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Genetics of Essential Hypertension

Historical perspective and current concept

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The term essential hypertension designates the permanently elevated systolic and diastolic blood pressure that gradually develops without a perceptible cause. It has been recognized as a specific morbid entity first in 1911 by Erich Frank, then a staff member of the University Clinic in Breslau (now Wroclav) under O. Minkowski. He called it "*hypertonische Diathese*". Many years passed by until this very frequent condition with which approximately 16.5% of all persons consulting an internist are afflicted became a popular diagnosis, different from arteriosclerosis.

In the early thirties the influence of Franz Volhard accounted for the generally accepted distinction of what he called "*white hypertension*" and "*red hypertension*". The first indicated renal, the second genuine or essential hypertension. After preliminary investigations of Volhard's associates the brilliant research of Goldblatt and his coworkers, of Irvine Page and many more American investigators greatly clarified the intricacies of renal hypertension. This, however, has no bearing on essential hypertension as Goldblatt believed.

The term "essential" hypertension, of course, is meaningless and designates only our ignorance about its nature. It became inadequate and useless when we had learned about its *etiology*. Wilhelm Weitz was the first who established *heredity* as the preeminent etiologic factor of this type of permanent systolic-diastolic hypertension in 1923 and was followed by an increasing number of authors in later years. Among prominent Americans I mention only Hines (1937), Fishberg (1939) or Rowntree (1940) who recognized the high frequency of heredity as constitutional predisposition to essential hypertension (Bauer, 1941).

Since 1933 I have repeatedly proposed to discard the term "essential" and to speak of *constitutional hypertension.* At that time I also emphasized the futility of looking for an abnormal structure or function of a specific organ to explain the pathogenesis of constitutional hypertension.

For a different reason the leading authority in this field, Arthur Fishberg, pleaded likewise for dropping the word "essential" which only masks our ignorance. Several cases of hypertension associated with tumors of the adrenal gland, the chro-

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maffine system, with Cushing's disease or with obstruction of the stem of the renal artery known in 1939 had branched off from the tree of essential hypertension. Further observations of similar kind might well elucidate this collective concept in the future and make it, in Fishberg's opinion, unnecessary and obsolete. The original concept of constitutional hypertension, however, remained unshaken and retained its specific identity.

In 1941 *constitutional hypertension* was distinguished from *symptomatic varieties of diastolic hypertension* because these belong to the symptomatology of definite specific diseases of various organs and types (Bauer, 1941). The symptomatic (or secondary) type of hypertension comprises renal, several endocrine (e. g. primary aldosteronism), metabolic (porphyria), cerebral and vascular diseases (e. g. coarctation of the aorta, polyarteritis nodosa, postpartal microangiopathy). Their etiology and pathogenesis depends on the respective disease. The etiology of constitutional hypertension, however, is an alteration in some part of the gene complex (genome), without a specific topic localization.

Simple dominant Mendelian heredity seemed to be the most probable type in constitutional hypertension. This was the opinion of Weitz in 1923 and still is that of Sir Robert Platt in 1959. The most appropriate way to study the type of heredity in constitutional hypertension appeared to me to focus our attention on the mechanism operative in the maintenance of blood pressure within normal limits in non-hypertensive persons.

If a single abnormal gene was actually the cause of constitutional hypertension, then its normal allele would logically be responsible for the maintenance of normal blood pressure. This maintenance is based on a highly complex feed-back mechanism that equalizes the normal fluctuation of pressure during 24 hours. The so-called supplementary pressure which is due to daily activity of a person is added to his basal blood pressure at night. Casual or habitual blood pressure remains practically unchanged throughout life although local distribution of circulating blood varies constantly according to the momentary requirement of different tissues.

There are many factors involved in the complex homeostatic mechanism of blood pressure: baroreceptors in the carotid sinus and the peripheral endings of the depressor nerves in the aorta, the moderator fibers in the IX and X nerves, the vasomotor centers, the chromaffine system, adrenal cortex, pituitary and the response of arterioles as the target organ of nervous and humoral stimuli, not to forget the participation of locally produced vasoactive hormonal substances as histamine, acetylcholine, renin, angiotensin, norepinephrine, serotonin, kinins or prostaglandin. *All these factors are integrated into one well coordinated biologic unit serving the homeostasis of blood pressure.*

It is hardly conceivable that this complex feed-back process should be governed by one gene, that is *one single* enzyme. It is evident that its decline and failure in constitutional hypertension must belong to the category of "*continuous variability*" produced by *multifactorial* or *polygenic heredity.* It is similar to many other genetic human traits such as height, shape of the head, stature, physiognomy, mental capac-

ity and intrinsic longevity. In each one of them quantitative variations not qualitative differences are caused by heredity. The " law of all or nothing " does not apply to them. There is no sharp line between normal blood pressure and constitutional hypertension. Our clinically accepted limits of normal blood pressure are arbitrary and non-existent.

In symptomatic hypertension the homeostasis of blood pressure is disrupted by a diseased organ. In constitutional hypertension a gradual decline of the homeostatic system develops, usually increasing very slowly and intermittently, in some cases, however, more rapidly (malignant hypertension). *Constitutional hypertension is a constitutional variant due to insufficient perfection of the homeostatic system and caused by polygenic heredity* (Bauer, 1960).

A concept of constitutional hypertension somewhat similar to my own advocated since 1933, was conceived by Bradley in 1948. He expressed it as follows: " Cortical, neural, humoral and local reflex vasomotor activity, all contribute in shaping the complex physiologic manifestation of the disease. Too little is known to assign preeminence to any one factor in this process ". At last Irvine Page propagated the same concept under a new term " *mosaic theory* " of essential hypertension. He calls it a " *disease of regulation* " which comes close to my term " *disease of homeostasis* " (Page, 1963, 1967).

A different way to study the nature of essential hypertension was chosen by Sir George Pickering in Oxford and his associates (1961). Epidemiologic-statistical method resulted in the same conclusion derived at on the basis of genetic considerations. Constitutional hypertension is not a specific disease but a *constitutional variant.* British authors, however, were unconvinced and criticized the inadequacy of the statistical method used by both Pickering and his counterpart R. Platt (Bauer, 1960).

Is essential hypertension as a constitutional variant a specific *disease* or is it only a definite *morbid predisposition?* The second alternative cannot be questioned. In any type of arterial hypertension the heart is subject to greater strain and, in the long run, will undergo hypertrophy and eventually may end in failure. In any type of arterial hypertension compensatory thickening of the wall of small peripheral arteries develops after a variable length of time and leads to arteriolosclerosis in different organs, especially in the retina and kidney. This establishes a vicious circle by elevating the blood pressure of its own. Several decades, but, in cases of malignant hypertension, only several months, may be necessary to cause blindness, death by renal failure, cerebrovascular accidents or coronary occlusion. Pickering (1961) showed convincingly that even the characteristic microscopic changes in the arterioles of malignant hypertensions develop as consequence of excessively elevated blood pressure.

As to the first alternative, it is a matter of semantics whether or not the constitutional variant of very slowly increasing permanent systolic-diastolic pressure should be called a specific disease. We must keep in mind that casual blood pressure varies considerably in different persons and also depends on the constitutional set-up. Only evidence of slowly progressive elevation of pressure characterizes constitutional hyper-

tension due to deficient homeostasis. Its course, consequences and outcome are unpredictable without clinical observation for some length of time. Only comparison with hypertensive close relatives of a person may sometimes offer a clue. It must be emphasized that even very low normal casual pressure does not prevent a decline of previously perfect homeostasis and development of constitutional hypertension in the 4th or 5th decade of life. It should be remembered, too, that any homeostatic mechanism in a healthy individual is subject to diminished perfection with advancing age (W. Cannon).

In 1942 I defined the term disease as follows. It is " an abnormal course of a vital process producing impairment of the individual and diminishing his fitness and efficiency. It may or may not be accompanied by subjective sensations of discomfort ". Many persons with constitutional hypertension are very much at ease; do they have a disease?

I am inclined to side with Pickering who changed somewhat his concept and now admits the constitutional variant of essential hypertension to be a specific " quantitative disease "; or as I expressed it, a *specific disease of homeostasis.*

As a disease it is amenable to treatment, as a constitutional predisposition to preventive measures. We deal with other similar situations, for instance in asymptomatic hyperuricemia or hypercholesterolemia, and use prophylactic management to possibly prevent gout or coronary occlusion, respectively. Diverticulosis or sicklemia with 25% S-hemoglobin in the mass of red blood corpuscles are not diseases but they are definite predisposing factors to sometimes serious diseases: diverticulitis and sickle cell disease,r espectively. Plain information about such abnormalities, their occasional implications and possible prevention are objects of preventive medicine.

Although we call constitutional hypertension a disease not every carrier of its initial and mild type is in need of specific treatment. Creation of fright and scare by calling a person's asymptomatic mild constitutional hypertension a disease and instituting a rigid treatment must be carefully balanced against the potential benefit of such treatment and the risk of its omission.

It stands to reason that many of the polygenes (or enzymatic agents) involved in a polygenic constitutional variant or quantitative disease may be expected to participate also in other morbid states of a similar etiology and pathogenesis. In other words, different types of insufficient homeostasis may share a group of deficient or otherwise abnormal enzymes and show therefore a mutual affinity (syntropy), that is a greater than accidental coincidence. Venn's diagram illustrates hypothetically this partial overlapping of four polygenomes and explains their clinically observed relationship (cf Figure). The frequent association of constitutional hypertension with arteriosclerosis, both atherosclerosis and presbyosclerosis, deserves particular attention. Arteriosclerosis may considerably raise the systolic and also lower the diastolic pressure due to loss of elasticity of the great arteries. Year long observation of persons with constitutional hypertension frequently shows a depression of the elevated diastolic pressure when arteriosclerosis becomes an associated complication.

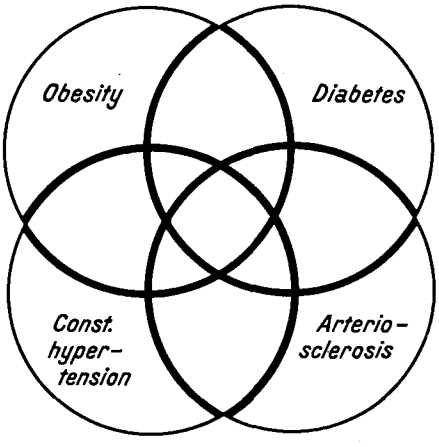

Figure. Venn's diagram

The present concept of essential hypertension as outlined in this paper is a *theory*, i. e. a product of synthesis and logical conclusion from facts. More facts must become known to support, modify or reject this theory. At the present time, however, it offers the best interpretation of the nature of essential hypertension. Pickering quotes a dictum of Conant: " Science advances not by the accumulation of new facts, ... but by the continuous development of new and fruitful concepts ". It is the duty of future investigators in this field to take cognizance of the present theory — Pickering calls his concept " idea " — and to side with it, to alter it or to reject it but not to ignore it and to pass by.

Summary

Essential hypertension was first recognized as morbid entity in 1911 and the word " essential " was substituted by " constitutional " in 1933. Diastolic hypertension may be constitutional or " symptomatic " if it belongs to the symptoms of a disease of specific organs (kidneys, endocrine, metabolic disease, cerebral or vascular disease). It is futile to search for such a diseased specific organ in constitutional hypertension (1933). Constitutional hypertension is a constitutional variant due to insufficient perfection of the homeostatic (feed-back) system maintaining the habitual blood pressure at a constant normal level. It is of multifactorial (polygenic) etiology (1960). It is a definite predisposition to actual diseases. It is a matter of semantics whether or not it should be called a disease of its own. The syntropy of constitutional hypertension and diabetes, obesity and arteriosclerosis is best explained by sharing various parts of polygenomes that are the common genetic basis of each of these morbid states.

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RIASSUNTO

L'ipertensione essenziale fu riconosciuta come entità morbosa per la prima volta nel 1911, ed il termine « essenziale » fu quindi sostituito con quello di « costituzionale » nel 1933. L'ipertensione diastolica può essere costituzionale o « sintomatica », se appartiene ai sintomi di una malattia di organi specifici (reni, ghiandole endocrine, malattie metaboliche, cerebrali o vascolari). Ma è senza senso cercare tali affezioni di organi specifici nella ipertensione costituzionale (1933). Questa è una variante costituzionale dovuta ad una deficienza del sistema omeostatico (« *feed-back* »), che mantiene la pressione sanguigna abituale ad un livello normale costante. Essa riconosce una eziologia multifattoriale (1960); rappresenta una precisa predisposizione a malattie effettive, ed è una questione di semantica se debba essere chiamata malattia di per sé. La sintropia dell'ipertensione costituzionale e del diabete, dell'obesità e dell'arteriosclerosi, viene spiegata nel modo migliore, dividendo varie parti dei poligenomi che costituiscono la base genetica comune di ciascuno di questi stati morbosi.

RÉSUMÉ

L'hypertension essentielle a été pour la première fois reconnue comme entité morbide en 1911, et le terme « essentielle » a été substitué par celui de « constitutionnelle » en 1933. L'hypertension diastolique peut être constitutionnelle ou « symptomatique », si elle rentre dans les symptômes d'une maladie d'organes spécifiques (reins, glandes endocrines, et maladies métaboliques, cérébrales ou vasculaires). Et il est inutile de chercher de telles affections dans l'hypertension constitutionnelle (1933). Cette dernière est une variante constitutionnelle due à une déficience du système homéostatique (« *feed-back* »), qui maintient la pression artérielle habituelle à un niveau normal constant. Son étiologie est multifactorielle (1960). Il s'agit d'une prédisposition à des maladies effectives, et il est une question de sémantique qu'elle soit ou ne soit pas une maladie elle-même. La syntropie de l'hypertension constitutionnelle et du diabète, de l'obésité et de l'artériosclérose peut être expliquée par une division en différentes parties des polygénomes, qui sont la base génétique commune de chacune de ces conditions morbides.

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ZUSAMMENFASSUNG

Essentielle Hypertonie wurde zuerst 1911 als Krankheits-Entität erkannt. 1933 wurde das Wort essentiell durch konstitutionell ersetzt. Diastolischer Hochdruck kann konstitutioneller oder symptomatischer Natur sein; wenn er in diesem Fall zur Symptomatologie einer specifischen Organerkrankung gehört (Nieren, endokrine, cerebrale oder vasculäre Krankheiten). Es ist aussichtsslos nach einer spezifischen Organerkrankung als Ursache der konstitutionellen Hypertonie zu suchen (1933). Konstitutionelle Hypertonie ist eine Variante infolge mangelhafter Präzision des komplexen homäostatischen « *feed-back* » Systems, dem die Erhaltung des habituellen Blutdruckes auf einem konstanten normal Niveau obliegt. Sie ist durch multifaktorielle Vererbung bedingt. Konstitutionelle Hypertonie prädisponiert zu Krankheiten bestimmter Art. Ob sie an sich als Krankheit angesehen werden kann, ist eine Frage der Semantik. Die Syntropie des konstitutionellen Hochdrucks, Diabetes, Fettsucht und Arteriosklerose erklärt sich am besten durch die Teilnahme verschiedener Anteile eines Polygenoms an der genetischen Grundlage dieser Krankheiten.

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