

The Close Association of Endocrinology with Genetics in Clinical Medicine

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The science of endocrinology and the science of genetics were born at about the same time around the onset of the 20th century. Both genes and endocrine hormones are *integrative agents* within the frame of an individual being. The genes, as we know them today, control specific enzymatic processes that are operative at various parts of the body, at different organs, tissues and functions. Hence the pleiotropic effect of one gene and the widely distributed manifestations of mutations of more than one gene, localized close together in the same chromosome (linkage of genes). The action of endocrine hormones extends upon various organs and functions; their integrative function needs no further discussion. It is not always sufficiently appreciated that hormonal effects depend to a large extent on the response of the target organs which, in turn, is determined by both their genetic and acquired reactivity. Thus the genetic set-up controls not only the activity of endocrine glands but also their effect on their target organs. The proper consideration of such interaction of genes and hormones is indispensable for the understanding of the variability of the clinical picture of human diseases with evident abnormalities of endocrine function.

It stands to reason that investigation of endocrine integration preceded by far that of genetic integration. The first operates with morphological and biochemical entities which can be studied with available clinical and laboratory methods. The latter depended on methods applicable only to plants, insects and other small, short-lived animals with rapid sequence of generations. For the study of human genetics these methods are unsuitable and must be replaced by others. At the initial phase of human genetics tangible media were lacking and speculative imagination was indispensable for the interpretation of facts presented by nature in abundance. As late as 1952 discussion of genetic integration in humans was considered "philosophical" by an American clinician (1). Unintelligible clinical observations of multiple aberrations from a normal constitution were attributed to some puzzling glandular disturbances or altered interrelationship of various glands. This was the customary hypothetical conception in central Europe until the third decade of the century. Not before that time had it been realized that many clinical observations require an explanation quite different from or additional to a purely endocrinological one.

Herewith the genic ¹ aspect entered the picture and gradually became an indispensable associate and companion of endocrinology. We shall follow the development of this concept *historically* and *psychologically*.

The familial syndrome of obesity, genital hypoplasia, retinitis pigmentosa, mental deficiency, polydactyly, sometimes syndactyly, and deformity of the skull is known as *Laurence-Moon-Bardet-Biedl syndrome*. It was thought to be due to a lesion of nervous centers and the hypophysis, produced by a primary malformation of the skeleton with hydrocephalus. The concept of a genic etiology of this whole syndrome is generally accepted today and was first advocated in 1927 (Bauer (2), Berta Aschner (3)). The question whether we have to deal with pleiotropy of one gene or with the effect of linkage of several genes was left unanswered.

The disproportionate length of the extremities is known as *eunuchoid proportions of the body* because it frequently is found in primarily hypogonadal persons. In 1924 it was demonstrated (4) that a genic (constitutional) factor is decisive whether or not such proportions develop in a hypogonadal individual. The *syndrome of gonadal aplasia and stunted growth* as it was termed recently by L. Wilkins (5) has been known for a long time. My interpretation of the syndrome as result of coordinated genic effects rather than of purely endocrine disorders dates back to 1927 (2). This has been ignored for 15 years until the correct concept was rediscovered by several American authors (6).

A constitutional, that is genically determined type of *precocious puberty* occurring in several members of a family has been generally recognized after E. Novak's publication of 9 pertinent cases in 1944 (7). It had escaped the attention that this variety of precocity which cannot be accounted for by a disease or abnormality of an endocrine gland or the central nervous system had been described and discussed long before (2). It is due to a mutation of a gene or gene-complex that controls the speed of the evolutive process (8). It is remarkable that either males or females, but not both sexes, in the same family may be affected with constitutional precocity. In 1952 a family with 27 affected male members in four generations has been reported and the conclusion drawn that the trait of precocity was transmitted by one sex-limited autosomal gene (9).

Sexual and somatic precocity is part of a syndrome first described by Fuller Albright et al. in 1937. In this syndrome it is associated with multiple bone cysts that have a tendency to be unilateral in some cases, and brown non-elevated nevi occurring on the same side as the bone lesions. A "disseminated neurologic lesion" involving especially the hypothalamic region had been offered as explanation of this syndrome without anatomic confirmation. Not before 1945 it was recognized as a genic disorder due to linkage of mutated genes or pleiotropism of one gene (6). The unilaterality of the manifestations suggested a somatic mutation, that is, a chromosomal alteration not of the germ cell but of one of the somatic cells during the first stages of embryonic development.

¹ We use the adjective "genic" instead of the customary "genetic" because it designates origin from genes specifically and unequivocally, whereas "genetic" expresses origin of any kind in its broadest sense.

The concept of genic etiology of diseases still lags far behind more tangible, visible though unsatisfactory interpretations. Medical writers still acknowledge heredity as "playing a role" in many morbid conditions but deficient abstract thinking accounts for the statement that the etiology is unknown. In fact, pathogenesis may be unknown; heredity (or somatic genic mutation), however, is an essential etiologic factor of its own, either alone or a predisposing and cooperating one among others. There is practically no endocrine gland that had not been made responsible for causing otosclerosis, alopecia areata, albinism, vitiligo and many others. Publications of this sort usually were followed by others demonstrating that such conclusions were unwarranted.

Fat boys with small or only apparently small genital organs used to be diagnosed as *Froehlich's adiposogenital dystrophy* until I pointed out the fallacy of this diagnosis in 1927 (10), which is recognized today quite commonly. The importance of a constitutional, genic factor in the etiology of obesity has not found the necessary evaluation although the role of the endocrine glands has been rightfully reduced. Excessive intake of food for various, especially psychological reasons can easily be understood without abstract thinking and appeals therefore to simple minds more than acceptance of genic, constitutional etiology. This is all the more remarkable as medical laymen, particularly farmers and animal breeders have a sounder concept of the problem. Even more difficult to comprehend seems to be the concept that developmental disorders, malformations, tumors or functional aberrations of endocrine glands may arise from primary genic mutations that produce clinical manifestations of their own. Gigantism or obesity for instance may in some cases erroneously be attributed to primary endocrine disorders instead of being recognized as genic in origin with sometimes resulting secondary involvement of the endocrine system. The mental soil does not seem to be ready yet for acceptance of what I had termed *endocrine stigmatization* (6, 8).

As late as 1928 the reviewer of my monograph on internal secretion in the J.A.M.A. of July 14 expressed the opinion that "one may question whether the introduction of such concepts as genotype personality and heredity without further analysis of the mechanism of these processes does not contribute more fog than clarity to an already difficult field". In 1935 I insisted successfully on an association of two groups of researchers working on, and interested in, endocrinology on the one hand, and genetics on the other hand, in a single scientific society which was founded in Vienna and called "Society of Human Genetics and Endocrinology". The necessity of such a combination was urged in an introductory paper (11).

Much has been learned in 30 years since 1928 and with the advent of concrete *morphologic evidence for hereditary factors* Anglo-American clinicians rapidly have risen to range among the leaders in the field of human genetics and its bearing on endocrinological problems.

M. L. Barr's description of a different *nuclear chromatin pattern* in males and females (1949) was followed 9 years later by an even more exciting morphologic discovery of C. E. Ford and his coworkers (1958). With the discovery of a new method of se-

parating and counting *human chromosomes* a tangible morphological basis became available for the study of human genetic problems that previously could be approached only with speculative methods. This tempting incentive appealed to the realistic and mechanically oriented mind of clinicians far more than abstract logical thinking. It became an important boost to proper appreciation of genetics in clinical medicine.

The unwarranted concept of *mongolism* as result of an endocrine and especially pituitary disorder eventually had to be discarded on morphologic evidence. An abnormal additional acrocentric autosome was found regularly in mongoloids. This was convincing; logical abstracts from clinical facts had not been. *Gonadal dysgenesis* with *Turner's syndrome* in apparent females was found to have a male nuclear sex pattern and a lack of one female sex chromosome. Instead of 46 there are only 45 chromosomes and the chromosomal sex of XO instead of normal female XX or male XY. *Klinefelter's syndrome* too has been proved to be primarily a genic and only secondarily, that is clinically, an endocrinological problem. The Klinefelter patient is male with a female nuclear sex-pattern and has an additional sex chromosome (XXY) among 47 chromosomes (12). Recently a chromosomal *super-female* with a chromosomal number of 47 and a chromosomal sex of XXX has been described (13). Clinically, however, she does not seem to me to deserve the epitheton "super-female". Hypoplastic genitalia, irregular and scanty menstruation, secondary amenorrhea and elevated gonadotropins in the urine are at variance with "super-female". Many problems await clarification.

One thing, however, is now obvious even to those who had been unable to evaluate and accept a concept based on logical conclusions before a tangible morphologic basis had been at our disposal: *the indispensable association of endocrinology and genetics in human pathology*.

Summary

Endocrinology more than any other medical specialty requires consideration and cooperation of genetics. History of the rapid progress of clinical endocrinology in the last 50 years shows that human genetics has been lagging far behind endocrinology in clinical medicine. The psychologic reason seems to be the mechanistic trend of modern medicine and reluctance to use abstract logical thinking applied to material facts.

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RIASSUNTO

L'Endocrinologia richiede, più di qualsiasi altra specializzazione medica, la considerazione e la collaborazione della Genetica. Passando in rassegna i rapidi progressi fatti negli ultimi 50 anni dalla Endocrinologia clinica, si nota che la Genetica umana è rimasta molto indietro rispetto all'Endocrinologia nel campo della Medicina clinica. La ragione psicologica di questo fatto sembra essere costituita dalle tendenze meccanicistiche della medicina moderna e dalla riluttanza ad applicare il pensiero logico astratto a fatti materiali.

RÉSUMÉ

L'Endocrinologie a besoin, plus que toute autre spécialisation médicale, de la compréhension et de la collaboration de la Génétique. Une rassegna des grands progrès faits le long de ces derniers 50 ans par l'Endocrinologie clinique montre que la Génétique Humaine est restée très en arrière par rapport à l'Endocrinologie dans le secteur de la médecine clinique.

La raison psychologique de ce fait peut être recherchée dans les tendances mécanistiques de la médecine actuelle et dans sa réluctance à l'application de la pensée logique abstraite à des faits matériels.

ZUSAMMENFASSUNG

Endokrinologie erfordert mehr als andere Spezialfaecher der Medizin Beruecksichtigung und Vereinigung mit Vererbungslehre. Der rapide Fortschritt der klinischen Endokrinologie in den letzten 50 Jahren ging dem der menschlichen Vererbungslehre weit voraus. Der psychologische Grund scheint der mechanistische Zug der modernen Medizin und damit die Zurueckhaltung zu sein, abstraktes logisches Denken zur Erklarung materieller Tatsachen heranzuziehen.