Genetic and Endocrine Determinants of the Plasma Urate Level

At the meeting of the American Rheumatism Association at Chicago in June 1948, Smyth, Cotterman, and Freyberg (*J. clin. Invest.*, in press) reported results of their investigation of genetic factors in gout and hyperuricemia. The discussion which followed indicated that quite similar conclusions had been reached independently by Stecher, Hersh, and Solomon (*Ann. int. Med.*, in press) at Cleveland City Hospital, and by Wolfson, Cohn, Levine, Hunt, and Rosenberg (manuscript in preparation) at Michael Reese Hospital. After mutual discussion it was agreed that the significance of the findings for normal and pathological physiology warranted a brief cooperative statement summarizing the essential results. The chief conclusions reached were:

(1) Asymptomatic hyperuricemia is a frequent finding in the relatives of patients with gout. Statistical analyses indicate that a single gene is probably responsible for the transmission of asymptomatic hyperuricemia; that this gene is dominant rather than recessive; and that the responsible gene is autosomal rather than sex-linked.

(2) Earlier reports (B. M. Jacobson. *Ann. int. Med.*, 1938, **11**, 1277; K. Brøchner-Mortensen. *Acta Med. Scand.* (Suppl. 84), 1937, 1; H. A. Bulger and H. E. Johns. *J. biol. Chem*, 1941, **140**, 427) of a higher average normal plasma urate concentration in males than in females are confirmed. The mean reported ratio of $\frac{\text{average female plasma urate}}{\text{average male plasma urate}}$ in 5 investigations has been 0.85 (Stecher, *et al.*; Wolfson, *et al.*; Jacobson; Brøchner-Mortensen; and Bulger and Johns). The values of this ratio, as found in individual studies, lie between a minimum of 0.80, reported by Bulger and Johns, and a maximum of 0.92, reported by Stecher, Hersh, and Solomon.

(3) The average plasma urate concentration is higher in gouty males than in gouty females (Wolfson, *et al.*). The average plasma urate in males who inherit asymptomatic hyperuricemia is higher than that in females who inherit asymptomatic hyperuricemia (Stecher, *et al.* and Wolfson, *et al.*). The average plasma urate is higher in those male relatives of gout patients who have not inherited hyperuricemia than in the corresponding group of female relatives.

(4) Since a sex differential in plasma urate levels occurs in normal adults, in patients with clinical gout, and in relatives of gout patients who inherit asymptomatic hyperuricemia, this sex differential or its underlying endocrine background cannot alone be the cause of gouty hyperuricemia. Similarly, the sex differential cannot be the sole mechanism through which the gene for hyperuricemia operates.

(5) Males who inherit asymptomatic hyperuricemia do not, as a rule, develop abnormally elevated plasma urate levels (above 6.0 mg%) until after puberty (Smyth, *et al.*). Female carriers of genetic hyperuricemia do not usually develop abnormally elevated plasma urate levels until just before, or after, the menopause (Stecher, *et al.*). These findings suggest that the presence of male sex hormones unantagonized by female sex hormones provides an endocrine situation in which the gene controlling inherited hyperuricemia becomes activated to display its maximum effectiveness in producing an elevation of plasma urate level (Smyth, *et al.* and Stecher, *et al.*).

(6) Abnormally elevated plasma urate levels are more common in male relatives of the gouty than in female relatives. Statistical analysis indicates that this probably does not mean that more males than females inherit the gene for hyperuricemia. Rather, the difference in sex incidence of abnormally high levels appears to depend upon two nonhereditary factors: (a) the fact that male carriers develop their maximum urate levels at an earlier age than female carriers, and (b) the existence of the normal sex differential in urate concentration.

(7) The data suggest a correlation between the duration and magnitude of hyperuricemia and the occurrence of clinical gout. The results are consistent with the view that clinical gout develops more frequently in males who inherit hyperuricemia because of three factors: (a) the plasma urate concentration of males is normally greater than that of females; (b) the gene responsible for the inheritance of hyperuricemia appears to be somewhat more effective in regard to the actual quantitative magnitude of elevation of the plasma urate level in males; and (c) since males who inherit hyperuricemia develop their maximal urate levels considerably before female carriers, this increased duration of hyperuricemia exposes the males to a proportionately increased risk of developing clinical symptoms. (The observation that the occurrence of clinical gout and the duration and magnitude of hyperuricemia are positively correlated should not be taken to mean that hyperuricemia is necessarily the direct cause of the symptoms of clinical gout.)

(8) Information is as yet incomplete in regard to the alteration in metabolism through which the gene for hyperuricemia produces an elevated plasma urate concentration and, similarly, as to the exact biochemical mechanism by which the normal sex differential in plasma urate level is maintained. Preliminary results suggest that the *sex differential* is associated with a reduction in males of the ratio of urate clearance/glomerular filtration rate. In turn, the reduction of this ratio seems to depend upon a tendency for urate clearance to be somewhat smaller in males than in females and for glomerular filtration rate to be somewhat greater in males than in females, when these values are expressed per unit of calculated surface area. However, in order to excrete this amount of urate, the male requires a higher plasma urate than the female because of his smaller ratio of urate clearance to glomerular filtration rates. *Genetic hyperuricemia*, when studied at the time of onset of clinical gout, and provided male gout patients are compared with male control subjects, appears to be associated with an approximately equal reduction in urate clearance and glomerular filtration rate. The available data suggest that this decrease in glomeru-

lar filtration rate, and presumably in urate clearance as well, occurs predominantly in the first two decades after puberty, following which the rate of decline in function appears to be slowed. The major decrease in these renal functions thus appears to occur in a period which approximately coincides with the period during which the male carriers of inherited hyperuricemia develop elevated plasma urate levels. Such findings suggest that the decrease in glomerular filtration rate, which is a usual observation in the gouty, may in fact be largely genetically determined, rather than a complication of gout, as is usually assumed (Wolfson, *et al.*).

(9) It is suggested that normal standards for the upper limits of plasma urate concentration be revised to take cognizance of the normal sex differential in plasma urate level.

The complete data on which the foregoing statements are based will be published in detail elsewhere.

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Book Reviews

Atomic energy: being the Norman Wait Harris lectures delivered at Northwestern University. Karl K. Darrow. New York: John Wiley; London: Chapman & Hall, 1948. Pp. 80. (Illustrated.) $2.00.

This brief absorbing treatment of the physics of nuclear energy retains the informal language of Dr. Darrow's lectures at Northwestern University. It is a contribution to the growing list of publications whose admirable objective is to explain the physics of nuclear energy to the layman and to scientists in other fields. Within its 80 pages the reader who seeks to obtain a general review of the field will find a surprising amount of sound information woven into an interesting story.

Starting with introductory information about the atomic structure of matter and an ingenious explanation of physical units in everyday language, the story proceeds with the aid of simple but effective diagrams to a brief description of nuclear forces and a careful cataloguing of the masses of simple nuclei. This leads to the apparent contradiction that in nuclear physics the whole is not equal to the sum of its parts, a problem which is solved by the explanation of the equivalence of mass and energy and a statement of Einstein's equation.

Following a more detailed discussion of energy units, the specific nature of nuclear forces and the inappropriate use of the term "atom smashing," the possibility of transmutation is examined and found to require giant machines of which the Van de Graaf generator is described as a typical case. With the aid of cloud chamber photographs, simple transmutations are explained and the verification of Einstein's equation noted.

A brief eulogy of Rutherford's phenomenal contributions leads to a discussion of the stability of heavy nuclei, radioactivity, and the peculiar advantages of the free neutron as an atomic projectile. The discovery of atomic fission with its excess production of neutrons leads to the awesome implications of the chain reaction with disturbing questions about the stability of our immediate surroundings. These are allayed with an explanation of brakes on the process provided by nature and the story of the removal of such brakes one by one to yield, on one hand, the uncontrolled reaction or bomb and, on the other, the controlled reaction or pile with its singularly appropriate name. The story ends on the hopeful note that the controlled reaction can aid humanity in many ways if man can avoid further use of the uncontrolled reaction.

Dr. Darrow's book is distinguished among its kind by its brevity and the clarity of presentation. He gives enough, but just enough, information for the nonscientist to follow the essential ideas without becoming lost in extraneous details.

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Hemostatic agents: with particular reference to thrombin, fibrinogen and absorbable cellulose. Walter H. Seegers and Elwood A. Sharp. Springfield, Ill.: Charles C. Thomas, 1948. Pp. xii + 131. (Illustrated.) $4.50.

Recent rapid developments in the field of blood clotting have made available for the first time highly potent agents for stopping hemorrhage and bleeding. These substances have many possible applications. Associated with this development are important points of technique, descriptions of which are scattered through the literature or have not been published. Hence, there is a definite need for a simple description of these materials and their uses. This small book appears to meet this need admirably. The authors have been actively identified with many of the developments in this field.

The substances described are: thrombin, fibrinogen, oxidized cellulose, fibrin foam, and gelatin sponge. The chemical and biological properties of each substance are discussed, followed by a review of clinical uses found to date. In an introductory chapter the current views on the clotting of blood are sufficiently presented to give an understanding of the basis for the techniques described and their application. Evidently the authors have purposely avoided recent theoretical complexities in favor of providing information of immediate practical use.

This book will be of greatest value to those with surgical interests, with its immediate applications to neurosurgery, plastic surgery, gastroenterology, rhinology, urol-