ON THE RELATIONS OF HEREDITY AND ENVIRONMENT, OF "CONSTITUTION" AND "CONDITION," TO PREDISPOSITION TO DISEASE[1]

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Medical men in their studies of the origin of disease have, during the past fifty years, been much more deeply interested in external (or exogenous) than in internal (or endogenous) causes. This fact is by no means surprising for we have just passed through a period when studies of harmful agents emanating from without and researches directed toward combating their influences have been extraordinarily rewarding. I need only remind you of the triumphs of modern surgery in overcoming the effects of trauma, and of modern bacteriology, parasitology, immunology and chemotherapy in the control of infectious and parasitic diseases to make clear to you that exopathic considerations have largely dominated medical thought, medical research, and the practical activities of physicians and surgeons of our time.

Through the ages, however, from the time of Hippocrates downward, there have always been medical men, especially among the active practitioners, who have been impressed fully as much with differences in susceptibility to disease, differences in disposition, differences in powers of resistance to external noxæ, and differences in rapidity and completeness of recovery from disease or injury as they have been with differences in the

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external causes themselves. They have wondered why one of two persons similarly exposed contracted pneumonia while the other did not, why one man developed cirrhosis of the liver though his bibulous comrade who drank as much or more escaped, why one patient died of typhoid and another in the next bed recovered, why a fracture in one person healed quickly and that of another showed delayed union, or why several members of one family were phthisical when all the members of a neighbor's family remained hale and hearty. These discrepancies were not wholly explicable by differences in character of trauma, in virulence of invading micro-organism or in mode of exposure. They could be accounted for only by differences in the persons acted upon, that is to say by differences in disposition, either inherited or acquired. And hence, doubtless, must be sought the explanation of the undying popularity with the profession and with the laity of the conceptions of good and bad or strong and weak "constitutions."

With the rise of the natural sciences and the application of their methods of precision to the solution of medical problems, it was natural that medical investigators should give preference to researches that permitted of exact quantitative measurements. Ideas of constitution and of disposition could not, it was thought, easily be subjected to mensuration as a test of their validity and there was, accordingly, a tendency to put them aside in order to make room for etiological hypotheses more susceptible of mathematically accurate establishment as truth. There was certainly some justification for the harsh comment of Germain See: "La disposition est un mot pour masquer notre ignorance." However, as Bauer has pointed out, the assumption of a constitutional disposition to a disease remained a convenient subterfuge for lack of knowledge only so long as it was adopted solely by exclusion and no scientific proof for it could be brought forward. Once the scientific basis for a doctrine of constitution

had been established, the circumstances were altered and consideration of the pathology of constitution and of disposition became both legitimate and imperative. During the past two or three decades, thanks to exact studies of heredity and of development, the scientific foundations for a general and special pathology of constitution and disposition have been laid. Biologists, who during the previous century had concentrated their attention upon the origin of species (doctrine of evolution), have in the present century directed their researches more particularly to the origin of individuals (phenomena of inheritance and development). Through experimental studies of heredity and development in animals and plants they have accumulated data and established principles that mark the beginning of a new era. The knowledge that has been gained of those processes in forms of life below man is full of promise for a better understanding of human heredity and development. It justifies the hope that our ability to control these processes in human beings will from now on make steady growth. It has occurred to me, therefore, that an examination of some of the relationships of heredity and environment to predisposition to disease might afford interesting materials for a general address, such as I have been asked to make on this occasion.

The Processes of Development

The development of a human being resembles in all essential respects that of other animals. The laws of heredity and differentiation appear to be fundamentally the same in man as in lower forms. The female sex-cell (ovum) is fertilized by the male sex-cell (spermatozoon). The union of the two sex-cells (gametes) to form a single cell (oosperm) starts a new individual (zygote). Under the influence of a suitable environment, this fertilized egg-cell develops, stage by stage, into an adult human being or person; and as the body develops there is a gradual

transformation of the simpler reactions and activities of the oosperm into the extremely complex and varied reactions and activities (exhibited as instincts, habits and intelligence) that characterize maturity. An understanding of the form and functions of the adult can be properly understood only by tracing them back to their origins, paying close attention to each stage of their differentiation from a generalized to a specialized condition. In this differentiation two sets of factors are concerned: (1) intrinsic factors represented by the organization of the oosperm (heredity), and (2) extrinsic factors represented in the surroundings of the developing organism (environment). The development is determined mainly by heredity, though it is modified (stimulated or inhibited) by the environment.

The Nature of Heredity

Knowledge of heredity has made great progress since biologists began to study the traits or constituent characters of organisms singly instead of limiting their attention to resemblances and differences of whole organisms considered as indivisible units. Species characters and racial characters are all inherited; they are firmly fixed by heredity. Many individual characters (structural and functional) are also known to be inherited, though some are due to the environment and are not inherited. All the possibilities for development of body and mind are inherent in the germ-plasm or idioplasm of the oosperm; the possibilities that become realities in the developed person are dependent for their realization upon stimuli originating in the surroundings. The "determination factors" of development are contained within the germ; the "realization factors" of development lie in the environment.

Studies of inheritance by the methods of Mendel have thrown great light upon the transmission of hereditary characters. They have shown (1) that certain characters are inherited as a

whole and are not further subdivisible (principle of unit characters), (2) that when contrasting unit characters are present in the two parents, one becomes dominant and the other recessive in the offspring (principle of dominance), and (3) that every single germ-cell is "pure" as regards any given unit character, even though it be derived from a hybrid parent (principle of segregation). Though these so-called Mendelian rules have had to be modified somewhat, their application is apparently as important for biology as the atomic theory has been for chemistry. They have permitted the analysis, by experiment, of the inherited constitution of organisms; by applying them it has been found possible to determine the true resemblances and the true differences of many animals and plants. They probably hold for man, though since man is a slow-breeding polyhybrid, has few children, and is relatively inaccessible to experiment, the study of his inheritance must always be less satisfactory and less accurate than studies of inheritance in lower forms. But there is in man as in animals a cellular basis to heredity, and in man the same distinction between germ-cells and soma-cells can be made. Furthermore, similar chromosomal mechanisms are concerned, the inheritance of certain unit characters is similarly sex-linked, and mutations likewise occur and are inherited. We can feel tolerably certain, therefore, that the general principles of heredity and development that have been and are being established through animal experiment are broadly applicable to man and can safely be used as foundations for medical studies.

Genotype, Paratype and Phenotype; Constitution and Condition

From what has been said, it is clear that we should, by abstraction at least, distinguish sharply in every organism (including man) between the part due to inheritance and the part due to

environment. The fertilized egg-cell (oosperm) represents through its chromatin the inheritance uninfluenced by environment. It begins, however, immediately to be influenced by its surroundings (substances and energies) and to undergo changes as a result. If development proceed normally, the reactions between the germ-plasm and the environment gradually lead to the fully-developed organism, in man the "realized adult person." To this realized organism the term 'phenotype' has been applied, whereas to the germinal material with all its hereditary peculiarities has been given the name 'idiotype' or 'genotype,' since this contains the elements (genes) that determine the reactions that give rise to the characters of the developed organism. Now the genotypic or idiotypic part of a phenotype, that is the part due to heredity, may well be designated 'constitution,' whereas the rest of the phenotype, the part of it due to environmental influences, may well, as Tandler has suggested, be called "condition," or, as Kahn has recommended, "constellation." The phenotype is, thus conceived, the resultant of the interaction of 'constitutional' factors with 'conditional' influences.[2]

If we adopt these definitions, the conception of "constitution" is purely hereditary in character. It is, as Grote puts it, "the

[2] Some contemporary writers use the term 'constitution' in a different way, including in it the whole organismal make-up ("genotypic or idiotypic constitution" plus "condition"), differentiating thus between 'genotypic or idiotypic constitution' (hereditary) and 'conditional or paratypic constitution' (acquired). I have up to now been inclined to reserve the term 'constitution' for the germinal and the term 'condition' for the environmental contributions to the body make-up. Nevertheless the objections raised to such a restriction to the meaning of the term 'constitution' are formidable. For we have to deal in reality with developed individuals, composed of cells and tissues and their functions integrated into persons. We can distinguish abstractly, but only with great difficulty practically, between what is inherited (genotypic constitution) and what is acquired (condition or constellation) in such persons. For the qualities of persons are not additions of condition to constitution, they are amalgamations of inherited and acquired. Thus vaccination gives an acquired immunity against smallpox but this acquisition presupposes a definite inherited constitution!

sum of all those morphological, functional and regulatory properties of the soma and of the psyche that are particularly determined at the moment of fertilization and that become realized in the course of personal development." The conception of "condition" is, on the other hand, purely non-hereditary in character. It includes the qualities that are acquired during development and in the course of the personal life (owing to food, geographical location, education, social position, disease, etc.), qualities that are not transmissible to the offspring since they are not represented in the germ-plasm. To repeat, then, according to the above definitions the total qualities of the realized person (phenotype) are partly "constitutional" and partly "conditional" in origin. But if it be desired to use the term "constitution" in a broader sense, we may speak of the phenotype or phenotypic constitution as consisting of two parts:—(1) a genotypic or idiotypic constitution (inherited), and (2) a conditional or paratypic constitution (acquired).

The Clinical Significance of the Conceptions of Constitution and Disposition

We who are clinical workers are daily occupied in the recognition of health and of disease in human beings. We study persons as wholes and we study also their constituent anatomical systems, the functional activities of those systems, and the regulatory mechanisms that control and integrate them. We try to distinguish between what we call "normal" and what we call "abnormal." But the term "normality" has a different meaning, according to the particular standard (norm or type) with which structures and functions are compared. The anthropologist will have one standard in mind, the morphologist another, the physiologist another and the moralist still another. As clinicians, we regard as "normal" a person whose vital responses correspond completely to those biological needs that

depend upon his collisions with a physical, chemical, psychical and social environment. When there is incongruity between vital responses and personal needs for biological performances, the person may be regarded as "abnormal." Or if one desire to avoid the terms normal and abnormal he may (with Grote) adopt the expressions "responsive" and "irresponsive" for persons respectively whose reactions correspond, or do not correspond, to their individual biological needs. This idea of "personal normality," or of "responsivity of the person" is clinically of real value, though it differs of course from the notion of normality of type based upon statistics or averages as well as from the notion of normality as identity with an ideal type—two fictive conceptions that, owing to the multifariousness of human differences, are of relatively little value for the clinic.

Considerable "variation" (morphological, functional, regulatory) in human beings is compatible with health, though each variation may entail some special individual predisposition to disease, since the variation may limit the powers of adaptation to the environment. The study of 'personal variants' becomes therefore of great importance, for an acquaintance with these and their corresponding dispositions to disease will be essential for the development of methods of special as contrasted with general prophylaxis. Morphological personal variants (exhibited as differences in habitus), functional personal variants (manifested as differences in biochemical composition or differences in modes of reaction) and evolutive and involutive personal variants (characterized by differences in times of reaching the developmental acme or in times of appearance of the phenomena of senescence) must always interest clinical workers who study single persons in the search for clues for disposition to disease and for criteria that will serve as guides for preventive intervention. A morphological variant exhibiting an asthenic

habitus is believed to be, other things being equal, more susceptible than others to pulmonary tuberculosis; a functional variant who metabolizes or eliminates purins slowly is in danger of paroxysms of gout; an evolutive variant who carries his infantile or adolescent modes of reaction and adaptation into adulthood runs the risk of psychoneurotic failure of social adaptation; and an involutive variant who shows a premature canities, an early arcus senilis of the cornea, or a premature menopause may, a little later on, show other signs of a partial or universal senilism or become the subject of a pathological abiotrophy, a progressive atherosclerosis or a chronic hypertrophic osteoarthritis.

So long, however, as these personal variants are adequately responsive, we do not call them 'diseased.' We clinically designate a condition as disease when the person becomes irresponsive, that is to say when his powers of adaptation become incongruous with his personal needs in the way of functional performance and endurance.[3]

The revival of the study of constitution emphasizes the individuality of each patient. It takes especially into account the structural and functional differences that distinguish persons from one another. No two persons are precisely alike. Each human being is a unique person; no-one just like him ever existed before; nor will anyone just like him ever exist again. The student of the pathology of constitution will ask himself when he studies a patient: Why does this particular person sicken of this disease? Why does the disease in him follow this particular course? Such questions are in line with a laudable clinical tendency, that of individualization in both diagnosis and therapy.

Disposition to disease in a given person may depend upon abnormalities of the genotype or idiotype chiefly, upon abnor-

[3] Though this definition of "disease" is practically useful in clinical work, a widening of the meaning may be desirable for anthropology and for general biology.

malities of the paratype chiefly, or upon a combination of both. The example usually chosen for illustration is pulmonary tuberculosis. From the standpoint of *inherited constitutional or genotypic disposition*, a person with a long, narrow thorax and voluminous lungs (habitus asthenicus) is believed to be much more liable, other things being equal, to progressive pulmonary tuberculosis than is a man with short neck and thorax and small lungs (habitus apoplecticus). From the standpoint of *non-inherited conditional or paratypic disposition*, a person who has recently recovered from measles or whooping cough is, other things being equal, in greater danger of pulmonary tuberculosis than is another. A person with asthenic habitus convalescent from measles has a *combined genotypic and paratypic disposition* to pulmonary tuberculosis, partly inherited, partly acquired, and is, accordingly, doubly endangered.

A growing interest has been manifested since the beginning of the new century in the analysis and classification of human phenotypes. French observers have attempted to divide developed human types into four main groups: (1) a respiratory type, (2) a digestive type (3) a muscular type and (4) a cerebral type, on the ground of external habitus. Clinicians in various countries have described several types of general anomalies of phenotype, for example, the status asthenicus (Stiller), the status thymico-lymphaticus (Paltauf), the status hypoplasticus (Bartel), the status exudativus (Czerny), the status arthriticus (*arthritisme* or *herpetisme* of French writers). Such general anomalies of body make-up are believed to predispose to special forms of organic and functional diseases. Interesting as these attempts to establish definite types of anomalies of constitution are, they are far from exact scientific establishment. The several anomalies mentioned show manifold overlappings; it would seem as though every new investigator in this domain felt it incumbent upon him to describe a new 'status' under a new

name, even though it appeared as only a slight modification of a status that had been earlier described. As J. Bauer has emphasized, the objection to be raised to these attempts at systematization of "states" lies in the fact that clinically so many mixtures of the "states" are seen and in such kaleidoscopic confusion that, for the present at least, they defy attempts at satisfactory classification. The reason I think is obvious. Clinicians have been trying to deal with complex wholes of constitution before knowledge of the simpler elements has sufficiently advanced. Clinical studies of the pathology of constitution and disposition are suffering from the limitations that characterized the studies of heredity by biologists before the application of the experimental analytical (especially the Mendelian) method.

Following the lead of modern biology in the attempt to deal with the inheritance of constituent characters rather than with that of organisms in their entirety, Davenport and Plate have catalogued over sixty pathological human traits that they believe to be inherited in Mendelian fashion. Some of these appear to be dominant, some of them recessive. A number of them, like hemophilia and color blindness, seem to be sex-linked. Though only a beginning has as yet been made in the scientific analysis of phenotypes (and of their genotypic and paratypic constituents) in relation to disposition to disease, it is certain, I think, that studies of this sort must soon increase in numbers and in clinical importance. An especially fruitful field is that of dispositions depending upon disorders of the endocrine functions, both those of genotypic and those of paratypic origin.

There can be no doubt that, as knowledge of constitution and of disease disposition grows, much will be gained for prophylaxis, therapy in general will become more individualized and, perhaps, we shall also make some advance in devising practical eugenic measures that will lead gradually to the betterment of our race.

Selected References

Bateson, W. *Mendel's Principles of Heredity*, Third Ed., 1913, Cambridge.

Bauer, J. *Die konstitutionelle Disposition zu inneren Krankheiten.* 2. Aufl., Berlin, 1921. J. Springer. 650 pp.

Bauer, E. *Einfuhrung in die experimentellen Vererbungslehre.* 3. Aufl., Berlin, 1920.

Borchardi, L. *Allgemeine klinische Konstitutionslehre. Ergebn. d. inn. Med.*, Berlin, 1922, 498–567.

Brugsch, T. *Allgemeine Prognostik, oder die Lehre von den aerztlichen Beurteilung des gesunden und kranken Menschen.* Berlin und Wien, 1918, Urban and Schwarzenberg, 498 pp.

Chaillou, A., and MacAuliffe, L. *Morphologie Medicate. Etude des quatres types humains.* Paris, 1912. O. Doin.

Conklin, E. G. *Heredity and environment in the development of men.* Third Ed., Princeton, 1920, University Press. 361 pp.

Davenport, C. B. *Heredity in relation to eugenics.* New York, 1911.

Grote, L. R. *Grundlagen aerztlicher Betrachtung: Einführung in begriffliche und konstitutionspathologische Fragen der Klinik für Studierende und Aerzte.* Berlin, 1921. J. Springer. 82 pp.

Hemmeter, J. C. *Constitution and the perspectives of to-day. Med. Rec.*, New York, 1921.

Jennings, H. S. *Heredity and personality. Science, n.s.*, 1911, xxxiv, 902–910.

Kretschmer, E. *Koerperbau und Charakter; Untersuchungen zum Konstitutionsproblem und zur Lehre von den Temperamenten.* Berlin, 1921. J. Springer. 192 pp.

Loeb, J. *The organism as a whole; from a physio-chemical viewpoint.* New York, 1916. G. P. Putnam's Sons. 379 pp.

Johannsen, W. *Elemente der exakten Erblichkeitslehre.* 2 Aufl., Jena, 1913. G. Fischer. 723 pp.

Kraus, F. *Die allgemeine und spezielle Pathologie der Person; klinische Syzygiologie.* Leipzig, 1919. G. Thieme. 435 pp.

Martius, F. *Konstitution und Vererbung in ihren Beziehungen zur Pathologie.* Berlin, 1914.

Morgan, T. H. *The physical basis of heredity.* Philadelphia, 1919.

Müller, F. *Konstitution und Individualität.* 1920.

Nettleship, E. *On some hereditary diseases of the eye. Trans. Ophthal. Soc.*, London, 1909, xxix.

Pearl, R. *The experimental modification of germ cells. J. Exper. Zool.*, 1917, xxii, also, *The Vitality of the American People, 1921.*

Siemens, H. W. *Einführung in die allgemeine Konstitutions und Vererbungspathologie.* Berlin, 1921. J. Springer. 229 pp.

Sigaud, C. *La forme humaine.* Paris, 1914.

Stockard, C. R., and Papinicolau, G. N. *Further studies on the modification of germ cells in mammals. J. Exper. Zool.*, 1918, xxvi.

Tendeloo, N. P. *Konstellationspathologie und Erblichkeit.* Berlin, 1921. J. Springer.

Treasury of Human Inheritance. London.