EVENTS

NU SIGMA NU LECTURE
December 7, 1955

RECENT ADVANCES IN THE STUDY OF STRESS. By Hans Selye, Professor and Director of the Institute of Experimental Medicine and Surgery, University of Montreal.

Stress is a specific syndrome induced by non-specific changes in the organism or a part of it. Among the manifestations of stress are gastric ulceration, thymic involution, lymphatic involution, eosinopenia, and an atrophy of the adrenal cortex. A stressing agent acts upon a target tissue with a direct effect of primary damage and local tissue response. These immediate effects are modified by an indirect or total body response which can act in a “prophlogistic” or “antiphlogistic” manner to augment, or depress, the initial form of the reaction to injury.

A series of experiments using rats in which the animals were injured in various ways followed by administration of appropriate doses of desoxycorticosterone or cortisol showed that cortisol depressed inflammatory responses and that desoxycorticosterone intensified them as compared to untreated controls. It was concluded that in general mineralocorticoids are “prophlogistic” and glucocorticoids are “antiphlogistic.” However, the apparently curative effects of the anti-inflammatory hormones are not desirable in all cases. Normal rats treated with ACTH, which elicits a predominantly anti-inflammatory adrenal cortical hormone response, were found to develop abscesses caused by ordinarily non-invasive bacteria illustrating that resistance was lowered by the failure of the inflammatory reaction to develop.

The effects of stress in perforating gastric ulcers were shown using the “granuloma pouch” technique in rats. The protection against peptic digestion and perforation afforded by the granulomatous response in gastric ulcers was overcome when psychic stress, ACTH, or cortisol was administered.

It was concluded that Pasteur’s idea of the pathogenesis of a disease might well be modified to include the effect of the total body response to the specific etiologic agent. This concept may be applicable in the exploration of many of the diseases such as the allergies and the collagen diseases which are poorly understood at present.

R. S. N.

YALE MEDICAL SOCIETY MEETING
January 9, 1956

THE INFLUENCE OF DIET ON THE SERUM LIPIDS IN DIABETIC RETINOPATHY. By W. F. Van Eck, Departments of Medicine and Public Health.

After one year on an experimental diet with fat restricted to 20 grams per day, four patients with diabetic retinopathy showed total remission of retinal exudates. The dietary carbohydrate was increased to keep the total caloric intake equal to that of the pre-experimental diet; this did not cause an increase in the amount of insulin required by the patients.

J. P. G.
NEUROLOGICAL STUDY UNIT

January 10, 1956

EXPERIMENTAL MALFORMATIONS OF THE BRAIN. By Samuel P. Hicks, New England Deaconess Hospital, Boston.

The attempt to bring about reproducible congenital anomalies has led to the use of over seventy different kinds of injurious agents including X-radiation, anoxia, drugs, hormones, and trauma. Of these, X-radiation proved to be the most selective and formed the main basis for the present work. The procedure involved fairly accurate notation of the time of conception and radiation of the pregnant rat with about 200 r. Removal of one or two fetuses by Caesarian section at predetermined intervals allowed observation of the immediate foetal radiation injury. Its effect on development and growth was watched in a serial manner on litter mates. By varying the time between conception and radiation various cranial anomalies were produced. Thus, radiation on the 9th, 10th, 11th, and 12th days produced, respectively, anencephaly, encephalocele, narrow aqueduct and hydrocephalus, and parencephaly. Radiation during the 13th to 21st days resulted in microcephaly.

In the rat central nervous system all cells seem to be injured by radiation, but the differentiated cell does not proliferate while the least differentiated does. It was also noted that the mature neural cell is very sensitive to oxygen and glucose blood levels, while the neuroectoderm has a much lower sensitivity.

Malformations are determined by the developmental stage of the organism at the time of injury, by the nature of the injury, and the repair process stimulated.

P. B., JR.

NU SIGMA NU LECTURE

January 18, 1956

RENAL TUBULAR EXCRETION. By John V. Taggart, Associate Professor of Medicine, College of Physicians and Surgeons, Columbia University.

The secretion of para-amino-hippurate (PAH), diodrast, and phenolsulphonephthalein (PSP), from blood to tubular lumen against a wide concentration gradient may profitably be studied as a model of that type of renal tubular activity which requires energy expenditure. Isolated flounder tubule will concentrate PSP 100 to 200 times when placed in a suitable medium: however, the addition of $2 \times 10^{-4}$ molar 2, 4, dinitrophenol (DNP) completely inhibits this concentrating power. Since DNP does not interfere with cellular respiration but uncouples phosphorylation, adenosinetriphosphate (ATP) may well be the energy source for this specific transport mechanism. In vivo observations on dogs with blood levels of PAH sufficient to exceed the normal Tm provide confirmation of this hypothesis; plasma concentrations of DNP similar to those used in vitro provide comparable inhibition.
Slices of cortex from rabbit kidney can concentrate PAH. Interestingly, while glucose and the phosphorylated intermediates of anaerobic glycolysis have little effect on this concentrating power, lactate, pyruvate, and especially acetate enhance it. Further studies show that dicarboxylic acids of the citric acid cycle, fatty acids of C5-C10 chain length, and 1-glutamate and l-alanine markedly inhibit PAH transport. The in vitro synthesis of hip-purate from benzoyl-Co-A and glycine and the isolation from kidney of the necessary enzyme, glycine-n-acylase, provide a clue to the explanation of these findings. Utilizing the fatty acids this enzyme can catalyze the formation of aliphatic acylglycines which, in turn, may compete with PAH for an unknown cellular transport mechanism, X. Apparently, acetate and its precursors form acetyl glycine which does not compete with PAH for X; a less competitive substance therefore forms and PAH transport increases. Confirming this idea, acetate stimulates PAH transport only in those species which have the glycine-n-acylase enzyme.

The general scheme of PAH transport may be represented as PAH + X ⇔ X · PAH ⇔ PAH + X where X again represents an unknown cellular intermediate. Work may be needed to form the intermediate complex or to rejuvenate the cellular component. Blockage of the available chemical linkage sites reveals that only interference with the —COO⁻ radical influences the transport; hence this must be the linkage site. Studies with —C≡O¹⁸ show that no significant O¹⁸ is lost in transport; therefore, the bond involved must leave the carboxyl radical intact after transport. Investigation of the various possibilities indicates that the most likely type of bond is purely ionic. This result is especially interesting in view of recent advances in understanding of cation exchange in the renal tubules. Perhaps an analogous anionic mechanism is involved.

R. I. B.

ALPHA KAPPA KAPPA ANNUAL LECTURE

January 19, 1956

Heart Disease and Ways of Life. By Paul Dudley White, Harvard Medical School.

The commonest types of heart disease in the United States today are coronary, congenital, rheumatic, cor pulmonale, thyrotoxic, subacute bacterial endocarditis, cardiovascular syphilis, and tuberculous pericarditis. Of these the former is most prevalent and has manifested in the past decade a strikingly increasing incidence. Coronary disease, as regards incidence, prognosis, and possibly etiology, is influenced by many factors; these can be divided into those over which man has, and does not have, control of some kind.

The degree to which such factors as race, sex, and age play a rôle is largely speculative; that they are in fact somehow involved in the natural history of coronary disease appears highly probable. Heredity, insofar as it involves the transmission of physical characteristics such as coronary artery wall abnormalities, coronary collateral circulation, body build, and "chemi-
cal constitution,” would also seem to be implicated. Certain personality types, e.g. the aggressive individual, are described as more prone to develop coronary disease; whether personality is in part an inherited characteristic is open to debate. The above factors are among those over which man has little or no control.

Still other factors must be considered as possibly related to the pathogenesis of coronary disease. These are such that man has, or could have, varying degrees of control over them. The “stresses and strains of our modern pace,” both emotional and physical, have been described as contributing to the rising incidence of this disease. Personal habits such as excessive use of alcohol and tobacco, amount of physical exercise and sexual over-indulgence have been implicated. Local customs, e.g. religious fasting, and the afternoon siesta, are thought to favor decreased incidence. The high fat, high cholesterol diet has been a most commonly indicated factor. Whether it is the fat content per se, or the resulting combination of protein and carbohydrate, is a question upon which there exists considerable disagreement.

J. C. C.

ARTHRITIS STUDY UNIT

January 19, 1956

Primary and Secondary Gout. By Alexander B. Gutman, Mt. Sinai Hospital, New York City.

Primary gout is an inborn error of metabolism. Secondary gout, a complication of prolonged hematological diseases such as polycythemia vera and chronic leukemia, follows the same clinical course. Both primary and secondary gout are characterized by hyperuricemia. If patients with primary gout are fed N\textsuperscript{15} glycine, a precursor of uric acid, the labelled uric acid excretion curve in some cases is identical with that of normal subjects, i.e., a normal peak occurs in two to three days. In others, though the peak appears at the same time it is four to five times greater, indicating increased uric acid synthesis. Into which group a patient will fall cannot be predicted from the clinical course, but the latter group excretes excessive amounts of uric acid in the urine. In secondary gout the peak is slowly reached in about two weeks and is usually somewhat higher and broader than normal. Hyperuricemia in secondary gout is possibly related to excessive uric acid formation associated with increased turnover of nucleoproteins in these chronic hemopoietic diseases. Thus there are at least two and probably more metabolic pathways of uric acid formation.

Another possible explanation for hyperuricemia in gout is that too little uric acid is excreted. Of the uric acid in the glomerular filtrate, 90-95\% is reabsorbed in the tubules. Probenecid inhibits this reabsorption by its action on the proximal convoluted tubules. One half to two grams of probenecid per day will result in a 30-50\% increase in uric acid excretion and blood levels fall to half their original values. The effect of a single dose lasts about 24 hours and the drug can be given safely for months or years.
Of 43 patients with tophaceous gout treated with probenecid for eight months to four years and kept on a restricted diet, 94% experienced improvement in joint stiffness and pain; tophi were reduced in size in more than 50% and in two patients tophaceous sinuses healed. With probenecid even old tophi can be mobilized.

Salicylates are potent uricosuric agents and this action can be potentiated by bicarbonate. However, small amounts of salicylate have the reverse effect. This paradoxical action is observed with other uricosuric agents. Perhaps small doses increase tubular reabsorption while large doses are toxic. Another explanation might be that a small amount of uric acid is excreted by the tubules and that a small dose only inhibits the secretory phase while a large dose inhibits the reabsorption as well.

Among other uricosuric agents some of the derivatives of phenylbutazone have proven at least as potent as probenecid. In particular, the phenyl-thioethyl derivative shows good uricosuric action, only slight sodium retention and fair anti-inflammatory properties. However, there has not been enough clinical use of this drug as yet for a proper evaluation.

With regard to acute attacks of gout it is conjectured that they are not due to uric acid per se but to another purine not yet discovered. Chromatographic analysis of urine has revealed several new methyl purine metabolites. Of these, 8-hydroxy-7-methylguanine is excreted in two to four times the normal quantity in patients with acute gouty arthritis and polycythemia vera. However, no causal relationship has been demonstrated thus far.

L. Z. B.

PHARMACOLOGY SEMINAR
January 24, 1956

Biochemical Approaches to the Study of Brain Function. By Bernard B. Brodie, Chief, Laboratory of Chemical Pharmacology, National Heart Institute, Bethesda, Maryland.

In investigating the potentiating effects of reserpine and chlorpromazine on barbiturates, the structural similarity between 5-hydroxytryptamine (serotonin), lysergic acid diethylamide (LSD), and reserpine was noted and all were seen to contain an indole nucleus. Serotonin, a naturally occurring vasoconstrictor, was given to mice—whose vasomotor system is not sensitive to the drug—with resultant sedation similar to that produced by reserpine. Mice pretreated with serotonin had a greatly potentiated reaction to hexobarbital. If mice were pretreated with LSD, the potentiating effect of serotonin was considerably reduced. In dogs and rabbits examination of the urine for the excretory product of serotonin, 5-hydroxy indole acetic acid, revealed a high level with a return to normal in eight hours following injection of reserpine.

A spectrophotofluorometric method for serotonin analysis was developed. With this technique the serotonin level was found to be high in the primitive parts of the brain, particularly the hypothalamus and brain stem, but absent in the cerebellum. A considerable reduction in serotonin content of
the small gut, platelets, and brain was found following the injection of reserpine. Barbiturates and isoreserpine, a stereoisomer, were without such effect.

After high doses of reserpine, brain levels of reserpine and serotonin in dogs were determined, with the former disappearing in four hours and the latter remaining low for as long as three to five days. It is postulated that reserpine causes the release of serotonin from cells followed by a rapid enzymatic destruction and excretion. Thus, there is a slow return to normal intracellular levels.

A working hypothesis of the mode of action of reserpine in psychiatric disorders, based on the above considerations, was presented.

P. B., JR.

ZOOLOGICAL JOURNAL CLUB

February 8, 1956

THE OMMATIDIUM AND COMPOUND EYE PHYSIOLOGY. By Talbot H. Waterman, Associate Professor of Zoology, Yale University.

Three basic physiological questions that may be asked about eyes are: (1) How are images formed? (2) Where does sensory excitation occur? (3) What sort of information is transmitted to the central nervous system? The following is a review of some recent work on these problems with respect to the structural and functional units (ommatidia) constituting the compound eyes of arthropods.

The basic elements making up single ommatidia are: a corneal lens, a crystalline cone, retinular cells, a rhabdom (a secretory product of the retinular cells?), optic nerve fibers, pigment cells (variable in distribution—usually two distal, several proximal), and a basal membrane. The sizes and relations between these elements vary greatly in different compound eyes.

The corneal lens and crystalline cone form the dioptric system of the ommatidium. The photosensitive structure is still unidentified, though the retinular cells, giving rise to the optic nerve fibers, must be stimulated in some way. The rhabdom has often been suggested in this rôle, primarily on the basis of the (often purplish) pigment seen in many rhabdons. The fading of this pigment has been shown not to be proportional to exposure to light, however, and many forms have unpigmented rhabdons. There are even some forms with good vision which lack rhabdons. This theory therefore seems not well founded.

The photochemical mechanism involved in compound eyes is unknown. Kampa has recently extracted "euphasiopsin," a carotenoid-protein complex, from the compound eyes of some pelagic shrimps, but nothing is known of its localization or reactions.

The distance from the crystalline cone to the rhabdom determines whether a given compound eye is a superposition (forms a single image) or an apposition (forms multiple images—one per ommatidium) eye. This distinction is not a hard and fast one, however, due to variations in struc-
ture. Barlow has made a theoretical approach to the optical properties of ommatidia of various sorts.

Hanaoka has shown a marked increase in generator potential activity at the level of the rhabdom and retinulae in the superposition eyes of crayfish. This may well be significant in indicating the site of light energy absorption. Wiersma and Waterman have found only one active nerve fiber per ommatidium in the king crab (*Limulus*), though there are ten or more retinular cells per element. Does the ommatidium act as a unit?

Waterman has shown that single ommatidia will respond to light throughout a cone of some 70° from the optic axis of the ommatidium. There is thus a great overlap of optical fields and J. Muller’s mosaic vision theory seems untenable. On the other hand, work with locusts shows that movements covering angles much smaller than the field of a single ommatidium (about 1°) are seen.

The eyes of many crabs show no continuous discharge in the fibers of the optic nerve studied. Responses to changes in light intensity and movement alone are recorded. The spiny lobster (*Panulirus*) also has additional fibers, however, which show continuous discharges.

Studies of behavior, especially using moving stripe patterns and the opto-kinetic nystagmus shown by stalk-eyed crustacea, are also contributing to understanding of these problems. The effects of polarized light, and the mechanism of polarized light sensitivity, are being studied.

M. S. G.

**CARDIOVASCULAR STUDY UNIT**

February 20, 1956

**Cardiovascular and Metabolic Consequences of Renal Failure.**

By J. Russel Elkington, School of Medicine, University of Pennsylvania, Philadelphia.

In order to arrive at a more satisfactory method of management of acute renal failure, the study of the clinical entity of tubular necrosis with ensuing acute renal failure was undertaken. A series of 59 cases accumulated over an eight-year period was used. Of this group, 23 were treated in a conservative manner employing such measures as the conventional restriction of fluids to 700 to 1,000 cc. per day, absolute salt restriction during the oliguric phase, digitalis, and cation exchange resins. A 64 per cent mortality was experienced in this group. The remaining 36 cases in the series were treated by the use of a Skegg-Leonard dialyzer. With this method of treatment mortality was only 36 per cent.

It is important to consider the patient as a closed system during the days preceding tubular functional regeneration and resultant diuresis. For this reason careful consideration of the patient’s fluid needs and electrolyte status is essential. In the above study, fluid intake was restricted to approximately 650 cc. per day, or the mean difference between the insensible loss and the water of oxidation. In the group treated conservatively, fluid was withheld entirely for 24 or more hours lest the patient exhibit weight gain.
in the face of anuria. It was concluded, however, that the treatment of choice and the one which provided the most facile control during the oliguric phase of the illness was to dialyze, using negative hydrostatic pressure. This allows for the correction of the manifestations of overhydration, acidosis, and hyperkalemia.

R. H. F.

BIOPHYSICS-ZOOLOGY SEMINAR

February 20, 1956

Effects of Radiation on the Egg Nucleus, and Cytoplasm of the Wasp Habrobracon. By R. C. von Borstel, Oak Ridge National Laboratory, Oak Ridge, Tennessee.

Habrobracon is a small wasp whose larvae live parasitically on the caterpillars of the Mediterranean flower moth. It has a life cycle comparable in length to that of Drosophila. Its eggs are airfoil shaped in longitudinal section and are some 600 micra long by 150 micra thick. The egg cytoplasm is mostly peripheral, in a layer about 10 micra thick, with the egg nucleus very near the surface on the convex side near the thicker end. The center of the egg is mostly yolk. Sex determination is of the haploid-diploid type—males being haploid, females diploid. Females alone, therefore, are produced from fertilized eggs.

The present work is a study of some of the effects of ultraviolet, X-, and alpha particle radiation on various stages of the eggs of this form.

Mrs. Whiting has found eggs in the first prophase of meiosis to be some twenty times more resistant to X-rays than eggs in the first meiotic metaphase. She also produced androgenic males by irradiating females, then mating them (males showing the influence of the male genome only are so produced). The present work has produced more androgenic males via X-irradiation at first metaphase than at first prophase. The characteristics of the dose-response curve indicate that damage to cytoplasmically determined characters is also of importance here.

With ultraviolet radiation, nuclear irradiation has far greater effects (by several orders of magnitude) on hatchability (per cent of eggs hatching) than cytoplasmic irradiation. The nuclear dose-response curve is in two parts, however, some 30% of the eggs being more resistant to u-v than the remainder. Perhaps nuclear movement deeper into the egg is a factor here.

Hatchability effects after nuclear u-v irradiation are partially reversible by exposure to light (photoreactivation). This does not occur with cytoplasmic irradiation.

Hatchability studies following alpha particle bombardment (particle range in tissue about forty micra) indicate that a single direct hit on the nucleus is enough to inactivate it. The inactivation cross-section is just a little less than the nuclear size. Cytoplasmic alpha irradiation is only weakly effective in reducing hatchability.

The u-v action spectra for both cytoplasmic and nuclear irradiation fairly closely parallel the absorption spectra of nucleic acids. Nucleic acids (prob-
ably as nucleoproteins) are thus likely the substances inactivated. There are differences in the mechanism of death following irradiation at different wave-lengths.

The embryological fates of the different parts of the egg are determined very early. Cytoplasmic irradiation produces defects in the appropriate areas in the adults hatching. Cytoplasmic influences on development are thus demonstrated.

M. S. G.

POLIOMYELITIS CONFERENCE
February 22, 1956

RECENT ADVANCES IN DIAGNOSIS. By Dorothy Horstmann.

The diagnosis of poliomyelitis is particularly aided by the use of tissue culture and serological methods. The recognition of the two clinically different types of poliomyelitis, the biphasic and monophasic, is important diagnostically, both unto itself and in relation to the tissue culture and serological procedures which are to be performed. Thus, in the biphasic or childhood type of disease, a Minor Illness of transient sore throat and headache often precedes, by about five days, the Major Illness, which is characterized by sudden rise of temperature and central nervous system symptoms of stiff neck and paralysis. Inasmuch as the Major Illness is usually the presenting clinical entity, tissue culture studies should be performed on throat and particularly feces specimens rather than on blood, since the viremia disappears with the Minor Illness. The Major Illness is also characterized by the presence of complement-fixing and neutralizing antibodies of which only the former is useful for obtaining significant diagnostic titers. These methods and principles are also applicable for the diagnosis of the monophasic or adult type disease.

The tissue culture method may give positive results in 7 to 14 days and is especially useful for distinguishing the specific polio viral types (I, II, and III). While the results of the complement-fixing test may be obtained within 24 hours, the viral type specificity cannot be determined. The practical application of these methods in the differential diagnosis of encephalitis and the aseptic meningitides unrelated to polio, as well as in the diagnosis of atypical forms of polio is to be noted.

THE CURRENT STORY IN VACCINATION. By Francis L. Black and John R. Paul.

In evaluating the Salk poliomyelitis vaccine for its safety, a consideration of the consequences of sensitizing materials and infectious agents which might be present is required. An analysis of this sort indicates that the only major potential source of danger in the vaccine is the presence of the live polio virus itself—witness the Cutter Laboratories incident of a year ago. This problem is related, in large part, to the aggregation of virus particles which allows some of the particles having slow rates of formaldehyde in-
activation to escape destruction. The new regulations governing the manufacture and release of Salk vaccine have stressed the use of more adequate filtration methods to prevent particle aggregation. They require, in addition, that larger quantities of vaccine be tested and that all such tests prove consistently negative for the presence of live virus. While these more stringent precautions have aimed at completely safeguarding the vaccine, it should be pointed out that on theoretical grounds absolute safety is not obtainable. At present, therefore, the safety of the vaccine is primarily based upon the fact that only a very few sporadic and ill-defined cases of polio have been traced to its use from among the very large population vaccinated during the last year.

Although the Salk vaccine is considered safe to use (with the reservations noted above), the more immediate objective is the development of a vaccine from live attenuated virus. This aim evolves from a consideration of the natural history of the disease as well as from the relatively marked effectiveness and safety of such presently used attenuated vaccines as those for smallpox and yellow fever.

S. H.