulphalein.

1. Compression of the abdomen by a girdle pressurized at 80 mm. Hg was followed, in five of eight studies, by a rise in the concentration of BSP in the peripheral blood and a fall in the estimated hepatic blood flow (EHBF). On two occasions, the hepatic venous BSP

concentrations decreased, but on all others an elevation was observed.

2. Epinephrine, 0.4 to 1.0 ml. intramuscularly, in six of seven studies, was followed by increases in the concentration of BSP in the peripheral and hepatic venous blood. EHFB always increased, occasionally as much as three hundred per cent.

3. Histamine, 0.36 to 0.60 mgm. intramuscularly, caused very little change in four studies. A transient effect similar to that caused by the epinephrine was twice observed.

4. Glucose plasma levels above 500 mgm. per cent had no effect upon EHFB in three studies.

Errors Encountered in the Use of the Goldberger Central Terminal. By J. MARION BRYANT (by invitation) and FRANKLIN D. JOHNSTON, Ann Arbor, Mich.

This study was undertaken to determine whether electrocardiograms obtained with the central terminal of Goldberger, where equal large resistances between the extremity electrodes and the terminal are omitted, differ significantly from electrocardiograms obtained with the Wilson central terminal containing the 5000 ohm resistances.

In a series of 500 consecutive routine electrocardiographic examinations the left arm potential (V_L) was obtained using both methods. This lead was recorded first with 5000 ohm resistances between both the right arm and left leg and the central terminal, and then without disturbing the limb electrodes the right arm and left leg electrodes were short circuited and a second curve recorded. A significant difference was found between the curves obtained with the two methods in approximately 10 per cent of the individuals examined. The most common variation was a difference in the amplitude of the R deflection ranging from 2 to 7 mm. in 47 individuals.

These observations indicate that omitting the resistances from the central terminal as recommended by Goldberger produces significant differences in a small percentage of cases.

Rate of Water Loss from the Skin of Normal and Trench Foot Subjects. By G. E. BURCH and (by invitation) H. L. MYERS, R. R. PORTER, and N. SCHAFFER, New Orleans, La.

The rate of water loss (insensible and sensible perspiration) was measured simultaneously and quantitatively from the skin of the plantar and dorsal surfaces of the feet of 25 normal young male adults and 25 patients with mild chronic trench foot. The method used to determine the rates of water loss have been described (Neumann, Cohn and Burch; Burch and Sodeman). The subjects rested comfortably in bed in a comfortable room atmosphere and then in a hot and humid atmosphere.

There was no difference in the rates of water loss from the skin of the plantar and dorsal surfaces of the feet of normal subjects and patients with mild chronic trench foot, thus indicating that the skin showed a normal functional state and ability to inhibit water loss by diffusion, and the sweat glands a normal functional ability to secrete sweat. Under comfortable environmental conditions, the plantar skin showed a greater rate of water loss than skin from the dorsum of the foot. A hot and humid atmosphere resulted in a much greater rate of sweating from the skin of the dorsal surface than that of the plantar surface, thus indicating the failure of the plantar skin to be concerned with emergency sweating for the purpose of heat loss. These findings are also probably of importance in the evolutionary development and preservation of man.

Measurements of the rate of water loss from the skin of the foot cannot be employed to detect a return to normal of relatively mild chronic trench foot.

The Significance of Rest and Exercise in the Diagnosis and Management of Infectious Hepatitis. By RICHARD B. CAPPS and (by invitation) M. HERBERT BARKER, New York, N. Y.

Heretofore the influence of rest and of exercise on the course of infectious hepatitis has not been recognized. We believe that this is the first systematic investigation of this problem. During an extensive experience in the army we have personally studied in over 600 cases the effect on both the clinical and laboratory picture of a 10-day graduated exercise tolerance test. In addition, observations have been made on comparable groups treated with different degrees of rest.

We have found that when active hepatitis is present, exercise will produce an increase in liver size, liver tenderness, symptoms and in the laboratory evidence of liver dysfunction. These findings persist for days or weeks and constitute a true exacerbation of the disease even with recurrent jaundice.

These observations demonstrate (*1*) that early and adequate bed rest is a most important therapeutic measure; (*2*) that recovery from this disease is not coincident with the disappearance of jaundice, and that the effect of exercise is a valuable criterion of recovery; (*3*) that the degree of liver enlargement and tenderness and the severity of symptoms at a particular time is related to the rest or exercise status of the patients; and (*4*) that an exercise tolerance test is a valuable diagnostic procedure but must be employed with discretion.

Action Spectrum of Ultraviolet Keratitis. By DAVID G. COGAN and (by invitation) V. EVERETT KINSEY, Boston, Mass.

The present study consists of a quantitative determination of the ultraviolet bands capable of producing an abiotic reaction in the cornea and a comparison of the radiations which produce a keratitis with those which produce erythema. For the cornea the action spectrum was found to have a sharp peak at 288 mu. which is not materially different from the corrected peak for skin. But whereas there is no substantial difference in the absorption spectrum and action spectrum of skin, there is a difference in the absorption spectrum of the cornea and the action spectrum of keratitis. It is concluded that the absorption spectrum of the cornea is largely determined

by the nucleoprotein (peak at 265 mu.) while the action spectrum is determined by a photolabile substance with absorption properties shifted toward the longer wave lengths (peak at 288 mu.). The action spectrum of keratitis is compatible with the assumptions that the photolabile substance is either one of the cytoplasmic proteins (albumen or globulin) or a specific portion (amino acids containing phenyl rings) of the nucleoprotein.

Since ultraviolet keratitis is a common occupational hazard (*e.g.* among welders), the transmission characteristics of various types of common glass were measured for that portion of the spectrum which is responsible for keratitis. By comparison of these characteristics with the action spectrum for keratitis, it is possible to determine the amount of protection provided by any one type of glass.

The Absence of Rapid Deterioration in Moderately Active Young Men on a Diet Restricted in Vitamins of the B Complex and Animal Protein. By ROBERT C. COGSWELL, GEORGE BERRYMAN, CHARLES R. HENDERSON, CHARLES W. DENKO, JANE SPINELLA, THEODORE E. FRIEDMANN, and ANDREW C. IVY (introduced by John B. Youmans), Nashville, Tenn.

Following a twelve-week period on an "adequate" diet, seven normal young men were fed for five weeks on a diet containing 0.16 mgm., 0.11 mgm. and 2.1 mgm. of thiamine, riboflavin and niacin, respectively, per 1000 calories of food consumed. The intake of the various lesser known B complex vitamins (para-amino-benzoic acid excepted) ranged from 28 to 66 per cent of that in the "normal" diet. The daily intake of protein was 48 grams, of which approximately 34 per cent was non-animal. Corn (maize) comprised 27 per cent of the total calories of the diet.

The effect of this dietary was reflected in one week in the level of urinary excretion of the various vitamins, all of which were greatly reduced. No decrease occurred at any time in the content of the vitamins in the feces, however. No effect on group averages of physical or psychomatic response was observed; but, examination in retrospect of certain of the individual measurements of physical efficiency indicate the possibility that in two individuals slight beginning changes may have occurred in this function though not in the tests measuring psychomotor function. These individual changes, while not statistically significant for the five-week period do, however, comprise a part of the statistically significant change observed at the end of fifteen weeks of the experimental diet.

Low Oxygen Consumption and Low Ventilatory Efficiency During Exhausting Work in Patients with Neurocirculatory Asthenia, Effort Syndrome, Anxiety Neurosis. By MANDEL E. COHEN (by invitation), ROBERT E. JOHNSON (by invitation), FRANK CONSOLAZIO (by invitation), and PAUL D. WHITE.

Oxygen consumption was measured minute by minute while subjects ran to exhaustion on a motor driven treadmill at 7 m.p.h. at a grade of 8.9 per cent. Comparison was made among 20 patients with neurocirculatory asthenia (N.C.A.), average age 28 years; 20 healthy men, age 29; and 129 healthy young men, age 20 (Heath's subjects). Maximum oxygen consumption per kgm. body weight and minute averaged 36.8 ml., 47.0 ml., and 51.8 ml. respectively. To rule out the possibility that this difference occurs because N.C.A. patients do not run as long as healthy subjects, comparison of oxygen consumption in the 3 groups during the first, second and third minute of running showed a progressively greater difference; average values in ml. per kgm. body weight and minute were: N.C.A., 33.8, 40.0, 37.7; healthy 29 year old men, 35.0, 43.9, 46.5; healthy 20 year old men 38.4, 48.2, 50.5. In general, men who ran the longest had the highest rate of consumption of oxygen.

In a given individual the concentration of lactate in blood drawn 5 minutes after the run described above was directly proportional to the time of running, but the absolute value per second of running varies from individual to individual. For 68 N.C.A. patients, the average value was 1.31 mgm. of blood lactate per 100 ml. blood and second of running; and for 46 healthy men of comparable age, 0.60.

Ventilatory efficiency (V.E. = (oxygen consumed)/pulmonary ventilation), was lower at all times in N.C.A. Average values in ventilatory efficiency were: N.C.A., 4.29, 3.88, 3.46; healthy 29 year old men, 5.42, 4.59, 3.92.

It is concluded that for the same amount and duration of hard work, N.C.A. patients consume less oxygen, have a lower ventilatory efficiency and show a higher blood lactate than do healthy control subjects of comparable age. The data are all consistent with the idea that aerobic metabolism in hard muscular work is abnormal in N.C.A. and suggests high oxygen debt.

These data do not answer the question whether this is a phenomenon of poor health in general, poor running ability or lack of physical training.

Galactose Removal Constant. An Expression of Galactose Disappearance from the Blood Stream. By HENRY COLCHER (by invitation), ARTHUR J. PATEK, JR., and (by invitation) FORREST E. KENDALL, New York, N. Y.

The rate of disappearance of galactose from the blood stream after intravenous injection of 0.5 gram per kgm. body weight was studied in normal adults, patients with Laennec's cirrhosis of the liver, chronic passive congestion of the liver, acute hepatitis, and other affections of the liver.

A total of 89 determinations were made in 64 patients. In each patient the rate of disappearance of galactose was proportional to its concentration in the blood. The determination of blood galactose was based upon Benedict's method for blood sugar, after removal of glucose by fermentation according to Raymond and Bianco's method. It was shown that galactose determinations made on samples of blood drawn 15 and 45 minutes after intravenous injection enabled one to calculate the "Galactose Removal Constant." This constant expressed the per cent by which the concentrations fell each minute. It is calcu-

lated by the following equation:

$$\text{G.R.C.} = \frac{2.3\ (\log C_1 - \log C_2)}{t_1 - t_2}.$$

Where C_1 and C_2 represent the concentrations at the times t_1 and t_2.

The Galactose Removal Constant varied between 4.2 and 9.5 in the control group of 10 adults, whereas it was below 4 in 43 patients with impaired liver functions. There was a good correlation between the changes in the Galactose Removal Constant and tests pertaining to other liver functions.

Metabolism of Thiourea: Additive Effects of Iodine and Thiourea in the Treatment of Hyperthyroidism. By THADDEUS S. DANOWSKI and EVELYN B. MAN (by invitation) and ALEXANDER W. WINKLER, New Haven, Conn.

The metabolism of thiourea has been studied in dogs and in humans. Thiourea is destroyed only in the kidney. It appears to exert its depressant effect on the thyroid gland without being destroyed itself in any measurable quantity. This destruction in the kidney is dependent, in certain patients, upon the level of metabolism; untreated myxedematous patients do not destroy the drug. There is no evidence, however, that in patients who are already capable of destroying thiourea this ability is enhanced in states with increased metabolism such as hyperthyroidism.

Serum precipitable iodine and basal metabolic rate were followed in 54 patients with hyperthyroidism under various forms of treatment. Iodine administered simultaneously with thiourea (0.2 gram daily) produced a more rapid and marked remission than did thiourea alone. Prolonged preliminary medication with iodine did not delay the response to thiourea. Omission of iodine medication in 6 patients maintained in remission on combined therapy for several weeks resulted in an exacerbation of hyperthyroidism in 4 of them. Thiourea and iodine medication supplement rather than interfere with one another in the treatment of hyperthyroidism, and should in general be given together.

Contrasts in the Effect of Blood Transfusions and of Liver Extract upon the Peripheral Blood and Bone Marrow in Pernicious Anemia. By CHARLES S. DAVIDSON, Boston, Mass.

Five patients with pernicious anemia in relapse were repeatedly transfused with red blood cell concentrates so that within a few days high red cell values were attained. Subsequently, liver extract was given intramuscularly. Transfusion was without detectable effect on reticulocytes, white cells, platelets, or significantly on the patients' clinical condition. In two patients whose red cells had reached 5 million per cu. mm., only slight reticulocyte increases occurred after the liver extract but white cell and platelet counts rose promptly to normal. In two patients whose red cell counts had reached about 3 million per cu. mm., moderate reticulocytosis occurred after liver extract and white cells and platelets returned to normal.

The fifth patient was transfused to 5 million red cells but further therapy was withheld for 54 days until his red cell count had fallen to 3 million per cu. mm. Liver extract administration was followed by typical responses of the reticulocytes, white cells and platelets.

In the three patients with red cell counts of 5 million per cu. mm. following transfusions, the bone marrow became more mature in erythropoietic elements, but the cells of the granulopoietic series appeared to be unchanged. However, following liver extract, administered to two of these patients, more mature granulopoiesis appeared. Thus, the megaloblastic bone marrow in pernicious anemia was significantly modified after artificial increase in its oxygen tension, while white cells and platelets responded only after liver extract.

Studies on Bacteria Developing Resistance to Penicillin Fractions X and G in Vitro and in Patients under Treatment for Bacterial Endocarditis. By HARRY F. DOWLING and (by invitation) HAROLD L. HIRSH and C. BARBARA O'NEIL, Washington, D. C.

Sixteen strains of bacteria were made resistant to penicillin X and penicillin G by serial passage in media containing increasingly larger amounts of these fractions. At the termination of the experiments, those strains whose resistance had been raised to penicillin X were relatively more sensitive to penicillin G and those strains whose resistance had been raised to penicillin G were relatively more sensitive to penicillin X. In every instance when the resistance to one fraction was raised, the resistance to the other fraction followed along, to the same or nearly the same extent.

The sensitivity of the etiologic organisms to penicillins X and G were studied in a patient with *Streptococcus viridans* endocarditis and in a patient with *Staphylococcus aureus* endocarditis. In each instance, while the patient was receiving penicillin, the organism responsible for the infection developed resistance to both penicillin fractions simultaneously.

It is concluded that organisms which cause human infections usually do not show great differences in their relative sensitivity to penicillin G and penicillin X. In most instances, when resistance to one of these fractions increases, resistance to the other fraction will also increase.

The Therapeutic Efficacy of Penicillin in Experimental Syphilis as a Function of the Method of Administration. By HARRY EAGLE and (by invitation) HAROLD J. MAGNUSON and RALPH FLEISCHMAN, Baltimore, Md.

The therapeutic efficacy of penicillin in experimental rabbit syphilis has been found to be profoundly modified by the interval between injections and their total number. Thus, the total curative dose was reduced from 60,000 units per kilogram to 360 units per kilogram by increasing the number of injections from 8 to 50, and a qualitatively similar decrease was effected by increasing the interval between injections from 1 to 4 hours. Further prolongation had no effect, up to the maximum time interval studied (1 to 4 days).

These results reflect the fact that the total time for which spirochetes are exposed to effectively spirocheticidal concentrations is of greater importance than the absolute tissue levels of penicillin. A quantitative formulation of these relationships has been derived which corresponds closely to the observed therapeutic efficacy of penicillin in 11 different treatment schedules.

If the results in experimental animals are applicable to man, there is reason to believe that penicillin may be given effectively on an ambulatory basis, as infrequently as once or twice daily, and perhaps even at irregular intervals. The only essential requirement is that the patient receive the requisite total number of injections within a reasonable period of time, provided they are not given so frequently as to produce cumulative effects on the blood penicillin level.

The Osmotic Fragility of the Red Cells of the Peripheral and Splenic Blood in Patients with Congenital Hemolytic Jaundice Transfused with Normal Red Cells. By CHARLES P. EMERSON, JR., and SHU CHU SHEN (by invitation) and WILLIAM B. CASTLE, Boston, Mass.

The red cells of patients with congenital hemolytic jaundice, before and after splenectomy, were found to be abnormally susceptible to destruction by hypotonic solutions and by trauma. Moreover, during *in vitro* incubation (erythrostasis), the osmotic and mechanical fragility of these cells increased at an abnormally rapid rate. Blood from the splenic vein, and particularly from the splenic pulp, exhibited a more pronounced increase in osmotic and mechanical fragility, and a higher proportion of such fragile cells, than did the peripheral blood.

Combined Ashby counts and osmotic fragility studies in patients transfused with normal blood several days before splenectomy indicated that the donor cells survived as in normal recipients. In the splenic pulp, however, the percentage of donor cells was significantly lower than in the peripheral blood, and the osmotic fragility of the donor cells, in contrast to the patient's cells, was essentially unaltered. Thus, the patient's red cells appear to be selectively retained and their fragility selectively increased in the spleen. It is concluded that the spleen contributes to excessive blood destruction in congenital hemolytic jaundice through the mechanism of erythrostasis, which results in abnormally rapid deterioration of the inherently defective red cells of the patient.

Hyperventilation: Mechanism of Symptoms. By GEORGE L. ENGEL, EUGENE B. FERRIS, and (by invitation) MYRTLE LOGAN, Cincinnati, Ohio.

Hyperventilation is an important neurotic symptom, occurring both as a physiological concomitant of the emotions of fear or anger, and as an hysterical manifestation. It is also seen during diffuse encephalopathies and during anoxia (altitude).

Study of patients and normal volunteers has revealed that there are two components to the symptomatology. Reduction in consciousness, with its associated symptoms of faintness, giddiness, fullness in head, etc., is correlated with change in frequency of the EEG, and this may be modified strikingly by changes in blood sugar, oxygen tension of inspired air, posture, and certain cerebral vasodilators. Tetany, on the other hand, is completely unrelated to changes in the electrical activity of the cortex and is apparently peripheral in origin. Of the two groups of symptoms, reduction in consciousness is much more common and more serious, both experimentally and clinically.

Studies of arterial and internal jugular venous blood have not been helpful in elucidating the mechanism of the changes in consciousness.

Although reduction in consciousness may be marked, actual syncope, with falling, is rare. Four mechanisms of syncope have been observed:

1. Vasodepressor syncope, concurrent or delayed;
2. Accentuation of already present orthostatic hypotension;
3. Hysterical syncope or convulsions;
4. Central type.

Differentiation of these types of fainting will be discussed.

Breathholding. Interchange of Gases between the Blood and Lungs during Voluntary Breathholding and the Factors which Influence the Maximum Breathholding Time. By EUGENE B. FERRIS, GEORGE L. ENGEL, CHARLES D. STEVENS, MYRTLE LOGAN, and JOSEPH P. WEBB, Cincinnati, Ohio.

It has been observed that during breathholding the buoyancy of subjects when submerged completely under water decreases at a constant rate which is only slightly less than the rate of total oxygen consumption of the body. The changes in buoyancy are measured by weighing the subjects as they lie under the water, suspended on a weighing pan. The loss of buoyancy or gain in underwater weight is shown to be due to loss of gas (chiefly oxygen) from the lungs.

By underwater weighing, serial study of the arterial blood gases and measurement of the effect of breathholding on the maximal expiratory lung volume, it has been determined that during breathholding the rate of diffusion of oxygen from the lungs into the blood is much faster than the rate of diffusion of carbon dioxide from the blood into the lungs under normal conditions. The higher the tension of inhaled oxygen in the lungs before breathholding, the more rapid is the rate of diffusion of oxygen through the lungs into the blood during breathholding. During breathholding, most of the carbon dioxide produced by the body remains in solution in the blood and tissue fluids and very little diffuses out into the lungs as a gas.

With respect to the duration of maximum time of voluntary breathholding, it has been determined that the stimulus to breathe is dependent upon arterial oxygen content, carbon dioxide tension and to some extent, on sugar content. At oxygen tensions of 75 to 150 mm. Hg in the inhaled air, the length of time of breathholding is directly proportional to the change in oxygen tension. At

higher oxygen tensions of inhaled air, and corresponding tensions of arterial blood there is still a relation, but the effect becomes less and less as the oxygen tension is raised. Serial studies of arterial blood gases and pH during breathholding with varying oxygen-nitrogen mixtures indicate that the decreasing effectiveness of higher oxygen tensions (above 20 per cent oxygen) in increasing the breathholding time is due to the fact that the capacity of the blood to carry oxygen to the respiratory centers is less influenced by raising oxygen tension once the hemoglobin is saturated.

With respect to the stimulus to breathe after maximum voluntary breathholding it is shown that arterial oxygen content and carbon dioxide are inversely and continuously interrelated as factors which influence respiratory activity over such a wide range of oxygen tension in inspired air as 75 to 750 mm. Hg.

These studies throw light on the interrelation of oxygen, carbon dioxide, and other metabolites as respiratory stimulants in man and offer a new approach to the study of pulmonary gas diffusion and respiratory activity in health and disease.

A Study of Congenital Methemoglobinemia. By CLEMENT A. FINCH, HOWARD A. EDER, and RALPH W. MCKEE (introduced by George W. Thorn), Boston, Mass.

A case of congenital intracellular methemoglobinemia was investigated. The patient, a 24-year old boy cyanotic since birth, when seen had a level of 40 per cent methemoglobin (Fe^{+++}).

With his hemoglobin initially converted into a bivalent state (Fe^{++}), the patient formed Fe^{+++} at a rate of 3 per cent a day. When his washed cells were transfused into a recipient, the rate of Fe^{+++} formation was precisely the same. This and *in vitro* studies indicated that the defect was localized in the red cell.

Methemoglobin was then produced by sodium nitrite. Whereas in the normal person Fe^{+++} is rapidly reconverted to Fe^{++}, in this patient there was a complete failure of this reconversion.

The ability of the erythrocyte to reconvert Fe^{+++} to Fe^{++} has been shown to be related to the glucose metabolism of the red cell. No apparent defect of respiratory enzymes, phosphorylation or glycolysis was found in this patient.

Methylene blue, an artificial intermediary between glucose metabolism and Fe^{+++} reconversion, was effective for three years in controlling this patient.

It was concluded that the patient has a biochemical lesion of the red cell, that the fault is one of reconversion of Fe^{+++} to Fe^{++}, and that his red cells lack a methylene-blue-like substance which normally links methemoglobin reconversion to glucose breakdown.

The Effect of Stress Situations on Lymphocytes in Psychoneurotic Patients. By JACOB E. FINESINGER and (by invitation) GREGORY PINCUS, MARY A. B. BRAZIER, and ARTHUR L. WATKINS, Boston, Mass.

The effect of stress situations on the lymphocyte count was studied in a series of psychoneurotic patients. The diurnal rhythm for each patient was established by determining the lymphocyte count at frequent intervals throughout a period of three successive days. A gradual increase in the absolute number of lymphocytes during the afternoon hours was found as has been previously observed in normal control subjects. The patients showed a decrease in the number of lymphocytes when they were interviewed and a disturbing topic was discussed for a period of one hour. This decrease was not observed when a casual topic was discussed with the same patients during an interview at the same time of day for a similar period. Other stress situations such as the exposure to cold for a period of one hour also decreased the lymphocyte count. Uric acid studies were done to determine whether the decrease in lymphocytes was due to a breakdown of lymphocytic tissue. It is concluded that the stress situation resulted in a relative lymphopenia, most probably caused by an increased secretion of adrenal cortical hormone.

Phosphorus Metabolism in Diabetic Coma. By MAURICE FRANKS, ROBERT F. BERRIS, and NATHAN O. KAPLAN (by invitation) and GORDON B. MYERS, Detroit, Mich.

On twenty-eight patients in diabetic coma, determination of blood inorganic phosphorous, glucose, chloride, CO_2 combining power, hematocrit and specific gravity were made at approximately four hour intervals for twenty-four hours. Quantitative urinalyses were made in parallel periods for phosphorus, chloride, glucose, and nitrogen. Blood phosphorus was invariably elevated on admission, and fell precipitously to subnormal levels in all but one case. Urinary phosphorus was subnormal after the first four hours.

Ten patients received either 1319 or 2638 mgm. of phosphorus intravenously as buffered sodium phosphate, injection beginning at 4.8 hours and completed within 2.4 hours. After a transient rise, plasma phosphorus fell to normal or subnormal levels despite the retention of most of the injected phosphorus. Distinct clinical improvement as judged by blood pressure, mental state, and CO_2 combining power occurred during phosphate administration in nine cases. Two died later of cardiac failure, one of pulmonary embolism, giving a fatality rate of 30 per cent compared with a predicted rate of 40.5 per cent, according to criteria of Collen. These cases were compared with seven treated according to method of Joslin with an expected fatality rate of 22.1 per cent and an actual rate of 14.3 per cent and with eleven cases treated with liberal glucose intake, having a predicted fatality rate of 34.8 per cent and actual rate of 27.3 per cent.

The Auriculo-Temporal Syndrome. By A. S. FREEDBERG, R. S. SHAW, and M. J. MCMANUS (introduced by M. D. Altschule), Boston, Mass.

In contrast to the extensive knowledge regarding denervation of sympathetic adrenergic nerves, little information is available concerning the effects of denervation of parasympathetic cholinergic fibres in man. The auriculo-

temporal syndrome affords an opportunity to study the latter. This syndrome is characterized by gustatory sweating on eating, and flushing over the cutaneous distribution of the auriculo-temporal nerve. Two patients have been studied who exhibited this syndrome many years following parotitis with incision and drainage.

Facial sweating and flushing were observed ten seconds or more after chewing food or tasting vinegar, but not after chewing paraffin or after psychic stimulation. During food stimulation no saliva was obtained in one patient from the involved parotid gland, while in the other patient, no differences in the salivary secretion on the two sides were observed. Previous cooling of the involved skin surface diminished or slowed, but did not abolish, the sweating.

In one patient, skin temperature measurements made during cooling and heating of the body showed a decreased response of the involved ear to warming. In the other patient after maximal response to heat occurred, chewing an apple resulted in profuse sweating over the involved cheek, and a sharp further increase in temperature of the involved ear. In both patients, heat sweating was diminished on the involved side.

The involved side showed sweating to significantly higher dilutions of acetyl-choline bromide introduced intradermally by means of a needle or by means of iontophoresis in each instance.

Procainization of the auriculo-temporal nerve on the involved side resulted in anesthesia and abolished the sweating reaction. In both patients after procainization of the superior cervical ganglion on the involved side, sweating occurred after eating.

The intravenous administration of 110 ml. of acetyl-choline bromide (80 μg. per ml.) resulted in slight sweating on the involved side in one patient.

The conclusions drawn from this study are:

(*1*) The auriculo-temporal syndrome is a manifestation of a reflex in which the efferent arc is through the auriculo-temporal nerve or through cranial autonomic fibres adjacent to it, and not through the cervical sympathetic nerves.

(*2*) There is a deficiency in vasomotor, thermo-regulatory, and sensory innervation over the involved area.

(*3*) A local hypersensitivity of the sweat glands to acetyl-choline bromide is present.

(*4*) The mechanism of this syndrome is probably related to denervation hypersensitivity of the sweat glands in the involved area analogous to the hypersensitivity to adrenalin which occurs after post-ganglionic division of sympathetic fibres.

Quantitative Microdetermination of Estrogens by Ultraviolet Absorption Spectrophotometry. By HARRY B. FRIEDGOOD and (by invitation) JOSEPHINE B. GARST, Los Angeles, Calif.

A quantitative spectrophotometric method for assay of estrogens has been developed because of the gross inaccuracy of bioassay and colorimetric techniques. Ultraviolet absorption curves of chemically pure crystalline estrone, estriol and estradiol were determined at intervals of 2 millimicrons between 226 and 300 millimicrons with the Beckman Quartz Spectrophotometer. Concentrations of 0.125, 0.100, 0.075, 0.050, 0.025 and 0.0125 mgm. per ml. were used to determine the concentration-extinction relationship and individual calibration curves. Mixtures of crystalline estrogens were hydrolyzed and extracted by various techniques and assayed spectrophotometrically.

The estrone and estriol absorption curves exhibited minimum density or maximum transmission at 248 millimicrons and maximum density between 280–282 millimicrons with secondary peaks at 288 millimicrons. Another maximum density occurred below 230 millimicrons. Estradiol showed the same peaks except at the lowest extinction which occurred at 252 millimicrons instead of 248 millimicrons. The peak at 280 millimicrons was selected for the construction of calibration curves for each estrogen. The relation between density and concentration followed Beer's law between $E = 0.10$ and $E = 1.00$ at 280 millimicrons.

The identification and quantitation of estrogens through ultraviolet spectrophotometry and chemical separation has made it possible for the first time to analyze and criticize accurately the various techniques currently used for the extraction and separation of urinary estrogens.

The Anti-Anemic Effect of Synthetic Lactobacillus Casei Factor (Folic Acid) in Man. By GRACE A. GOLDSMITH, New Orleans, La.

Synthetic *L. casei* factor was administered to 2 patients with pernicious anemia, 4 patients with nutritional macrocytic anemia, and 1 patient with normacytic anemia with hypoplastic bone marrow. Marked clinical and hematological improvement occurred when 5 to 120 mgm. *L. casei* factor was given daily, either orally or parenterally. Reticulocytes increased 5 to 10 days after therapy was instituted, followed by a gradual rise in erythrocytes and hemoglobin to normal levels in 2 instances, and slightly below normal in 5. The bone marrow, whether initially hypo- or hypercellular, returned to normal in 4 patients in whom studies have been completed. When the initial leukocyte count was low, it increased during therapy.

Four patients have been maintained in good condition for 6 months with the oral administration of 15 to 30 mgm. of *L. casei* factor daily. One person with nutritional macrocytic anemia has been studied for 2 years. The therapeutic effect of liver extract, yeast, several B vitamins and *L. casei* factor will be compared.

Two patients with sprue and 1 with celiac syndrome were benefited by treatment with *L. casei* factor; diarrhea ceased, fat in the stools diminished and lingual papillae regenerated. The erythrocyte count increased in 1 patient, but remained at the initial level of 3.5 to 4 million in the others. Two patients with aplastic anemia and 1 with macrocytic anemia of unknown origin failed to improve when *L. casei* factor was administered.

L. casei factor has marked anti-anemic activity which resembles but is not identical with that of liver extract.

Alteration of Intermediate Metabolism in Hypoleydigism and in Hypopituitarism in Man. By JAMES A. GREENE, Houston, Texas.

The non-protein respiratory quotient was obtained by studying four patients with primary hypoleydigism, four patients with hypopituitarism and secondary hypogonadism, one patient with only hypopituitarism and a normal prepubital boy in an open circuit metabolism chamber for 24 hours after constant diets.

The non-protein respiratory quotient was reduced in all untreated patients, it returned to normal in two primary hypoleydigism cases following testosterone therapy, it was not altered by testosterone therapy in those secondary to hypopituitarism, but was increased to a certain extent following a pituitary extract treatment. It was depressed in a case of hypopituitarism without gonadal abnormality and was normal in a normal prepubital boy.

The decrease of the non-protein respiratory quotients when interpreted in the usual fashion indicate a diminished oxidation of carbohydrate in the metabolic mixture in cases of hypopituitarism or hypoleydigism and suggest that the pituitary gland is responsible for this abnormality. The alteration is an abnormality and not a normal prepubital condition.

The Mechanism of the Fall in Arterial Pressure Produced by High Spinal Anesthesia in Patients with Essential Hypertension. By RAYMOND GREGORY (introduced by George M. Decherd, Jr.), Galveston, Texas.

The problem has been investigated by repeated simultaneous recordings of arterial and venous pressures before and during high spinal anesthesia in 5 patients with normal blood pressure and in 12 studies on 10 patients with a clinical diagnosis of essential hypertension. The cardiac output studies with the acetylene method have been made before and during high spinal anesthesia in patients with normal blood pressures and in patients with clinical diagnosis of essential hypertension. The data show no uniformity in the changes in arterial and venous pressures. The venous pressure may fall without any fall in the arterial pressure. The arterial pressure may fall greatly for a number of minutes before the venous pressure falls. The venous pressure may rise to control levels while the arterial pressure remains at the lowest level of fall caused by the spinal anesthesia. It is concluded that high spinal anesthesia in patients with essential hypertension produces no uniform change in the relationship between arterial and venous pressures; that the changes in the arterial and venous pressures are not causally related; and that the fall in arterial pressure probably is not due to a diminished cardiac output produced by increased venous return.

The Incidence of Penicillin Resistant Staphylococci in War Wounds in Relation to Penicillin Therapy. By J. D. HAMILTON, T. E. ROY and L. GREENBERG (introduced by Donald McEachern), Montreal, Canada.

A series of 503 war wounds, 4 to 20 days of age, were examined bacteriologically at Base Hospitals in Italy. These comprised two groups: One had previously received parenteral penicillin therapy as a prophylactic measure; the second had received no penicillin.

The total dose of penicillin averaged 450,000 units per case given in 3-hourly intramuscular injections of 15,000 units. Cultures were taken only after arrival at Base Hospital, and in the treated group this was from 2 to 14 days after the end of penicillin therapy.

The incidence of pathogenic Staphylococci was not greatly reduced in the penicillin treated group (33 per cent) compared to the control group (37 per cent). There was a marked difference in the proportion of penicillin resistant strains. In the penicillin treated group 49 per cent of strains were resistant and 17 per cent in the control group. Older wounds showed the same differences as the younger ones.

The elimination of sensitive strains from some of the treated wounds, hospital cross infection with resistant strains, and penicillin resistance induced *in vivo* are discussed as factors concerned, but no single factor adequately explains the findings. The difficulty of interpretation is probably related to the interaction of many factors.

The Effect of Roentgen Therapy on Experimental Ocular Vaccinia in Non-Immune and Partially Immune Rabbits. By GEORGE T. HARRELL and (by invitation) HAL W. PITTMAN, LAWRENCE B. HOLT, CHARLES H. REID, J. M. LITTLE, JAMES W. MANKIN, and LESLIE MORRIS, Winston-Salem, N. C.

An accidental human ocular infection with vaccinia secondary to inoculation of the arm was treated with roentgen therapy without the development of residual scarring. The response led to investigation as to whether immunity or roentgen rays were responsible for the improvement. Primary ocular vaccinia and that secondary to inoculation from a separate site have not always been differentiated; hence, the role of immunity cannot be established from the literature. Preliminary experiments suggested that roentgen therapy to primary corneal vaccinia in rabbits diminished the residual corneal opacities and hastened the regression of the acute lesions. Best results were obtained when irradiation was given after the lesion appeared and before it reached its height. In subsequent experiments groups of 15 rabbits were used: (*1*) primary infection, treated with x-ray (*2*) primary infection, untreated; (*3*) secondary infection after inoculation of the flank, treated with x-ray; (*4*) secondary infection, untreated; (*5*) primary infection with subsequent inoculation of the flank; (*6*) trauma of inoculation without infection, treated with x-ray—negative control. Opacities of the cornea were measured by a photoelectric colorimeter. Roentgen therapy did not markedly reduce residual corneal opacities resulting from primary or secondary inoculation. The partial immunity produced by preliminary inoculation of the flank three days before ocular inoculation did not reduce residual corneal opacities. Secondary inoculation of the flank three days after ocular inoculation did not reduce corneal opacities.

Experimental Serum Sickness: Relationship Between the Nature of the Antigen, the Serologic Response, and the Pathological Change in Rabbits Given Purified Bovine Plasma Proteins. By CLINTON VAN ZANDT HAWN and WILLIAM C. BATCHELOR (by invitation) and CHARLES A. JANEWAY, Boston, Mass.

Two different purified fractions of bovine plasma have been injected into rabbits and the fate of the injected protein followed by quantitative immunologic methods. Whereas crystallized bovine serum albumin (CBA) disappears rather slowly from the circulation, bovine serum gamma-globulin (BG) disappears within two weeks of injection. This slow rate of disappearance of CBA has also been observed in dogs and humans.

These differences are paralleled by differences in antigenicity. Both bovine serum and BG appear to be powerful antigens whereas CBA is much less antigenic. The pathological lesions found in rabbits after single large intravenous injections of these proteins differ in extent and distribution, CBA giving rise predominantly to generalized arteritis, and BG to lesions in liver and renal glomeruli. It is possible to correlate both the occurrence and the stage of the lesions with the serologic response—healing occurring when antigen disappears from and antibody appears in the blood.

These observations provide further experimental proof that anaphylactic reactions of the serum sickness type give rise to inflammatory lesions and that the character of the lesions is dependent on the chemical nature of the inciting antigen.

Circulatory Adjustments during Treatment with Large Doses of Sodium Salicylate or Acetylsalicylic Acid. By HANS H. HECHT and B. V. JAGER (introduced by Maxwell M. Wintrobe), Salt Lake City, Utah.

Thirty-five patients received a total of 41 courses of salicylate therapy. Each course was at least of 4 weeks' duration. The plasma salicylate levels were maintained at 250 μg. per ml. or higher. In 32 of these patients an average initial drop of 10 per cent in the volume of packed red cells (venous blood) was observed. The maximum reduction occurred during the first two weeks. Levels equal to or higher than those found prior to treatment were usually observed when salicylate therapy was discontinued. In the presence of anemia, however, an initial reduction in volume of packed red cells was frequently not obtained. In 4 patients with cardiac enlargement and in one without organic heart disease, the onset of pulmonary edema during treatment coincided with the reduction in the hematocrit values. Two of the patients in whom high plasma salicylate levels were obtained died with signs and symptoms of congestive failure which were not apparent when therapy was started. In 100 rabbits which died from salicylate intoxication, gross postmortem studies revealed acute congestion of the lungs, liver and spleen in all instances.

A detailed examination of the cardiovascular system before, during and after treatment with large doses of salicylates in 10 subjects who received 13 courses of therapy revealed a decided increase in the circulating plasma volume during therapy, as determined by chromatographic analysis of dye-plasma mixtures. The average increase in circulating plasma volume amounted to 22 per cent. A change in the opposite direction was noted when treatment was discontinued (average decrease 19 per cent). The average increase in the total circulating blood volume, computed from the plasma volume and hematocrit readings was less striking, though apparent in all cases. This was expected as the circulating red cell mass was not significantly altered in all instances. A great increase in circulating total blood volume was noted in cases with anemia where both the plasma volume and the red cell mass increased considerably under treatment. That the alterations observed did not represent changes in distribution of plasma and red cells in various parts of the venous system was suggested by the observation that simultaneous arterial and venous hematocrit readings were identical.

These cardiovascular changes were associated with a slight decrease in the circulating total proteins and a somewhat greater change in the total circulating albumin. There were no consistent changes in weight, urine volume, venous pressure or vital capacity or in the size of the thiocyanate space. No alterations of plasma and urine sodium concentrations were noted before, during or after treatment in 5 patients maintained on a controlled sodium intake. No difference in response was noted when sodium salicylates were replaced by acetylsalicylic acid.

The changes observed point to possible deleterious effects resulting from treatment with massive doses of salicylates. The increase in circulating fluids apparently is not accompanied by a definite increase in the extracellular fluid space and is not associated with sodium retention. It differs, therefore, from the alteration in fluid balance observed in congestive heart failure.

Elevation of Serum Precipitable Iodine During Pregnancy. By MARTIN HEINEMANN, CARL E. JOHNSON and EVELYN B. MAN (introduced by John P. Peters), New Haven, Conn.

Circulating thyroid hormone is measured more accurately by determinations of serum precipitable iodine than of basal metabolism. Since the latter increases during pregnancy, serum precipitable iodines were investigated in pregnant women. Their histories and physical findings excluded thyroid abnormality. Compared with a mean of 5.6 ± 1.3 μg. per cent in approximately 75 normal women, 35 determinations in 16 normal pregnant women ranged from 6.2 to 11.2 with an average of 8.4 μg. per cent, concentrations otherwise indicative of hyperthyroidism. This increase was noted as early as the third week of pregnancy and subsided within two weeks after delivery. It is not, therefore, correlated with the rise of basal metabolism which is a phenomenon of late pregnancy.

The implications of increased serum iodines during pregnancy are not clear. Thirty drops daily of Lugol's solution for one month did not diminish elevated serum

iodines in 2 cases. Iodine concentrations were identical in umbilical and maternal venous serum at birth in 2 instances. Of two pregnant females with serum iodines less than those of the 16 normals, one miscarried for unknown reasons during the third month. The second threatened to miscarry in the fifth month but continued pregnancy after intravenous administration of thyroxin.

Elevated serum iodine concentrations seem to be physiologic during pregnancy.

Folic Acid in Pernicious Anemia. Studies on Effect, Mechanism of Action, and Excretion. By ROBERT W. HEINLE and (by invitation) ARNOLD D. WELCH and EVELYN M. NELSON, Cleveland, Ohio.

Although no failure in treating pernicious anemia in relapse with synthetic folic acid (2 to 100 mgm. daily) has been reported, only minimal reticulocyte responses occurred in one patient following each successive period of intramuscularly administered folic acid: 1, 6 and 12 mgm., respectively. With continued vitamin administration, xanthopterin given orally appeared to produce a fourth small response. Since 15-unit liver extract subsequently produced a theoretically maximal response, factors accessory to folic acid may be involved in certain cases.

A less than theoretically maximal, delayed response occurred in another patient with pernicious anemia in relapse, after daily intramuscular administration of synthetic folic acid (5 mgm.). Xanthopterin did not perceptibly augment the effect of the vitamin.

A third patient, extremely sensitive to liver extracts, relapsed while taking 16 'Extralin' capsules daily. Forty mgm. of synthetic folic acid daily by mouth caused remission.

Normal gastric juice, duodenal content, or both together, did not split *L. casei* factor from purified conjugated folic acid. Studies on therapeutic activity and human enzymic splitting of the conjugate are in progress.

The daily urinary excretion of *L. casei* factor in treated patients varied widely: oral—9 to 24 per cent; parenteral—15 to 75 per cent.

Radioactive Iodine Treatment of Graves' Disease—A Progress Report. By SAUL HERTZ, Boston, Mass., and (by invitation) ARTHUR ROBERTS, Cambridge, Mass.

Before the meeting of this society in May, 1942, a preliminary report by the authors presented data on their first trials of radioactive iodine in the therapy of patients with Graves' disease. Since that time, additional cases have been treated and a follow-up on the entire series of thirty-one (31) cases is presented in this report. The results are analyzed in the light of the entire experience at the Massachusetts General Hospital and elsewhere to date of January 15, 1946, with respect to the application of atomic energy for the internal Beta-irradiation of the hyperplastic thyroid of these subjects.

Clinical data are given which indicate strongly the therapeutic efficacy of this method in the treatment of Graves' disease by non-surgical means. The specific manner in which the therapy may be practically employed in a relatively inexpensive, highly effective, and safe program is outlined. The prediction is made that this method may displace the surgical ones now in vogue for the treatment of this disease when atomic energy sources are made readily available for controlled medical usage. The advantages and disadvantages of the several techniques which have been employed to date in this therapeutic program are discussed.

Quantitative Studies in Man of the Removal of Bromsulphalein from the Blood. By F. J. INGELFINGER, Boston, Mass.

After bromsulphalein, 150 mgm. per sq. m. surface area, is injected intravenously, its disappearance rate from the blood of normal subjects is such that a constant percentage of the dye present in the blood is removed per minute (between 10 per cent and 15 per cent per minute). When similar doses are given to patients with extra- or intrahepatic biliary obstruction, or when larger or repeated doses are given to normal subjects, the disappearance rate progressively decreases, possibly as a result of saturation of the removal mechanisms. In cases of cirrhosis without jaundice, the disappearance rate remains fairly constant, but ranges between 1.5 per cent and 5 per cent per minute.

When a constant intravenous infusion of bromsulphalein is given immediately after an initial injection of 50 to 200 mgm., a constant blood level of the dye can be achieved if less than 3 mgm. per sq. m. is infused per minute. This figure is not appreciably affected by the size of the initial dose, although the height of the constant level achieved varies with the amount initially injected.

Others have suggested that bromsulphalein is removed from the blood in two stages: a rapid take-up in a storage space, and a slower excretion by the liver. These studies support this suggestion and indicate that the maximum excretory rate of the liver approximates 3 mgm. per sq. m. per minute.

Tropical Nutrition. Biochemical and Clinical Observations on Troops. By R. M. KARK and W. B. BEAN and (by invitation) H. F. AITON, C. R. HENDERSON, E. D. PEASE, R. E. JOHNSON, and L. M. RICHARDSON, Ottawa, Can., Ft. Knox, Ky., Chicago, Ill., and Boston, Mass.

During 1945 two separate teams who trained together and used almost identical methods made systematic observations on the nutrition, health and fitness of troops in the tropics. The U. S. team studied 600 men in the Pacific; and the Canadian, 1019 Indian soldiers fighting in Burma. Data on environment, work, catering and food intakes were collected. Medical examinations and fitness tests were administered. Samples of the urine and blood of each subject were analyzed in specially constructed airborne field laboratories for hemoglobin, protein, salt, vitamins and acetone. The results could be interpreted by comparison with data collected in a similar way under rigidly controlled field conditions in North America.

Effects of Stress with a Note on "Tropical Deterioration." With stress men deteriorate similarly in tropical, temperate or cold environments. When diet was ample

and tropical disease well controlled, even white troops were efficient and healthy after two years of arduous field service.

Interrelations among Dietary Intake, Biochemical Measurements, Physical Efficiency and Clinical Findings. Close correlations existed between calculated dietary intakes and biochemical measurements. Few statistically significant correlations were found among biochemical values, fitness scores and clinical findings.

Nutritional Requirements for the Tropics. No support is given to the proponents of a large intake of vitamins or a low intake of animal protein.

Acute Osteoporosis of Disuse: A Metabolic Study. By F. Raymond Keating, Jr., Marschelle H. Power, H. Herman Young, and Haddow M. Keith (introduced by J. H. Means), Rochester, Minn.

A 15-year-old boy who had so-called vitamin D resistant rickets was immobilized by a plaster cast from the waist down after osteotomies on both femurs. Metabolic balance studies were conducted during immobilization and following resumption of activity. Diet and excreta were analyzed for calcium, phosphorus and nitrogen, and frequent analyses of the blood and periodic roentgenograms of the skeleton were made.

Marked hypercalcemia and hypercalcinuria, accompanied by marked reduction in the concentration of alkaline phosphatase in serum, occurred during immobilization. These data suggested that immobilization had seriously impaired osteoblastic activity and permitted rapid demineralization of the skeleton. Roentgenograms showed the demineralization to be pronounced and largely limited to the legs and lower part of the spinal column. The hypercalcemia probably occurred because calcium was released by demineralization at a rate exceeding the maximal capacity of the kidney to excrete it.

During a period of increasing physical activity, the level of calcium in serum decreased and that of alkaline phosphatase rose concurrently, but hypercalcinuria persisted until calcium in serum had returned to normal levels. Further orthopedic surgery permitted additional studies throughout a second prolonged period of immobilization. The intense changes previously noted did not recur. The significance of these observations is discussed.

Oxidation and Reduction Systems in Articular Cartilage. By Friedrich Klemperer (introduced by William W. Beckman), Boston, Mass.

Although respiration of articular cartilage is negligible, it was shown by Bywaters that in the presence of methylene blue appreciable amounts of oxygen are consumed. Hills found that this reaction was accompanied by CO_2 production and, without convincing experimental evidence, postulated that in the presence of methylene blue, cartilage is able to oxidize lactate to pyruvate, which is then decarboxylated with the formation of acetic acid. In the investigation to be reported it was impossible to demonstrate that oxidations that form part of the glycolytic cycle account for the reduction of methylene blue by bovine cartilage. Concentrations of iodo-acetate which inhibit glycolysis completely do not decrease the rate of methylene blue reduction, thus disproving the possibility of a reaction of phosophorylated glyceric aldehyde and methylene blue. In the presence of iodo-acetate, no formation of lactic acid was observed. Nevertheless, under these conditions the dye-induced oxygen uptake did not decrease the small amount of preformed lactic acid, and the addition of lactic acid had no accelerating effect on the reaction. Thus it would appear that lactic acid is not the substrate of methylene blue reduction. Neither glucose nor glycogen was oxidized by methylene blue in the presence of cartilage, and ammonia was not formed. Coenzymes, which are necessary for the maintenance of glycolysis in frozen and ground cartilage, were not involved in the oxygen uptake catalyzed by methylene blue. The reaction was not inhibited by fluoride arsenate or selenite but was abolished by heating and by caprylic alcohol. The mechanism for reduction of methylene blue in cartilage remains unexplained.

The Pathogenesis of Renal Failure in Patients with Severe Thermal Burns. By S. M. Levenson, W. E. Goodpastor, C. C. Lund, and F. H. L. Taylor (by invitation), and H. J. Tagnon, Boston, Mass.

Lasting impairment of renal function is seen frequently in patients dying as a result of severe thermal burns, and often contributes to the fatal outcome. In an attempt to elucidate the pathogenesis of this serious complication, a detailed clinical and pathologic study was carried out in 47 patients with fatal thermal burns.

A high correlation was found between clinical evidence of kidney dysfunction and significant renal changes observed at post mortem. Lasting impairment of renal function, as evidenced by persistent decrease in clearance on nonprotein nitrogen products, azotemia and oliguria or anuria persisting beyond the period of shock, was associated with definite morphologic changes at post mortem examination. These changes consisted principally of pigmented casts, epithelial casts, tubular necrosis, and, in cases surviving 48 hours, the beginning of tubular regeneration. The pigment casts gave positive staining reactions for red blood cell pigments. Patients with normal kidney function showed no significant renal changes at autopsy.

Hypoproteinemia, alkalinization, and toxic effects of sulphonamides, mercurial preservatives in plasma, or blood transfusion reactions were ruled out as contributing to the renal damage. The important etiological factors were: extent of third degree burn (over 30 per cent of the body surface), deep and prolonged shock, and hemoglobinuria consequent to the hemoglobinemia which was constantly seen in patients with severe burns.

It appears that under the conditions of prolonged renal ischemia, secondary to severe shock, the products of hemolysis are "toxic" to the kidneys, leading to both clinical and pathologic evidence of renal damage.

A Small Visual Comparator for the Rapid Determination of Plasma Volume. By ALICE LOWELL, FOREST E. KENDALL and WALTER MEYER (introduced by David Seegal), New York, N. Y.

A small visual comparator (3.75 × 3.75 × 1.75 inches) has been developed for the rapid determination of plasma volume. Measurements are made on serum samples taken before and 10 minutes after the intravenous injection of a known amount of the blue dye, T–1824. Repeated measurements can be made in the same patient.

This instrument has been used in 108 plasma volume determinations covering a range between 1300 and 6000 ml. The validity of the results obtained was checked by measurements made with a Bausch and Lomb spectrophotometer. The values derived from the two methods agreed within the margin of error inherent in plasma volume determinations. The average difference was 0.065 per cent; the standard deviation, 3.15 per cent.

This inexpensive instrument, because of its simplicity and compact size, can be used at the bedside or in the hospital emergency ward. It was originally developed to meet a possible need in an appropriate Army medical unit.

The Functional Capacity of Thyroid Tumors as Judged by Radioactive Iodine Uptake. By JANET W. MCARTHUR (by invitation) and OLIVER COPE, Boston, Mass.

Radioactive iodine in tracer dosage was administered preoperatively to eighteen patients with discrete nodules of the thyroid. The radioactivity of digests of the tumor tissue was determined and compared with that of the adjacent uninvolved tissue.

Of the eighteen tumors, twelve were benign. They included four involutional nodules, four struma nodosa micro et macrofolliculare, two fetal adenomas, one papillary adenocystoma and one Hurthle cell adenoma. The iodine collected by the less differentiated tumors, such as the fetal adenomas and Hurthle cell adenoma, was one-fiftieth to one-hundredth of that collected by the uninvolved portion of the gland. Four of the differentiated tumors collected more iodine than the uninvolved tissue, one twenty times as much. Two other differentiated tumors absorbed all of the iodine, the uninvolved tissue none; the patients had mild hyperthyroidism.

The six malignant tumors included papillary adenocarcinoma, metastasizing struma nodosa and adenocarcinoma. These collected from none to one-fourth of the radioactive iodine taken up by adjacent uninvolved tissue. In three instances there was a detectable collection of iodine by the tumor metastases.

The Circulation at Rest during Convalescence. By GEORGE R. MENEELY, E. BUIST WELLS and ALBERT SEGALOFF (introduced by Hugh J. Morgan), Nashville, Tenn.

The following measurements were made upon a group of convalescent patients who had undergone infectious disease or surgical operation: height, weight, pulse, respiration, blood pressure, pulse pressure, venous blood pressure, blood velocity from arm to tongue, hands, perineum and feet, cardiac output per stroke and per minute, transverse diameter of the heart and cardiothoracic ratio, oxygen consumption, basal metabolic rate, ventilation, tidal air, utilization coefficient, hematocrit value, total blood volume plasma volume and cell volume, plasma total proteins, total circulating plasma protein and an electrocardiogram. All studies were done under the basal conditions. None of these observations indicated any characteristic abnormality of the circulation when the results were compared with currently accepted normal standards. Individual deviations were frequent but were understandable clinically as manifestations of the disease from which the patient had suffered, for example, anemia following therapeutic malaria. One may therefore conclude that none of these tests are of any use as a routine procedure for the clinical classification of convalescence.

Follow up studies revealed small but important alterations from "normal" which could only be detected by comparing the individual with himself as a control. These differences were approximately one-half liter blood volume deficit and approximately 35 per cent venous pressure deficit during convalescence. It was also observed that the patients gained an average of 3.87 kilograms.

The Treatment of Lymphoblastic Leukemia with Crude Myelokentric Acid. By F. R. MILLER and (by invitation) H. W. JONES and P. A. HERBUT, Philadelphia, Pa.

Crude myelokentric acid was extracted from the urine or feces of patients with chronic myeloid leukemia.

The material was emulsified with alkaline water at a pH of 7.5. After sterilization it was given to seven patients with lymphoblastic leukemia. This was done in an effort to stimulate myeloid proliferation.

Twelve partial remissions occurred in treating the seven patients. These consisted of diminution of the size of lymph nodes and spleens, improved appetites and increase in body weight, as well as peripheral blood changes. A shift from a lymphoblastic to a lymphocytic blood picture occurred and was followed by a moderate to marked leukopenia, and then by the appearance of myeloid cells, including reticulocytes and platelets in the peripheral blood.

Eventually all died and five necropsies were obtained. All organs exhibited less leukemic infiltration than untreated cases. The infiltrations were not uniform as in lymphoblastic leukemia but exhibited considerable pleomorphism, an increase in reticulum cells, reticulum and also a few cells resembling Sternberg cells. The bone marrows appeared almost hypoplastic and the livers showed a "washing out" of lymphoid elements.

Conclusion: Partial remission occurred with this treatment. The necropsy findings might be interpreted as either beginning healing or changes simulating the onset of Hodgkin's disease.

Comparative Studies of the Treatment of Diabetic Acidosis with and without Glucose. By MAX MILLER and (by invitation) ROBERT DUMM, ERNEST BUEDING, IRENE RASKOWSKI and JACK OWENS, Cleveland, Ohio.

To evaluate the relative merits of the use of glucose from the beginning of treatment, eight instances of

diabetic acidosis were studied. All cases received insulin at approximately similar rates; three cases were not given glucose until four to seven hours after onset; the remaining five received 50 to 75 grams intravenously the first hour, and 10 to 20 grams each hour thereafter. One patient was admitted in acidosis twice, with approximately the same initial CO_2-combining power, blood sugar and blood acetone levels; the first time she received insulin plus glucose; the second, insulin alone. In a second subject, acidosis was precipitated on two occasions by withdrawal of insulin, and was treated with the same amount of insulin, fluids and saline, glucose being added the second time.

No deleterious effects of the use of glucose plus insulin were detected. On the contrary, it was found that blood pyruvic acid rose only when glucose was given with insulin, indicating enhanced pyruvate formation and increased utilization of carbohydrate. Similarly, blood acetone values fell as rapidly, or more so, with glucose. Glucose balances indicated increased retention (hence either utilization or storage) with insulin plus glucose.

Water and Electrolyte Metabolism in Burned Patients. By FRANCIS D. MOORE and (by invitation) JOHN L. LANGOHR, Boston, Mass.

The requirement of the burned patient for water and electrolyte has been studied by a variety of technics. These have included studies of electrolyte balance including analyses of the burn exudate, studies of the volume of body water available for the solution of extracellular anions and cations, histochemical examination of burned skin, and variations in treatment schedules.

The results are quite consistent and demonstrate an early and persistent expansion of the extracellular space, an early negative potassium balance with positive sodium balance reversing itself after 48 to 72 hours, and an ingress of sodium into the cells of burned skin.

These changes divide themselves into two phases, an early "shock phase" and a subsequent water retention phase."

Therapy based on these physiologic considerations, taking into account the weight of the patient and his expected extracellular space expansion, appears to be more effective than treatment carried out according to surface area or hematocrit alone.

The Histologic Changes in the Nervous System and Muscles in Rheumatoid Arthritis. By L. RAYMOND MORRISON and ALFRED O. LUDWIG (by invitation) and CHARLES L. SHORT, Boston, Mass.

Post mortem histologic examination of the nervous system was carried out in 40 patients with rheumatoid arthritis and in a control group of similar age distribution but without arthritis. No specific lesions were found in the brain or spinal cord but alterations usually attributed to aging, including degeneration and absence of anterior horn cells and loss of myelin with concomitant gliosis, were more pronounced in the cases with rheumatoid arthritis.

In addition, lesions were found in the peripheral nerves and muscles like those reported by several other investigators. In 26 out of 30 cases, small collections of hematogenous cells, chiefly mononuclear, were present in the nerve sheath, usually the perineurium. While these lesions were not ordinarily in direct relation to the parenchymatous tissue, the axons and myelin sheaths often showed pathologic changes along with retrograde anterior horn cell degeneration. Similar cell collections were found in the muscles in 4 out of 10 cases, usually in the perimysium rather than in the muscle tissue itself. While the peripheral nerve and muscle lesions suggested specificity, closely corresponding collections were found in cases of dermatomyositis and acute disseminated lupus erythematosus.

Involvement of the neuromuscular system by the disease process may thus account for the neurological manifestations frequently present in rheumatoid arthritis. A similar explanation now seems likely for the spontaneous skeletal muscle activity found by the authors in electromyographic tracings, since it resembles that observed in certain known diseases of the nervous system.

Influence of Stilbestrol on Advanced Cancer of the Breast. By IRA T. NATHANSON, Boston, Mass.

A number of carcinogenic hydrocarbons possess the property of retarding the growth of normal and malignant tissue. Estrogens are similar in chemical structure to some of the carcinogens. This prompted a group of English investigators to treat advanced cancer with certain estrogens. Accordingly we treated a series of women with advanced cancer of the breast with relatively large doses of stilbestrol. Preliminary observations indicate that stilbestrol may exert an initial beneficial although apparently temporary effect on the primary tumor in a number of patients. In this group ulcerations decreased in size or became epithelialized, masses became smaller, skin changes appeared and cicatrization was observed. The effect on the metastases is still open to question. In general, the favorable responses were confined to older women. Usually the disease in younger women was unaltered in its course or was possibly accelerated. This phenomenon is of interest since it is one of the few examples in which a malignant tumor is influenced by an administered humoral agent. The mechanism of action is not clear.

Action of Penicillin on Staphylococcus in Vitro. By R. F. PARKER, Cleveland, Ohio.

When a growing culture of *Staphylococcus aureus* is exposed *in vitro* to the action of penicillin in appropriate concentration, there is a progressive fall in the number of viable cells. If after a period of exposure to penicillin the cells are transferred to fresh medium containing no penicillin, there may be a further decline in the number of viable cells. Multiplication then begins again, but only after a period during which the population is stationary. If the culture is exposed for a short time to an appropriate concentration of penicillin, and the cells then

transferred to penicillin free medium, there is no detectable decrease in the number of viable cells. However, multiplication of cells begins only after the lapse of a time during which the population is stationary. The time between removal of the cells from penicillin-containing to penicillin-free medium and the beginning of active cellular multiplication is characteristic of the strain of Staphylococcus, and appears to be directly related to its penicillin sensitivity.

Eunuchoidism Due to Hypopituitarism Limited to the Gonadotrophic Hormone. By K. E. PASCHKIS, A. CANTAROW and A. E. RAKOFF (introduced by Hobart A. Reimann), Philadelphia, Pa.

The three cases to be presented are adults exhibiting the typical picture of eunuchoidism. Repeated hormone assays revealed absence of gonadotrophin excretion, indicating pituitary failure, whereas patients with eunuchoidism due to primary testicular failure excrete excessive amounts of gonadotrophin. We have not encountered a report of similar observations in the literature. All studies, including roentgenograms, 17-ketosteroid excretion and insulin tolerance tests revealed no other evidence of hypopituitarism.

These patients were accordingly treated with gonadotrophin rather than testosterone. In one case treated with chorionic gonadotrophin over a sufficiently long time to evaluate results, the patient, at the age of 22 years, went through a puberty induced by the administered hormone. Not only did his secondary sex characters develop but he had erections and ejaculations containing live spermatozoa. Observations were made also of the effect of implantation of pellets and pituitary gonadotrophic hormone on the development of sex characters and the excretion of gonadotrophins.

The practical importance of such observations is obvious, because testosterone therapy usually applied in such cases without adequate studies does not permit of initiation of spermatogenesis and fertility. These studies raise the interesting question of the mechanism of pituitary deficiency in a single hormone.

Electrophoretic Distribution of Proteins in Serum, Plasma and Synovial Fluid of Patients with Rheumatoid Arthritis. By GERTRUDE E. PERLMANN and DOROTHY KAUFMAN (introduced by Walter Bauer), Boston, Mass.

The electrophoretic method has been used to study the apparent distribution of albumin, alpha-, beta- and gamma-globulins in plasmas, sera and synovial fluids of 23 patients with rheumatoid arthritis. The results obtained thus far suggest an elevation of the alpha-globulins during the early courses of the disease, which is followed by a predominance in the gamma-globulin in later stages of the disease. In some cases the protein pattern returned to normal as the disease became quiescent.

A comparative study of the electrophoretic patterns of synovial fluid and serum in rheumatoid arthritis supports the hypothesis that there is an increased permeability of the tissues between the blood and the joint space. Two types of fluids were distinguished. In one type the apparent distribution of the proteins followed closely the one recorded for the corresponding serum. In other cases, however, a marked elevation of a component having the same mobility as gamma-globulin was found in synovial fluid in the presence of a relatively low concentration of this component in serum. This suggests the possibility of a local production of proteins or an enhanced tissue breakdown.

Renal Regulation of Sodium Exchange. By AURELIA POTOR (introduced by L. H. Newburgh) Ann Arbor, Mich.

When the concentration of a solute in urine is different from that in glomerular filtrate, work has been done to establish this difference. This osmotic work can be calculated.

Our studies are concerned with renal tubular osmotic work involved in regulation of sodium concentration in extracellular fluid. Normal subjects can reduce the concentration of urinary sodium to less than 40 mgm. per 24 hours, when sodium intake is very small. Since in this case the work results in dilution of sodium in urine, it follows that for increasing urinary volumes, an increasing amount of work must be done, other factors remaining constant. The total urinary sodium of a person with diabetes insipidus was reduced to 40 mgm., on an intake of 250 mgm. of sodium, even though 8 liters of urine were produced daily. By contrast, patients with nephritis may be unable to do a comparable amount of osmotic work, and sodium deficit will result unless they receive high sodium diets. The lowest level of urinary sodium achieved by a patient on an intake of 300 mgm. of sodium was 750 mgm. daily. This excessive loss of sodium was accompanied by a proportionate loss of water, and the ensuing dehydration resulted in collapse.

Pathogenesis of Burn Shock. By MYRON PRINZMETAL and (by invitation) H. C. BERGMAN and H. E. KRUGER, Los Angeles, Calif.

Local fluid loss is an inadequate explanation for shock resulting from burns, for it has been demonstrated that following severe burns, shock and death may occur with little or no local fluid loss. Contrariwise, following less severe burns which are accompanied by considerable loss of fluid, severe shock does not develop. The nervous system is not implicated since denervation of the burned areas does not prevent the onset of shock. In burned animals without edema formation there is a marked diminution in the circulating blood volume as represented by the bleeding volume. It has been found that the "lost blood" remains in atonic visceral capillaries. The number of open capillaries and the hemoglobin content of the viscera of burned animals following exsanguination is greatly increased over that of controls. The capillary atony is a primary disturbance because it occurs immediately following severe burns. A humoral factor responsible for the capillary disturbance has been directly

demonstrated by two methods: (*1*) transfusion of blood from burned animals into normal animals causes a reduction in the bleeding volume of the recipients, and (*2*) perfusion of blood from burned animals through the kidneys of normal animals produces the capillary lesion identical to that found in burn shock.

The Effect of Estrogen Therapy in Acromegaly with Observations on the Use of the Serum Phosphorus Level as an Index of Pituitary Growth Hormone Activity. By EDWARD C. REIFENSTEIN, JR., (by invitation) LAURENCE W. KINSELL, and FULLER ALBRIGHT, Boston, Mass.

The authors have observed that the serum "inorganic" phosphorus level is elevated without a corresponding fall in the serum calcium level in most acromegalic patients. The same is true in growing children.

The authors have also observed that the high serum phosphorus level and many of the symptoms in acromegaly respond to estrogen therapy. It is known from the literature that estrogen administration inhibits growth in animals and that this inhibition is prevented by simultaneous administration of growth hormone. It is, therefore, suggested that, other factors being equal, a high serum phosphorus level may be an index of pituitary growth hormone activity.

Thirdly, the authors have observed that the negative calcium balance which is a common finding in acromegaly responds to estrogen therapy as does the calcium balance of post-menopausal osteoporosis.

This presentation will include the evidence for the above observations and a discussion of certain implications, both academic and clinical.

Observations on Thiamin Deficiency in the Rhesus Monkey. By J. F. RINEHART and (by invitation) MELVIN FRIEDMAN and L. D. GREENBERG, San Francisco, Calif.

Studies of thiamin deficiency on the Rhesus monkey have revealed the following: Food consumption and weight begin to decline approximately 2 weeks after the onset of thiamin deprivation. At this time the blood thiamin concentration is 4 μg. or less per 100 ml.[1] Apathy and weakness follow. If thiamin is administered there is an immediate increase in food consumption and gain in weight. If depletion is prolonged the animals become ataxic and at times develop respiratory distress, ptosis, and tremors. Acute or recurrent thiamin depletion has produced a moderate anemia characterized in the acute phase of deficiency by suppression of reticulocytes. Reticulocytes rise on administration of thiamin. In this species thiamin is definitely related to erythropoesis.

By subjecting animals to recurrent depletion, striking lesions develop in the central nervous system. Symmetrical areas of degeneration are found in the putamen and caudate nuclei in a majority of the animals, and in one or more cranial nerve nuclei in nearly all instances. These observations suggest that thiamin deficiency might be a contributory factor in Parkinson's disease and other selective degenerations of the basal ganglia. The peripheral nerves show no lesions.

Peculiar degenerative changes and focal necroses which occur in the cardiac muscle fibers are described.

[1] Normal values range from 5.5 to 10 μg. per 100 ml.

Newer Antithyroid Drugs. By ROBERT H. WILLIAMS, and WALTER F. ROGERS, JR. (by invitation), Boston, Mass.

In the course of using thiouracil in the treatment of 280 individuals with thyrotoxicosis it was found that this drug was not only of advantage in the preoperative preparation of the subjects but it offered distinct promise in the medical management of the disease. In almost one half of a group of 100 patients, treated for an average of about 9 months, on cessation of treatment remissions have been sustained. Moreover, in most of the subjects with prolonged treatment the size of the thyroid gland decreased.

These results prompted a search for a compound with the beneficial effects of thiouracil but without as significant toxic effects. More than 100 substances were tested for antithyroid action in rats and 12 of these were tested clinically. Tetramethylthiourea, diethylthiourea, thiothymine, thiobarbital, orthophenylene thiourea, p-aminobenzoic acid and 3, 5, diiodo-o-aminobenzoic acid were not found to offer distinct advantages over thiouracil. However, in the clinical studies conducted thus far, compounds with methyl, propyl, butyl, or isobutyl radicles substituted in the sixth position of thiouracil appear to be superior to the latter. Pharmacologic studies reveal significant variations in the rate of absorption, distribution and excretion of these compounds, as well as in the amount of antithyroid action. Therefore, the dosages of the drug are varied accordingly.

The Effect of Atabrine on the Central Nervous System. Clinical and Electroencephalographic Studies. By JOHN ROMANO, GEORGE L. ENGEL, and EUGENE B. FERRIS, JR., Cincinnati, Ohio.

Clinical and electroencephalographic observations were made on five normal adults during the administration of atabrine. Daily dosage ranged between 0.2 gram to 1.2 grams until plasma level exceeded 100 gamma per liter or until the severity of symptoms led to discontinuation. Period of the drug administration did not exceed ten days. In all cases evidence of marked psychologic stimulation occurred, and the EEG showed a significant shift toward faster frequencies. These manifestations appeared by the third day and persisted for six to eight days after the drug had been discontinued and until the plasma level had fallen to less than 40 gamma per liter. These data constitute evidence that atabrine acts as a cortical stimulant.

The Effect of Estrin in Osteogenesis Imperfecta. By MARIAN W. ROPES, ELSIE C. ROSSMEISL (by invitation), and WALTER BAUER, Boston, Mass.

Six patients with osteogenesis imperfecta, ranging in age from 3 to 14 years have been studied. In accordance

with the results of previous investigators, the concentrations of calcium and phosphorus in the serum and the excretion of calcium and phosphorus on high calcium diet were found to be within normal limits.

Five of the patients were treated with estrin (using alpha-estradiol benzoate or diethyl-stilbestrol). In 4 an increased retention of calcium (varying from 0.1 to 0.3 gram per day) occurred from 12 to 18 days after therapy was started. The calcium retention persisted while therapy was continued but the calcium excretion returned to the normal level with cessation of estrin treatment. In the fifth patient, aged 3 years, no definite alteration in calcium excretion occurred. In one case methyltestosterone caused a similar though less marked retention of calcium (0.1 gram per day). In 3 patients the serum alkaline phosphatase level rose 1 to 6 units under therapy. Since the institution of therapy, fractures have not occurred in the 4 patients with increased retention of calcium despite the fact that they have had severe falls, in some cases with resulting joint sprains. Roentgenograms showed a significant increase in calcification of the bones only in one case, who was treated intermittently over a period of 4 years.

The results indicate that estrin therapy can in some cases cause retention of calcium in osteogenesis imperfecta.

The Precordial Electrocardiogram in Pulmonary Infarction. By FRANCIS F. ROSENBAUM (introduced by Frank N. Wilson), Ann Arbor, Michigan.

Observations of the precordial electrocardiogram have been made in four patients with pulmonary infarction. Prominent S waves in lead I, conspicuous R waves in V_R, and other less specific changes occurred in the standard and unipolar limb leads in all cases. The precordial electrocardiogram in one patient was characteristic of right bundle branch block. In two other instances the records from the precordium were not suggestive of either right bundle branch block or right ventricular hypertrophy, even though the simultaneous standard leads displayed conspicuous S waves in lead I. One of these patients did display late R deflections in leads V_1 and V_E 17 hours later. Sharp inversion of the T waves in leads V_1, V_2, V_3 and V_E and sometimes V_4 was a consistent finding in all cases. This change in the S waves in lead I disappeared completely in follow-up studies. The variability of the findings in individual cases suggests that the extent of the pulmonary infarction influences the character of the electrocardiogram. It is clear that the transient changes in the QRS complex of the limb leads considered characteristic of pulmonary embolism are not due to right bundle branch block or any other conduction defect that can be detected by means of the usual precordial leads. Whether they are the result of a change in position of the heart due to dilatation of the right ventricle or to a local disturbance in the activation of the conus arteriosus is not clear.

The Metabolism of Inorganic and Hemoglobin Iron. By JOSEPH F. ROSS, Boston, Mass.

Uncertainty exists regarding the relative therapeutic effectiveness of iron administered by mouth and by parenteral injection. Furthermore, the immediate fate of the iron contained in transfused erythrocytes and in intravascularly liberated hemoglobin is obscure. We have investigated these problems with the radioactive iron technique. Inorganic salts of iron, normal human erythrocytes and hemoglobin solutions "labelled" with radioactive iron have been administered to human subjects by mouth and by intravenous injection. The extent and rate of utilization of the labelled iron in the circulating erythrocytes of the recipient have been determined. We have found that the rate of utilization of iron is identical regardless of mode of administration. Thus the iron liberated from erythrocytes or hemoglobin destroyed after transfusion appears in the erythrocytes of the recipient just as rapidly but not more so than inorganic iron given by mouth or injection. Utilization is complete in approximately twenty-one days in all instances, and approximately sixty per cent of the amount of iron absorbed appears in the circulating erythrocytes, an amount proportional to the percentage of total body iron existing in circulating erythrocytes.

These findings indicate that once iron has been introduced into the body it enters a "metabolic pool" of body iron and is metabolized in identical fashion regardless of its mode of entry. The rate of metabolism of this labelled iron sheds new light on the rate of erythropoiesis and hemoglobin formation.

Heredity (? Sex-linked) Anemia. By R. WAYNE RUNDLES (introduced by David T. Smith), Durham, N. C.

Two families of north European ancestry have been studied in which a severe hypochromic, microcytic anemia with pronounced erythrocyte deformity, splenomegaly and sometimes hepatomegaly has recurred through several generations. The hematologic features of the anemia are comparable to those of severe Mediteranean anemia except for the absence of excessive hemolysis, icterus or reticulocytosis, leukocytosis with myeloid immaturity, and skeletal changes. Ordinary antianemic measures and splenectomy have been of no therapeutic value.

The anemia occurred only in those of the male sex, and was transmitted from generation to generation by females who, although not anemic, could be identified as carriers of the disease trait by the presence of splenomegaly or minor red cell abnormalities. Four anemic males and 11 carrier females were identified among the 47 living members of the 2 families examined. Neither the anemia nor the carrier state was inherited in parallel with the agglutinogens A_1 A_2, B, M or N, the "secretor factor," or the taste perception of phenylthiocarbamide. The inheritance pattern was compatible with that of sex-linkage in which the disease was recessive, or incompletely recessive, in females. The findings did not completely exclude, however, inheritance as an autosomal dominant character

reaching full expression in males and being incompletely recessive in females.

An Analysis of the Variable Amplitude of the First Heart Sound in Complete A–V Block. By DAVID A. RYTAND, San Francisco, Calif.

In phonocardiograms of 14 patients with complete A–V block, the peak amplitude of the first sound was measured in 1194 cycles and correlated with the corresponding P–Q intervals of those cycles in a simultaneously recorded electrocardiographic lead.

Confirming earlier studies, peak amplitude was greatest with short (about 0.10 second) P–Q intervals; it then averaged twice "normal." As the interval lengthened, the amplitude diminished until it was only one-fourth "normal" at intervals of 0.20 to 0.30 seconds. In most of the elderly patients, the first sound continued at this low level as the P–Q interval increased even up to one second.

In the youngest children, however, P–Q intervals of 0.25 to 0.50 seconds were associated with an abrupt and considerable increase in peak amplitude; this in turn was sometimes followed again by a fall with longer intervals. Some adults showed similar changes, but these were more gradual and of less magnitude.

Analysis of these results suggests that variations in the first sound can be best explained by the position of the auriculo-ventricular valves at the onset of ventricular systole, the loudest sounds being associated with the greatest separation of the leaflets and vice versa.

Liver Biopsy in the Diagnosis of Liver Disease. By LEON SCHIFF and (by invitation) W. E. MOLLE and H. H. STEINBERG, Cincinnati, Ohio.

Sixty-six biopsies were performed in sixty-one patients with various forms of liver disease. Specimens of liver tissue were obtained through the anterior abdominal wall or by a transpleural approach with a Silverman needle or by the aspiration technique of Roholm and Iversen. In eleven instances the diagnosis was established by this means only. In thirteen patients, metastic neoplasms were demonstrated and in three the diagnosis of primary hepatic carcinoma was made. The results of the biopsy were confirmed by microscopic examination of liver tissue obtained subsequently at operation or at autopsy in fifteen cases. Inadequate specimens were obtained in eight patients and neoplastic tissue was missed in two. There were no untoward reactions except for two instances of mild pleural shock.

The procedure should be given extensive trial in order to properly assess its value and safety.

Diphtheritic Neuritis. By EMMANUEL B. SCHOENBACH (by invitation) and GEORGE D. GAMMON, Philadelphia, Pa.

During the war diphtheria, faucial and cutaneous, often with complicating neuritis, became a problem in the troops of various theatres. The identification of the nature of the neuritis and distinction from infectious polyneuritis, or the so-called Guillain-Barré syndrome, proved difficult because of negative throat cultures and the fact that an elevated spinal fluid protein occurred in both. A study was carried out on 75 cases of neuritis in German troops. These could be classified on clinical grounds into diphtheritic and non-diphtheritic types, the former group with history of pharyngitis, atypical paralysis of palate and accommodation, and later generalized neuritis. Control groups, of (*1*) recent diphtheria and (*2*) no diphtheritic lesions or neuritis, were also studied.

Cultures were made of nose and throat for *C. diphtheriae* and antitoxin levels of serum were titrated. The normal controls proved to carry virulent *C. diphtheriae* in nose and throat in 17 per cent of the cases, a figure higher than that found in the diphtheritic neuritis cases. Apparently the organism disappears from the nose and throat in many cases by the time the generalized neuritis develops. This test, therefore, is of little value in identifying the case as diphtheritic, particularly when the carrier rate is high.

Antitoxin levels were lower in the diphtheritic neuritis and also in recovering diphtheria than in controls and in other forms of neuritis but the titre did not differ sufficiently to serve as a diagnostic test in individual cases.

The other varieties of neuritis encountered were sulfonamide, post-infectious, serum neuritis, and a few whose etiology was not clear.

Results of Various Tests of Liver Function in One Hundred and Fifty Patients with Acute Infectious Hepatitis and a Statistical Analysis Comparing the Changes Observed with Levels of Plasma Bilirubin. By ROBERT E. SHANK (by invitation) and CHARLES L. HOAGLAND, New York, N. Y.

The changes that occur in the concentration of certain of the constituents of plasma and in various tests of liver function in acute infectious hepatitis have been studied in 150 patients. It was found that notable changes were produced in the ratio of free to total cholesterol, total lipid, phospholipid, alkaline phosphatase, vitamin A, hippuric acid synthesis, bromsulfalein retention, and cephalin-cholesterol flocculation reaction. When determinations were repeated at weekly intervals it was possible to observe the return to normal values of these tests as the patients passed from the icteric phase of the disease into the period of convalescence. In a statistical analysis of these data designed to show the limits of application of each type of test of liver function and to indicate whether or not the relationships between any two of the tests were linear, observed regression lines were plotted and compared with calculated regression lines derived by the method of Pearl. By such means it was possible to demonstrate that the results of certain of the tests bore nearly linear relationships with the changes produced by the disease in other tests of liver function and particularly with the changes in bilirubin concentration of the plasma.

Penicillin-Resistant Staphylococci: Mechanisms Involved in the Development of Resistance. By WESLEY W. SPINK and (by invitation) VIOLA FERRIS, Minneapolis, Minn.

Investigations carried out *in vitro* with strains of patho-

genic Staphylococci isolated from human patients indicate that there are three possible mechanisms whereby this species of microorganisms becomes resistant to Staphylococci. The first mechanism relates to strains which are naturally resistant. This type of resistance is associated with a potent inactivator of penicillin produced by the bacterial cells identified as penicillinase. The resistance appears to be a permanent characteristic of these strains. The second mechanism may be demonstrated by exposing penicillin-sensitive strains *in vitro* to increasing concentrations of penicillin. Although a high degree of tolerance for penicillin may be readily acquired in this manner, the resistance is only temporary and not associated with the production of penicillinase. The third mechanism reveals the presence of a remarkable biological phenomenon. Strains of Staphylococci, which were initially resistant to penicillin and produced penicillinase, were subcultured daily in tryptose phosphate broth without the presence of penicillin, and in a relatively brief period of time a much greater degree of resistance was acquired. A logical explanation for this increase in resistance is the presence of penicillin-resistant variants in the original cultures which multiplied rapidly following frequent transplants in the broth. These variants also produced penicillinase. Strains of penicillin-sensitive Staphylococci did not acquire an increased tolerance against the *in vitro* action of penicillin when transferred daily in tryptose phosphate broth. The application of these phenomena to human infections will be stressed.

Observations on the Urinary Excretion of Corticosteroid-like Substances by Normal and Abnormal Subjects. By N. B. TALBOT and (by invitation) A. H. SALTZMAN and R. L. WIXOM, Boston, Mass.

With the aid of colorimetric assay procedure designed to measure the urinary output of unconjugated 11-oxycorticosteroid-like substances (the adrenal cortical "S" hormone of Albright) approximately 300 determinations have been made on a group of normal young adults and patients with various conditions. The data obtained show that:

(*1*) Patients with hypoadrenocorticism tend to have abnormally low values (normal range .1 to .4 mgm. per day), particularly if there is a tendency to hypoglycemia episodes.

(*2*) Hypothyroid patients tend to have abnormally low values which return to normal with thyroid therapy.

(*3*) Hypopituitary patients resemble patients with hypoadrenocorticism.

(*4*) Patients with hyperadrenocorticism of the Cushing's type have very abnormally high values When the condition becomes inactive, the values return to normal levels.

(*5*) Patients with hyperadrenocorticism of the virilism type have an essentially normal urinary corticosteroid output.

(*6*) Patients with severe burns tend to excrete excessive amounts of corticosteroids until convalescence is well advanced (? Alarm Reaction of Selye).

These preliminary observations apparently are in keeping with biological assay measurements reported from other laboratories and suggest that the present colorimetric assay gives information concerning the rate of production of adrenal cortical "S" hormone.

Attempts to Induce Subcutaneous Nodules in Rheumatoid Arthritis Patients. By ROBERT H. TALKOV (by invitation) and GRANVILLE A. BENNETT, Chicago, Ill.

Gross lesions clinically similar to subcutaneous nodules were induced in 15 out of 34 rheumatoid arthritis subjects (18 times in 47 attempts) by subcutaneous injection of the patients' own blood. In 11 healthy persons 20 autoinoculations resulted in only one such lesion.

The microscopic findings in 7 induced nodules removed from 6 of the arthritis patients and from the one control bore no resemblance to a rheumatoid arthritis nodule. The tissue reactions consisted of varying degrees of edema, chronic inflammation and foreign body reaction.

Eleven induced lesions from 9 patients revealed changes that may be of significance. The observed pathological alterations included marked proliferative changes among fibroblasts and endothelial cells and the production of new connective tissue and clusters of capillaries. These changes were more marked than would be expected from the type of tissue injury induced. The changes resembled those consistently found in spontaneous rheumatoid subcutaneous nodules, although in no instance was a lesion identical with a typical nodule produced. It is felt that these results lend support to the view that the tissues of rheumatoid arthritis patients may possess the ability to respond to different agents in a specific manner.

In 6 patients with rheumatoid arthritis, portions of spontaneously occurring nodules were reintroduced subcutaneously. In each instance the transplant gradually disappeared. Microscopically there were no remnants of nodule tissue detectable. Bacteriological studies of the transferred nodules were negative. These observations suggest that the transplanted nodules did not contain an agent capable of causing the characteristic mesenchymal tissue changes found in rheumatoid arthritis.

Adrenal Cortical Function in Various Endocrine Disorders. By ELEANOR H. VENNING (by invitation) and J. S. L. BROWNE, Montreal, Can.

By means of a sensitive biological method developed in our laboratory, which measures the excretion of adrenal cortical metabolites having an effect on carbohydrate and protein metabolism, another aspect of adrenal function can now be evaluated. The assay of these active compounds in conjunction with the measurement of 17-ketosteroids is of assistance in the differential diagnosis of certain endocrine disorders. The method is based upon the deposition of glycogen in the livers of adrenalectomized mice and has been standardized against 17 OH-11 dehydrocortocosterone, one glycogenic unit being equivalent to the activity contained in 1 microgram of this compound.

The excretion of glycogenic corticoids in normal adult

women ranges from 25 to 55 glycogenic units with an average of 38 units, while in normal adult men it varies from 40 to 85, with an average of 62 glycogenic units.

The following endocrine disorders have been studied with regard to the excretion of 17-ketosteroids and glycogenic corticoids. Addison's disease, panhypopituitarism, Cushing's syndrome, hirsutism and acromegaly. In the first two diseases, low or negative values for glycogenic corticoids were found. In contrast 2 cases of Cushing's syndrome excreted 200 and 500 glycogenic units respectively. Cases of hirsutism showed slightly raised values while the findings in cases of acromegaly were essentially normal. Other diseases studied were hypertension and anorexia nervosa.

Damage, such as surgical operation, burns or fractures, causes a marked rise in the excretion of these hormones in the previously healthy individual, the level and length of the altered excretion depending to some extent upon the degree of damage.

In several patients where the excretion of corticoids was above the normal level, the administration of testosterone propionate caused a marked reduction in the output of these hormones.

The Elimination of Poliomyelitis Virus from the Human Mouth or Nose. By ROBERT WARD and (by invitation) BURRILL WALTERS, New York, N. Y.

The precise pathways pursued by poliomyelitis virus in travelling from the infected host to the susceptible individual have not been clearly defined. Although there is considerable evidence to support the intestinal-oral circuit, there are those who consider the respiratory channel (droplet infection) as the principal mode of transmission. While poliomyelitis virus has been detected in the pharyngeal wall, in washings of the nasopharynx, and more recently, in swabs of the pharynx, there has been no evidence that virus is actually expelled under natural conditions from the mouth or nose.

Material for the *present study* was collected during the 1945 outbreak in New Jersey from 19 patients in the first 3 days of poliomyelitis. Sterile cloth masks were placed over the patient's mouth and nose and the patient was induced to talk, blow, cough and spit into the mask for 30 minutes. The nose and pharynx were then swabbed separately and all those materials were held in the frozen state until inoculated into monkeys.

Poliomyelitis virus was recovered from the mask of 2 patients. In the first of these the nose swabs, in the second, the throat swabs were also positive. Positive throat swabs only were obtained on 5 additional patients. From the remaining 12 patients no virus was recovered. The finding of virus in 2 of the masks means that, under the conditions of this experiment, poliomyelitis virus can be eliminated from the mouth (or nose).

This fact suggests that the pathway of elimination of this virus is not solely by way of the intestinal tract. The epidemiologic significance *or insignificance,* of this finding cannot be stated at present.

The Control of the Cardiac Output in Man. By JAMES V. WARREN and (by invitation) EMMETT S. BRANNON, Atlanta, Georgia.

Although it has long been recognized that the cardiac output may vary considerably under different circumstances, little is known regarding the mechanisms producing those changes. Newer methods such as right heart catheterization and ballistocardiography have enabled us to carry out the following studies in man.

The principal means of varying the cardiac output is by alteration in the stroke volume, changes in rate playing a minor role. The stroke volume, in turn, depends upon the diastolic filling of the ventricles which theoretically might be altered by variation in filling pressure (atrial pressure), or by alteration in the degree of diastolic relaxation of the ventricular musculature.

Observations on patients with anemia, thyrotoxicosis, arteriovenous fistulas, and anxiety demonstrated that there may be a considerable elevation of the cardiac output above normal, yet the atrial pressure remained within normal limits. Furthermore, in normal subjects large changes in atrial pressure produced by intravenous infusions and removal of blood caused only minimal changes in cardiac output. With an adequate blood volume, therefore, the level of the cardiac output does not appear to be directly related to the height of the atrial pressure.

Further observations demonstrated changes in stroke volume unaccompanied by changes in atrial pressure which could only be explained by alterations in diastolic relaxation of the ventricle. Epinephrine produced a marked increase in cardiac output with little change in atrial pressure. This was interpreted as an increased diastolic relaxation of the ventricles produced by a humoral stimulus. In patients with large arteriovenous fistulas another type of change in stroke volume was demonstrated. Upon temporary closure of the fistula, there was an almost immediate diminution of the stroke volume and lowering of the pulse rate. These occurred without change in atrial pressure. Atropinization blocked the slowing of the pulse rate, but not the stroke volume change. Similar phenomena were observed in normal subjects with large areas of reactive hyperemia produced by tourniquets about the legs. These alterations in stroke volume appeared to be the result of variations in ventricular relaxation produced by reflex stimuli.

In the presence of an adequate blood volume, many variations in the cardiac output appear to be the result of changes in the heart itself, rather than merely changes in the venous return to the heart. Alterations in the stroke volume may result from either humoral or reflex stimuli affecting diastolic relaxation of the ventricles.

The Nature of Nitrogen Loss After Injury: A Theory. By SIDNEY C. WERNER, New York, N. Y.

The loss of nitrogen after injury has been explained as the result of catabolism or of anti-anabolism. A two-year study of 32 patients with various operations and injuries treated with a mixture of pure amino acids presents data not explainable by either theory.

The catabolic hypothesis implies nitrogen loss from tissues independent of nitrogen intake. However, when nitrogen intake was not given, the excess nitrogen that is found in the urine with high nitrogen intakes was not present, according to the data of this study. The anti-anabolic theory implies complete wastage of incoming nitrogen, without its utilization. However, the data of the present series demonstrate that increasingly more nitrogen was retained as intake was increased, to the point of positive balance. Also, underlying active catabolism is shown by the continued high loss of nitrogen in the urine when nitrogen intake was suddenly stopped.

It is therefore proposed that both anabolism and catabolism are increased in activity after injury but maintain their normal relationships as before the trauma. This is analogous to fever, where cooling and heat conservation are normal but are set to maintain a higher temperature level. Two possible prerequisites for the reaction to occur are: (*1*) an intake of nitrogen, and (*2*) the presence of a reserve protein supply.

Circulatory Adjustments to the Head-Down Posture.[1] By ROBERT W. WILKINS and (by invitation) STANLEY E. BRADLEY and CARL K. FRIEDLAND, Boston, Mass.

Studies of cardiovascular and renal function in normal human subjects in the head-down as compared with the horizontal or upright positions have revealed the following: Arterial pressure (Hamilton method) is reflexly adjusted in each position so as to remain essentially unchanged at about the level of the base of the heart, while above and below this level arterial pressure is greater or lesser by the hydrostatic difference alone. When the subject is tilted from the horizontal to the head-down position, venous pressure in the right auricle (catheter method) usually decreases moderately, and when tilted upright decreases more. If tilted head-down from upright the auricular pressure is higher than if tilted head-down from horizontal, and is also higher than if tilted head-down while venous return from the legs is prevented by inflating blood pressure cuffs on the thighs. In all positions venous pressure at points below the auricle exceeds that in the auricle by the hydrostatic difference. However, venous pressure at points above the auricle may not be related to auricular pressure because of collapse of the veins. Thus, internal jugular venous pressure increases markedly when tilted into the head-down position but changes only slightly when tilted from horizontal into the upright position. In the head-down position, cardiac output (ballistocardiographic) and stroke volume increase, while pulse rate decreases; renal blood flow (clearance method) remains essentially unchanged.

Duration of Reflexes in Hyperthyroidism and Hypothyroidism. By JOHN R. WILLIAMS, JR., Rochester, N. Y., and (by invitation) SARA BARNUM, Dallas, Texas.

It has been shown previously that the duration of reflexes is prolonged in hypothyroidism. By a relatively simple apparatus we have measured the duration of reflexes in several hundred patients. Every patient with unquestioned myxedema has had abnormally slow reflexes. No individuals without myxedema have had similar slowing. All individuals with unquestioned thyrotoxicosis have had relatively quick reflexes. A few patients with upper motor neurone lesions have had similarly rapid reflexes.

The test has been of value in the recognition of these disorders in patients with heart disease and in others in whom metabolic rate determinations tend to be an inaccurate index of thyroid function.

It can apparently be shown that nerve conduction over the reflex arc is faster in hyperthyroidism and slower in myxedema, but this change does not seem to be of sufficient magnitude to account for the observed differences in time.

The duration of reflexes is shortened by hypoglycemia produced by the injection of insulin, and also by exercise. It is apparently not prolonged in Addison's disease or pituitary hypofunction in spite of the lowering of the metabolism. The actions of various drugs have been tried with no clear-cut alterations in duration of reflexes.

Nephrogenic Diabetes Insipidus Occurring in Males and Transmitted by Females. By ROBERT H. WILLIAMS, Boston, Mass.

The clinical picture of diabetes insipidus was found to appear during the first few months of life in 7 members of one family, extending over 5 generations. The disease was found only in males, but was transmitted only by females. In spite of the enormous water exchange, growth and development were but slightly impaired in 5 of the patients; of the other two, one died in infancy and the other one, who is now 8 months old, weighs only 9 pounds.

In all of the patients the fluid intake was several times normal, and in 3 the average was more than 18 liters per day. Three individuals developed circulatory collapse on withholding fluid. Three patients were treated with pituitrin, but experienced slight or no antidiuresis. The possibility of excessively rapid inactivation of pitressin by the serum or body cells was considered, but it was demonstrated in one of these patients that the antidiuretic effect in rats, of the patient's serum was the same as that of normal controls whether pitressin was added to the serum *in vitro,* or whether the pitressin was administered to the individuals intramuscularly and serum samples were obtained 45 minutes later.

In the light of the foregoing observations, the role of the kidneys in the pathogenesis of the syndrome was investigated. Five of the 7 patients are known to have varying degrees of impairment in kidney function. In one of the individuals, a physician, clearance studies with mannitol, diodrast, and creatinine indicate impairment in tubular function. However, the abnormality was of such a nature as to permit water diuresis, but not to cause sufficient metabolic impairment to be incompatible with life. Thus, it would appear that the best explanation for this extraordinary syndrome is that there exists in the afflicted

[1] Done under a contract with O.S.R.D.

individuals physiological or anatomical defects, permitting excessive diuresis of water.

Studies on the Mechanism of Nausea. The Relation of Duodenal Function to Nausea in Man. By STEWART WOLF, New York, N. Y.

In experiments carried out during military service in New Guinea, nausea was induced in healthy subjects while the motor activity of the first portion of the duodenum was being observed by (*1*) recordings from an inlying inflated balloon, (*2*) fluoroscopic examination of an inlying diodrast-filled balloon and (*3*) fluoroscopic examination of the barium-filled duodenum.

The nauseating stimuli were (*1*) irrigation of the external ear with cold water, (*2*) chemical emetics and (*3*) in the case of one individual, a fear-producing situation. Nausea and vomiting were induced at will in this soldier when a discussion of either the horrors of the battlefields or the terrors of the jungle was initiated. In all subjects, profound changes in the pattern of activity of the duodenum occurred coincident with the experience of nausea however aroused. There was a narrowing of the lumen of the first portion of the duodenum and the prevailing pattern of normal contractions was interrupted and replaced by contractions of slower frequency and longer duration.

Coincident with the subsidence of the experience of nausea these changes disappeared and the normal phasic rhythm of duodenal contractions was resumed.

The changes described were never observed in the absence of nausea and conversely nausea was never experienced without them.

Surface Phagocytosis—Its Relation to the Mechanism of Recovery in Pneumococcal Pneumonia. By W. BARRY WOOD, JR., and (by invitation) MARY RUTH SMITH, St. Louis, Mo.

A systematic study of the effect of chemotherapy upon the pulmonary lesion of experimental pneumococcal pneumonia has revealed that pneumococci are destroyed in the lung by phagocytosis and that the phagocytic process takes place in the absence of antibody. Further study has demonstrated that the phagocytosis is due to a hitherto undescribed mechanism which is not related either to opsonins or capsular injury but is dependent upon access of the phagocytes to a surface of suitable physical properties. Not only did all tissue surfaces tested support phagocytosis of virulent pneumococci, but even the surfaces of such inert materials as filter paper, cloth and fiber glass rendered the phagocytes highly active.

Direct visualization of the surface phenomenon shows that the phagocytic cells first pin the pneumococci against the surface before engulfing them. Those pneumococci which remain floating freely in the fluid medium are never successfully attacked except in the presence of specific opsonins. The non-antibody phagocytic process appears to be directly related to the mechanism of recovery in pneumococcal pneumonia and offers an adequate explanation for important questions hitherto unanswered by the conventional techniques of immunology.

Use of Transfusions in the Study of Hemolytic Anemia. By LAWRENCE E. YOUNG and JOHN S. LAWRENCE, Rochester, N. Y.

Transfusion studies employing the technique of differential erythrocyte agglutination provide a valuable means for investigating *in vivo* the destructive processes operating in certain types of hemolytic anemia. Studies of 2 unusual cases of chronic non-spherocytic hemolytic anemia are cited as illustrations.

In Case 1 phlebotomy was performed twice, and was followed immediately by transfusion of normal red cells. Donated normal cells survived normally in the patient's circulation but the patient's erythrocytes, 73 per cent of which were reticulated, were rapidly destroyed after transfusion to a small child. It was demonstrated, however, that the reticulocytes were not destroyed until they had become mature and that the *in vivo* maturation time was approximately 6 days. The patient's plasma had no demonstrable hemolytic effect on the red cells of a normal adult recipient. It is concluded that in this case the abnormality was in the erythron.

In Case 2 all red cells received from 30 donors were rapidly destroyed, possibly because of the action of cold hemagglutinins and alpha-one agglutinins of high thermal amplitude. It is considered likely that in this patient, who responded well to splenectomy, the abnormality was in the reticulo-endothelial system.

A conjectural classification of "intrinsic" hemolytic anemias on the basis of results of transfusion experiments is suggested.