CONSTITUTIONAL DISORDERS OF HOMEOSTASIS. THE GENETIC ASPECT OF DIABETES MELLITUS, ESSENTIAL HYPERTENSION AND OBESITY

by

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The maintenance of an approximately constant « milieu intérieur » (Claude Bernard) in spite of its continuous alterations by extrinsic and intrinsic factors is an attribute of living organisms. W. Cannon coined the term *homeostasis* for the designation of this fundamental function, that is, the adaptability to stimuli of most different kind. I prefer the word « stimuli » to its more fashionable synonym « stress » which is « a collective term used at present to describe a change in circumstance or environment » (1), in order to avoid any conscious or subconscious association with Selye's teaching. The precision of homeostasis and the number of adaptive mechanisms increased in the course of phylogenetic evolution.

« The perfection of the process of holding a stable state in spite of extensive shifts of outer circumstance is not a special gift bestowed upon the highest organisms but is the consequence of a gradual evolution. In the eons of time during which animals have developed on the earth probably many ways of protecting against the forces of the environment have been tried. Organisms have had large and varied experience in testing different devices for preserving stability in the face of agencies which are potent to upset and destroy it. As the construction of these organisms has become more and more complex and more and more sensitively poised, the need for more efficient stabilizing arrangements has become more imperative. Lower animals, which have not yet achieved the degree of control of stabilization seen in the more highly evolved forms, are limited in their activities and handicapped in the struggle for existence » (W. B. Cannon, p. 23) (2).

Many of the homeostatic mechanisms have been elucidated by the efforts of physiologists and clinicians. We are able to define the organs involved in these processes although the amazing regulatory force of these very complex processes induced many biologists to subscribe to a neo-vitalistic concept of life. We know that the bone marrow replaces a loss of blood corpuscles and that the thyroid and other endocrine organs as well as some autonomic centers exert a stimulating action upon it; we also know that the spleen inhibits liberation of blood cells from the marrow; why under normal conditions the overactivity of the marrow stops at the right time we don't know. The parathyroids adapt their function to the calcium and phosphorus level in the blood, the pituitary regulates the production of sex hormones, thyroid and adrenal cortical hormones according to the requi-

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rements of the body. Kidneys and lungs participate at the maintenance of the acid-base balance. Many similar mechanisms can be listed along the same lines. It stands to reason that any diseased organ involved in any kind of homeostasis must bring about a more or less serious disturbance of the respective mechanism. Pathologic anatomy comes to the fore as our teacher in such conditions.

There is, however, a group of *disturbed homeostatic mechanisms that are not due to particular diseased organs.* The pathologist in the autopsy room does not contribute greatly to our understanding of such cases, his competence is limited facing a case of death resulting from diabetes mellitus or essential hypertension, he cannot explain excessive obesity found at autopsy. Pathology has to yield to another branch of biology in this situation. Human genetics is here more competent.

Homeostasis of blood sugar, for instance, depends on proper function and adequate response of a variety of organs. The pancreatic islets, the adrenal medulla, the adrenal cortex, the pituitary gland, the autonomic nervous system, the enzyme system in the liver as well as in peripheral organs where it is necessary for utilization of glucose, all are involved in this process. Other endocrine organs like the thyroid or the ovaries exert an indirect influence by their relationship to the directly concerned hormone-organs, other parts of the central nervous system do that by their connection with the autonomic system. If any of these various tissues fails to cooperate in the homeostasis of blood sugar because it is affected by a localized pathologic process, diabetes mellitus may result. In these cases the pathologist may detect the cause of diabetes. This is what I (3) called *symptomatic diabetes* because the homeostasis had been impaired by the disease of a special organ; diabetes was one of the symptoms of pancreatic destruction, of pheochromocytoma, of an adrenocortical tumor, of acromegaly or Cushing's disease, of a hypothalamic lesion or of von Gierke's glycogenosis.

In the far more common variety, in *constitutional diabetes*, this is different. There is no distinctive pathology, no evidence of one particular organ being diseased, and no possibility of a cure by removing the cause. One of the most experienced pathologists in this field, Shields Warren, expressed his findings in the following words: « Perhaps the most striking characteristic of the lesions that may be found at autopsy of a diabetic is their heterogeneity » (4). The cause of constitutional diabetes remains obscure to the pathologist, it becomes evident only to the geneticist, that is, the properly investigating clinician. Attempts to elucidate the mode of hereditary transmission of the genetic predisposition to constitutional diabetes have failed so far. The reason of this failure will be discussed later. The complexity of homeostasis of blood sugar, however, makes it understandable that it may suffer by even slight functional deficiency of any one or more of the links in the chain of involved organs which may not necessarily show anatomical signs of their defect. Constitutional diabetes is a disease due to failure of homeostasis of blood sugar on a genetic basis. The different clinical varieties of the disease, fat or lean, old or young, sthenic or asthenic, insulin-sensitive or insulin-resistent, depend on the chiefly involved links in the whole chain of regulatory organs. It is interesting that long continued insulin treatment with unnecessary, excessive doses can produce a state of poor regulation in a diabetic by provocation of overshooting counterregulation. Therapeutic efforts by

clumsy interference with an already impaired homeostasis may be harmful. More details about the distinction of symptomatic and constitutional diabetes mellitus and their occasional combination may be found elsewhere (3).

We encounter a similar situation in so-called essential or better *constitutional hypertension*. A great number of organs participate in the homeostasis of blood pressure: The elasticity, function and reactivity of the peripheral arteries and arterioles, the vasomotor centers, the adrenals, the pituitary and all those parts of the organism that influence the function of these regulators, particularly higher cerebral centers and other endocrine glands. We have to distinguish a *basal blood pressure* measured during sleep or immediately after awaking and a *supplementary increase* during the day due to elevation of the basal pressure by the usual physical and mental activity. What we measure in our office or clinic is the so-called *casual blood pressure* or *habitual blood pressure*. The more activity or emotional upset preceded the examination, the higher will be the level of the pressure. The more sensitive and irritable the person is, the greater will be the supplementary pressure. This, however, does not mean constitutional hypertension at all. Competitors at Olympic games or those who had experienced the most extreme emotional turmoils in concentration camps do not develop constitutional hypertension as result of these excessive stresses unless they were constitutionally predisposed to this condition. It is, therefore, not the degree of supplementary blood pressure elevation, it is rather the capacity of bringing the temporarily elevated blood pressure down again, that is the homeostasis, which is of prime importance.

The habitual blood pressure of healthy normal persons varies greatly. A person with habitual blood pressure of 145/95 may be healthy and remain so just as well as one with a blood pressure of 90/60. Both, however, may become victims of progressive constitutional hypertension if their homeostasis fails to operate properly. Chinese are known to have a considerably lower habitual blood pressure than Caucasians. It is remarkable that Chinese may present all the manifestations of constitutional hypertension including hypertrophy of the heart, ocular changes and apoplectic strokes at a blood pressure as relatively low as 130-140/85-90 (5). Neither the constitutionally determined basal or habitual level of blood pressure nor the degree of temporary supplementary elevations of this level, only the homeostatic regulatory mechanism is the determining factor.

Arterial hypertension may be the result of a well defined disease of various organs. Hypertension belongs to the symptomatology of certain renal diseases, of polyarteritis nodosa, adrenal tumors, Cushing's disease, lesions of the diencephalon and others. This is what I call *symptomatic hypertension*. Essential or *constitutional hypertension*, however, fails to be associated with a characteristic organic disease discovered at autopsy. What the pathologist may find, the thickening of the arteriolar walls, sometimes with patchy necrosis and hyalinization, and the consequences of this arteriolosclerosis chiefly in the kidneys, is the secondary consequence — perhaps at best a parallel manifestation of the disease — not the primary cause of hypertension. Sometimes only hypertrophy of the heart found at autopsy indicates the previous hypertension. Constitutional hypertension is first a functional disease.

There is reason to assume that all organs that potentially can produce symptomatic

hypertension are also links in the chain which is involved in the homeostasis of blood pressure. The same holds true for the tissues which participate in the reduction of blood pressure. The carotid sinus and depressor nerves, the autonomic vasodilators and various vasodepressor substances counteract the rising pressure. Hypotensive substances probably involved in the regulation of blood pressure are the ubiquitous histamine, acetylcholine, the vasodepressor material produced by the liver and identified as ferritin (E. Shorr), and amine oxidase around sympathetic nerve endings chiefly in blood vessels (6). This enzyme destroys nor-epinephrine and to a lesser extent epinephrine; it is for the sympathetic transmitter what cholinesterase is for the parasympathetic transmitter acetylcholine. Sympathetic denervation diminishes the amine oxidase. This might explain the well known increased excitability by epinephrine of denervated sympathetic target organs.

Every person is continuously exposed to vasopressive stress factors. If the homeostatic « feed-back mechanism » becomes deficient and the normal reduction of a physiologic temporary elevation of blood pressure fails to occur, the stage for the development of permanent hypertension is set. It stands to reason that highly emotional, irritable persons with a neuropathic constitution will more often than others need the action of their feed-back regulation in order to counteract their more frequent and more intense physiologic temporary blood pressure elevations. They are the hyperreactors to cold or exertion and even cigarette smoking. Only if they inherited a weak and exhaustible feed-back mechanism, however, they will become permanent hypertensives. We understand that the weight of the adrenals is higher than the average in constitutional hypertensives and that usually clinically irrelevant cortical adenomas are more frequent in hypertensives than in others. They are not the cause of constitutional hypertension, however, even if some hirsutism and low sodium chloride concentration in sweat point toward hyperactivity of the adrenal cortex. Almost total bilateral adrenalectomy carried out in such a case of constitutional hypertension caused no eventual change in the level of blood pressure (7). Thorn and his group also emphasize that complete bilateral adrenalectomy in severely hypertensive patients does not necessarily decrease the level of basal blood pressure in spite of increased excretion of sodium and chloride (8).

Cannon realized that homeostatic mechanisms quite generally are liable to *senile deterioration*. It may well be that progressive failure of the homeostatic regulation of blood pressure due to the aging process contributes to the etiology of constitutional hypertension if a genetic weakness of this mechanism presented the necessary predisposition. We also understand that constitutional hypertension may befall even those who have lived for decades with a blood pressure at the lower end of the normal range because the breakdown of homeostasis can occur at any level of the constitutional blood pressure.

Now we can understand that, in general, blood pressure rises with age and that a genetic factor may precipitate this rising. We also understand that recent British investigators « suspect that essential hypertension has no real existence as a specific clinical entity. It is a convenient term for those subjects whose arterial pressures exceed a certain level chosen on arbitrary grounds and in whom there is no other disease present that accounts for the high pressure » (9). Constitutional hypertension becomes, indeed, a disease if

its consequences, overstrain of the heart and vascular changes, interfere with the health of its carrier.

A third type of disturbed homeostasis is *obesity*. In contrast to the unfortunately still common clinical teaching in U.S.A. obesity is not simply explained by assuming an imbalance between intake and output of energy. This is a tautology, not an explanation. There cannot be any question that in many instances of obesity the genetic factor is paramount.

Our insight into the extremely complex homeostatic mechanism of energy intake and output, that is, of relative constancy of body weight, is rapidly increasing. Facts derived from laboratory experiments on both experimentally induced and genetically obese animals, as well as from clinical observations substantiate the concept of constitutional obesity as result of genetically abnormal homeostasis.

Abnormal utilization of food and specific alterations of the intermediary metabolism have been demonstrated in obese animals (10). The interrelation of diencephalic centers which regulate food intake, and metabolic disturbances, the influence of higher cortical (mental) mechanisms upon these diencephalic centers, and their relation to endocrine functions has been studied. The relative autonomy of adipose tissue as to synthetizing fat from blood constituents (glucose, acetate) (11) and its regulations by hormones and nervous impulses has been established. All these factors are integrated into the constitutionally determined homeostatic mechanism of body weight. This mechanism may be disturbed by a disease process involving any of its constituent parts (*symptomatic obesity*), most commonly, however, it is disturbed by a genetic aberration (*constitutional obesity*).

It has been shown that the efficiency of the homeostatic mechanism varies with the constitutional habitus (somatotype). It is most efficient in the longitudinal, slender (leptosome, ectomorph) type, and least efficient in the lateral, broad (pyknic, endomorph) type (12). This is one more argument in favor of the constitutional nature of the common type of obesity. The observed caloric intake of ectomorph and endomorph children relative to their body build is actually opposite to the expected pattern (13). Observations on patients with hypothalamic diseases revealed that the amount of food intake and the degree of polyphagia or anorexia did not always correspond to the findings of obesity or emaciation, respectively (14). In three cases with marked bulimia no obesity resulted; in fact, in one case the patient was emaciated. Another patient had bulimia, and only much later did obesity develop. One patient had anorexia, but was obese. Thus it is clear that the problem of obesity is not simply a matter of imbalance between intake and output of energy.

We have been able, in my opinion, to demonstrate that certain genetically determined disease processes can best be interpreted as result of a failing fundamental function of the living organism, that is, of the function of homeostasis. This concept explains that no characteristic anatomic findings can be expected that could elucidate the nature and cause of these diseases. It also explains that we meet a counterpart of these constitutional disease types. The same clinical abnormalities — in our examples diabetes, hypertension and obesity — may be encountered as symptomatic manifestations of structural alterations of

various organs which represent links in the chain of the respective homeostatic mechanisms.

Our concept also is in accord with the fact that no rigid limits exist between the normal and the abnormal with regard to the precision of homeostasis. Limits used by clinicians have been construed arbitrarily for practical purposes only. These limits are based on statistical figures not on a fundamental principle. What Hamilton and coworkers emphasized for hypertension (9) is likewise true for diabetes and obesity. When is a patient prediabetic only and when is he actually diabetic? Are we ever sure whether he will not remain prediabetic all his life with diminished glucose tolerance but without the actual disease diabetes? Are there definite figures of weight in proportion to body build which justify the diagnosis obesity? Homeostasis may be deficient in various degree and may or may not break down almost completely at any age. Usually it weakens with progressive years.

If for some readers our argumentation may have more the flavor of philosophy than of exact medical science, then I agree. I must emphasize, however, that medicine is not exclusively applied exact science, it is also an art and, in particular, it remains incomplete without some philosophical outlook.

What is the genetic basis of the constitutional disorders of homeostasis? The highly complex homeostatic mechanisms involve precise cooperation of many functional processes and varying activities of many organs. They are attributes not only of individuals, families, races, species or genus but, quite generally, of viable living beings with higher organization. It is, therefore, not their presence but only their *precision* and their *pace of decline* which may be a distinctive characteristic of an individual and may be subject to hereditary variations. It is a matter of conjecture whether Mendelian (chromosomal) genes or cytoplasmic genes (plasmagenes) account for these individual variations. Their *presence* is not modified by sexual mating and is, therefore, not dependent on one or a few genes but on the potential power of development of a fertilized ovum as a whole, that is, on the sum total of genes which are the carriers of life itself.

We know that physiologic duration of life, for instance, is an inheritable and innate characteristic of a living organism. We can hardly postulate a specific gene securing the physiologic — that is, undisturbed by environmental factors — duration of life. It is inherent to the genus, species, race, family and individual. It is modifiable, however, by amphimixis, that is, by a new combination of the sum total of genes taking place in sexual propagation. This is known as « *continuous variability* ». It applies likewise to many human traits such as height, head shape, other body proportions or all degrees of pigmentation of human skin, from nearly albinotic to deep black. It is the basis of racial variability and « probably the most important in evolution » (Dobzhansky) (15). In an early era of scientific genetics this continuous variability was believed to be non-Mendelian. During the second quarter of our century, however, it has been demonstrated that it also obeys Mendelian laws, however difficult to analyze and interpret because of multifactorial, that is, polygenic causation. The polygenes exert only very small individual effects of their own and are scattered at random in the chromosomes. The varying distribution and and number of polygenes is the basis of continuous variability. The adaptive value to

environment of the many variants decides the survival under conditions of natural selection,

Can we expect to discover a special type of Mendelian inheritance in constitutional disorders of homeostasis? Hypertension usually is considered to be a Mendelian dominant, in diabetes and obesity no particular type has actually been demonstrated. Can we assume the existence of a specific gene controling the precision and pace of decline of a homeostatic mechanism? I have done just that with regard to constitutional hypertension (16). It would be justified if constitutional hypertension could be proven beyond any doubt to behave as a Mendelian dominant. Today I am inclined to accept a multifactorial type of heredity, difficult to be unraveled further within the frame of continuous variability. Gradual differences of precision and decline rather than sharp limits between normal and abnormal characterize constitutional disorders of homeostasis. For this reasons any efforts to determine the exact mode of hereditary transmission have been and will be very difficult if not futile.

We mentioned the decisive role of continuous variability in creating variants which are best adapted to environment and have therefore the best chances of survival under conditions of natural selection. Different environments create different races by different adaptive value of the variants. All this is valid as long as civilization and artificial interference with the natural selective process does not take place. Under these conditions known as « *domestication* » the adaptive value becomes unimportant. The less fit or unfit variants survive owing to interference of medical science and social care in our civilization. Has the progress of civilization diminished the selective value of perfect homeostasis? Do persons with genetically determined weakness of certain homeostatic mechanisms survive by virtue of our advanced civilization? They certainly do. Homeostasis of blood pressure has become a great deal more complex in bipeds. Erect posture and changing effect of gravity on circulation in different positions involves a considerable strain on this homeostasis. Orthostatic hypotension indicates that not all persons achieved sufficient homeostasis. Quadrupeds apparently do not have constitutional hypertension. This is an acquisition of humans and occurs with appaling frequency. Its selective disadvantage would exist only under conditions of natural selection, it does not count in our civilization. The incidence of diabetes mellitus is steadily increasing not only because it is more frequently discovered and people live longer but also because the propagation of the genetic defect has been furthered by the medical conquest of the disease in childhood.

We see that constitutional disorders of homeostasis deserve special interest from various viewpoints: from a biologic, clinical diagnostic and therapeutic, and from a eugenic viewpoint.

Addendum: An interesting contribution to our problem has recently been published by Drazin (Diabetes 2: 433. 1953). Glucose tolerance test was given to 42 patients with obesity, 52 with hypertension, and 60 with both conditions. More than 70% of the obese hypertensives, 45% of the obese normotensives, and 15% ot the non-obese hypertensives had decreased glucose tolerance. Il seems that several constitutional homeostatic mechanisms may be at fault simultaneously. Drazin's findings corroborate our concept of these three diseases.

Summary

There are abnormal states leading to diseases that are not confined to lesions or functional defects of particular organs but that are best interpreted from a broader view as result of deficient homeostatic mechanisms. Constitutional diabetes mellitus, hypertension and obesity belong to this category. The respective homeostatic defect involves the function of many organs and is genetic in nature. In contrast to these constitutional states diabetes, hypertension and obesity can develop also as manifestation of localized and well defined diseases of any one of the organs which are links in the chain securing the respective homeostasis. These much less common disease types are symptomatic diabetes, hypertension or obesity. There is reason to assume that the constitutional types have a multifactorial (polygenic) causation which makes further elucidation of the mode of hereditary transmission very difficult.

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SOMMARIO

Esistono stati anormali che portano a malattie che non si limitano a lesioni o difetti funzionali di organi particolari, ma sono meglio interpretati da un più ampio punto di vista come risultato di meccanismi omeostatici deficienti. Il diabete mellito costituzionale, l'ipertensione e l'obesità appartengono a questa categoria.

Il rispettivo difetto omeostatico comprende la funzione di molti organi ed è di natura genetica. In contrasto con questi stati costituzionali, il diabete, l'ipertensione e l'obesità possono svilupparsi anche come manifestazioni di malattie localizzate e ben definite di uno qualsiasi degli organi che sono anelli nella catena che assicura la rispettiva omeostasi. Questi tipi molto meno comuni di malattia sono il diabete, l'ipertensione e l'obesità sistematici. Vi è ragione di supporre che i tipi costituzionali abbiano una causa multifattoriale (poligenica) che rende molto difficile una ulteriore delucidazione del modo di trasmissione ereditaria.

RESUMÉ

Il existe des états anormaux lesquels donnent lieu à des maladies qui ne se bornent pas à des lésions ou à des défauts fonctionnels de certains organismes, mais qui doivent être interprétés d'un point de vue plus vaste comme la résultante de mécanismes homeostatiques défectueux. La diabète méllite constitutionnel, l'hypertension et l'obésité, appartiennent à cette catégorie.

Le défaut homeostatique, qui embrasse la fonction d'un grand nombre d'organes, est de nature génétique. En contraste avec ces états constitutionnels, le dibète, l'hypertension et l'obésité peuvent également se développer en tant que manifestations de maladies localisées et bien définies d'un quelconque de ces organes qui forment les anneaux de la chaîne qui assure la respective homeosthase. Ces types de maladies beaucoup moins communs, sont le diabète, l'hypertension et l'obésité systématiques. Tout permet de croire que ces types constitutionnels possèdent une causalité multifactorielle (polygénique) qui rend de beaucoup plus difficile une ultérieure délucidation du mode de transmission héréditaire.

ZUSAMMENFASSUNG

Es gibt abnorme Zustaende, die zu Krankheiten fuehren, welche nicht durch anatomische oder funktionelle Defekte besonderer Organe charakterisiert sind und am besten von einem weiteren Gesichtspunkt als Folge insuffizienter Homeostase gedeutet werden koennen. Konstitutioneller Diabetes mellitus, konstitutionelle Hypertension und Fettsucht gehoeren hierher. Der betreffende homeostatische Defekt betrifft die Funktion zahlreicher Organe und ist genetischen Ursprungs. Im Gegensatz zu diesen konstitutionellen Formen koennen Diabetes, Hypertension und Fettsucht sich auch als Manifestation lokalisierter und gut umschriebener Erkrankungen der einzelnen Organe entwickeln, die Glieder in der Kette darstellen, welche die betreffende Homeostase gewaehrleisten. Diese symptomatischen Formen von Diabetes, Hypertension oder Fettsucht sind viel seltener als die konstitutionellen Formen. Es besteht Grund zur Annahme dass die Konstitutionellen Formen multifactoriell (polygen) bedingt sind, was eine weitere Analyse des Erbmodus aeusserst schwierig macht.

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