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College of Medical Evangelists, Los Angeles, California

CONSTITUTIONAL PATHOLOGY OF ERYTHROPOIESIS

by

Julius Bauer, M. D.

Clinical Professor of Medicine

The term "constitutional pathology" is not very popular in the U.S.A. The chief reason is the equivocal definition of "*constitution*". Here the word "constitutional" is mostly used to designate general manifestations of a disease concerning for instance fever, leukocytosis, loss of appetite and others. These manifestations, however, should be called "systemic" rather than constitutional, in order to conform to clear terminology. Many confuse "constitution" with "habitus", that is the general external make-up of a person. They believe that the essential if not only objective of constitutional pathology is the detection of relationships between the individual habitus, the proportions and measurements of the body, on the one hand, and the reactions of the individual to various stimuli, and particularly certain disease inclinations, on the other. They believe that constitutional pathology must find as many details of the general make-up as possible that may correlate with a particular morbid predisposition. They also try to correlate certain psychological features with the habitus but so far tremendous expenditure of time, effort and money has been and is being wasted because nothing significant has resulted from these studies beyond Kretschmer's well known concept.

Although the Italian medical school of Bologna (Di Giovanni, Viola) was among the leaders in somatic typology which is continued by W. H. Sheldon in America at the present time, it is refreshing to read that Gedda considers this "costituzionalismo morphologico" as completely useless for medical purposes. Gedda accepts the definition of constitution advocated by Tandler and Bauer as early as 1913 and 1917 respectively. Constitution in the biological and medical sense means the sum total of an individual's characteristics as they are potentially determined at the moment of fertilization. Individual constitution comprises all traits induced by the specific and unique constellation of the individual's genes, the influence upon their manifestation exerted by environmental factors notwithstanding. *Constitutional pathology is therefore concerned with all patho-*

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logic phenomena arising from the action of one or more abnormal genes. This is, in my opinion, the only clean and clear-cut definition and concept of constitutional pathology.

The problems of human genetics, however, are not exhausted by stating what morphologic or functional characteristics of the organism may be inherited and what type of inheritance they may show, whether dominant, recessive, sex-linked, etc. The chief problem lies in the recognition and complete isolation of what we call mendelian units or genes. It is necessary to reduce the phenotype, that is, the actual appearance of an individual, to its genotypical basis, and to unravel as far as possible the intricate complex of genes. One must realize that the potential energies represented by the genes do not always correspond to simple morphologic or functional characteristics perceptible in the human being. They represent categories of their own. Genes for definite stature and body proportions, for the amount and distribution of fat tissue accumulated, for the hair pigment, for the shape of the nose or the pinnae, for metabolic functions, for psychic features, for the speed of evolution and maturation, as well as for the wear and tear of various organs, for the reactivity to certain infections — and for all the manifold constitutional traits — are gathered in a double set in the chromosomes of the fertilized ovum. This of course has not the slightest resemblance to the actual appearance of an individual. The chief problem of constitutional pathology is to identify abnormal single genes and to discover the whole sphere of their action which may extend to different parts and functions of the body (pleiotropism of genes). Knowledge of such abnormal genes is also a prerequisite to study and comprehend the normal human constitution, that is, the actual genic composition and structure of a human being.

In the following paragraphs we intend to identify a number of genes which control the production and quality of red blood corpuscles.

Several types of morphologically abnormal red corpuscles are known to occur as a constitutional trait in certain families: *Spherocytosis, leptocytosis* (*target cells*), *ovalocytosis* (*elliptocytosis*), and *drepanocytosis* (*sickle cells*). They may exist as harmless constitutional characteristics of an individual, thay may lead to certain adaptive alterations in the body which may or may not impair the health of its carrier, or they may cause excessive blood destruction with resulting *hemolytic anemia* (*jaundice*). Excessive destruction of the red corpuscles may take place slowly and continuously, anemia may develop in more or less acute crises, or such crises may be superimposed on the chronic type of hemolysis. The pathogenetic mechanism is different in various types of these genopathies.

Constitutional spherocytosis usually is associated with increased osmotic fragility and with a considerably shortened lifetime of the spheroid corpuscles. This constitutional condition may remain innocuous as long as the bone marrow in capable to deliver new red cells at the same accelerated rate as the old cells are destroyed, chiefly in the spleen; and as long as the liver is capable to cope with the increased amount of transformation of broken down hemoglobin into bilirubin. This compensated state may turn into hemolytic anemia and jaundice at any time if the compensation breaks down. In the course of this chronic state of constitutional hemolytic anemia with acholuric jaundice there occur acute crises which had been believed to be hemolytic in nature but have been shown by Owren to be actually "aplastic", that is, due to acute inhibition of the bone marrow and

complete temporary cessation of erythropoiesis. There is some reason to assume that functional hypersplenism might cause this inhibition of the bone marrow by virtue of its hormonal influence. Splenectomy usually is the most effective treatment although the constitutional anomaly, that is, spherocytosis and abnormal osmotic fragility of the red corpuscles, remains unchanged. It need hardly be emphasized that spherocytosis and increased fragility of erythrocytes is not necessarily of genetic origin but can be a manifestation and result of an acquired hemolytic state.

Constitutional leptocytosis is characterized by abnormally thin red blood corpuscles. Hemoglobin may be seen only in the central circular area and the ring-shaped periphery of the erythrocytes. Hence the term " *target cells* ". They seem to be cells with a large envelope in relation to their contents. Their resistence toward hypotonic salt solutions in vitro is increased as compared with normal red corpuscles. Constitutional leptocytosis is the characteristic finding in *Cooley's erythroblastic anemia* (*Mediterranean anemia, thalassemia*). It is believed that the mild or even fully "compensated" consequence of this constitutional anomaly (*thalassemia minor*) arises from a heterozygous state whereas the full-fledged and fatal *thalassemia major* would result from the homozygous anomaly. 25% to 50% of the leptocytes from such patients transfused into normal persons show accelerated elimination. In the carrier state (thalassemia minor) the leptocytes have a normal life span. Normal erythrocytes transfused into patients with Cooley's anemia survive at a normal rate (Kaplan and Zuelzer). Removal of the enlarged spleen is as little effective as any other therapy in these cases. Target cells, as a matter of fact, are often seen as acquired anomaly of the red cells under various circumstances. Only in Cooley's anemia they are of genetic origin. There is reason to believe that the structural defect of constitutional leptocytes is due to faulty hemoglobin formation (Dameshek).

Constitutional ovalocytosis (*elliptocytosis*) is a hereditary anomaly of the red cells which has been observed in various human races, perhaps as an atavistic trait. It is the most innocent of the constitutional abnormalities of the red corpuscles. They show normal osmotic fragility and their carriers are, as a rule, healthy persons. Only exceptionally hemolytic anemia has been reported in association with constitutional elliptocytosis. There is recorded one case of a female child with hemolytic hypochromic anemia and splenomegaly whose parents both had elliptocytosis as a constitutional trait (Wyandt, Bancroft, and Winship). This observation points toward homozygosity of the trait as etiologic factor of the hemolytic anemia.

Constitutional drepanocytosis or *sickle cell trait* (*sicklemia*) has become one of the most interesting constitutional anomalies since the direct effect of the abnormal gene was disclosed to be an abnormal molecular structure of hemoglobin. This genic defect may produce the complex clinical picture of sickle cell disease with or without anemia, a disease which was rightfully termed by Pauling a " molecular disease ". Constitutional drepanocytosis is encountered almost exclusively in the Negro race and only in a small group of white people living in certain districts of Greece (Choremis et al.). The characteristic features of constitutional drepanocytosis are: Red corpuscles containing reduced hemoglobin but not oxyhemoglobin assume the elongated shape of sickles; this deformation is reversible by oxygenation; resistance of drepanocytes toward hypotonic

solutions in vitro is increased, toward mechanical injury decreased; their sedimentation rate is slower than that of normal red corpuscles; sickle cells are birefringent under the polarizing microscope. These anomalies depend on the hemoglobin because Ponder has demonstrated that, after hemolysis, the " ghosts " of the erythrocytes do not undergo sickling on exposure to low oxygen tensions.

In 1940 I wrote: " ... investigations on the electric charge of sickling cells which may offer a clue for elucidation of the problem, have not yet been carried out ". Nine years later Pauling, Itano and associates actually discovered first that the globin portion of the hemoglobin of drepanocytes has a greater positive electrical charge under certain experimental conditions than that of normal erythrocytes. The hemoglobin of sickle cells has, therefore, a different molecular architecture (S-hemoglobin) than hemoglobin of normal corpuscles (N-hemoglobin). Furthermore it was shown that the solubility of reduced S-hemoglobin is very much smaller than that of S-oxyhemoglobin as contrasted with only a 50% diminution of solubility of reduced N-hemoglobin compared with that of N-oxyhemoglobin (Perutz and Mitchison). It appeared probable, therefore, that the phenomenon of sickling might represent incipient crystallization of the reduced S-hemoglobin (Ponder, Granick, Perutz and Mitchison). This hypothesis was corroborated by rather convincing experiments of Harris. Concentrated solutions of reduced S-hemoglobin showed markedly increased viscosity and assumed a semi-solid gel-like state. Under the microscope formation of so-called " tactoids " was observed in these solutions of reduced S-hemoglobin. Tactoids designate an orderly grouping of long, thin, rod-like particles which are arranged parallel and equidistant to each other. These tactoids formed in reduced S-hemoglobin solutions reveal a striking resemblance to drepanocytes. All these phenomena were readily reversed by reoxygenation of the S-hemoglobin solutions. It is therefore probable to consider the birefringent sickled erythrocyte as a membrane-covered hemoglobin tactoid (Harris).

The problem of constitutional drepanocytosis became more complicated and fascinating by the investigations of K. Singer and his associates and the interpretation of the phenotypical, that is, clinical manifestations of this genetic molecular abnormality of hemoglobin. It has been known that constitutional drepanocytosis most frequently exists without causing impairment of health (*sicklemia, sickle cell trait*). Only in a small percentage of persons with constitutional drepanocytosis it is accompanied by a more or less severe disease, usually, but not always, with anemia as outstanding manifestation (*sickle cell anemia*). In carriers of the trait without anemia the drepanocytes are less numerous and are not as readily detected without artificial desoxygenation of the blood in vitro. Their life-span after transfusion is normal. The life-span of drepanocytes from patients with sickle cell anemia, however, is considerably shortened (from 15 to 60 days as compared with the normal survival rate of about 120 days). Drepanocytes of sickle cell trait-persons were found to contain only 23 to 45 per cent S-hemoglobin and 77 to 55 per cent N-hemoglobin, whereas drepanocytes of patients with sickle cell anemia contain 76 to 98 per cent S-hemoglobin. The genetic defect obviously shows quantitative differences of its phenotypical manifestation.

It has been known since the work of von Koerber in 1866 that hemoglobin of the

normal fetus and newborn differs from that of normal adults by being more resistant to denaturation by alkali. The fetal hemoglobin (F-hemoglobin) can also be distinguished from N-hemoglobin by immunologic, crystallographic, spectrophotometric methods and by its oxygen dissociation curve. F-hemoglobin is gradually replaced by N-hemoglobin under normal conditions until it completely disappears at the end of the second year of life. This was found to occur also in carriers of the sickle cell trait. Persons with sickle cell anemia, however, had only F-hemoglobin besides S-hemoglobin regardless of their age, that is, they had 2 to 24 per cent F-hemoglobin and no N-hemoglobin at all. Persistence of F-hemoglobin was also discovered in Cooley's anemia (thelassemia major), in some cases of constitutional spherocytosis and, irregularly in small amounts, in leukemia and some types of acquired anemia. This latter fact is suggestive of an acquired reversal of the bone marrow to the embryonic type of hemoglobin production. Although the significance is " not understood " (Singer) it seems to me that it might represent an additional sign of the " status degenerativus " with its multiple constitutional abnormalities which are so frequently encountered in persons with sickle cell disease (Bauer 1940-1947). In any case it is a most interesting infantilism of the hemopoietic system.

It has recently been found that the sickling trait is more than twice as common (12.6%) among tuberculous Negroes as it is among nontuberculous Negroes admitted to the same hospital (5.3%). Furthermore, exudative tuberculosis occurred twice as frequently in tuberculous Negroes with the sickle-cell trait (74%) as in tuberculous Negroes without the trait (38%) (Weiss and Stecher 1952). These facts can be understood only from a more general, holistic rather than a localistic-mechanistic viewpoint (Bauer 1917). Carriers of the sickle cell trait are less adapted to their environment, are less resistant and less viable, therefore also more apt to become victims of tuberculosis. This, of course, holds true for individuals with status degenerativus generally, though statistically only, not individually.

Our recently acquired knowledge about constitutional drepanocytosis though highly illuminating does not yet suffice to offer an undisputed interpretation of the anemia resulting from drepanocytosis. We understand that the short life span of drepanocytes with high concentration of S-hemoglobin increases the turnover of erythropoiesis in a similar way as does constitutional spherocytosis. Hemolytic anemia and jaundice will result when the bone marrow, the reticuloendothelial system and the liver are overburdened. We also understand that temporary inhibition of erythropoietic activity of the bone marrow as it might occur in the course of acute infections will lead to considerable " aplastic crises " in sickle cell anemia (Singer; Chernoff and Josefson). There are, however, crises of increased hemolysis with subsequent aggravation of anemia with icterus which accompany attacks of joint pain, acute abdominal pain and other clinical manifestations of the disease. Whereas Singer expresses our ignorance of the exact mechanism of these hyperhemolytic crises my explanation given in 1940 might still appear the most satisfactory. Vascular occlusion by disfigured, elongated drepanocytes is a common occurrence and readily demonstrated on microscopic sections. Its consequence is, among others, thrombosis and disintegration of the trapped red corpuscles with resulting increased hemolysis.

It is these attacks of vascular occlusion by drepanocytes which may or may not be accompanied with hemolytic anemia that endanger the carrier of sickle cells. Our observation (Bauer and Fisher) that serious clinical states due to such vascular occlusion may develop without anemia induced me to speack of sickle cell *disease* with or without anemia. Cases of this sort without anemia have been reported later by numerous authors in confirmation of our concept (Abel and Brown; Thompson, Wagner, and McLeod; Coodley and Kert; Pratt-Thomas and Switzer; Goodwin, Alston, and Semans; Green and Conley).

It is generally believed that all constitutional abnormalities of the red blood corpuscles so far discussed, that is, spherocytosis, leptocytosis, elliptocytosis and drepanocytosis are transmitted as dominant Mendelian genes. Neel demonstrated by extensive studies that drepanocytosis inherited from only one parent, that is, in the heterozygous state, appears phenotypically as sickle cell trait, if inherited from both parents, that is, in the homozygous state, it causes sickle cell anemia. There are, however, exceptions (Bauer and Fisher; Singer; Choremis et al.) which, in my opinion, do not disprove Neel's concept. Quantitative factors determining the relation of the abnormal S-hemoglobin to the normal N-hemoglobin or fetal F-hemoglobin respectively, are decisive as to the clinical manifestations. Even in heterozygous state enough S-hemoglobin might be present in numerous erythrocytes to cause disease rather than to represent the trait only. This probably is also the case if no anemia but occlusive vascular processes occur in a carrier of sicklemia. *There is only a quantitative difference between sickle cell trait and sickle cell anemia. Sickle cell disease exceptionally may develop even in carriers of the trait only.*

It is of considerable interest that drepanocytes have been found in the blood of various species of deer. This discovery was made in the London Zoo by Gulliver as far back as in 1840. Undritz confirmed this observation on three varieties of deer and considers drepanocytosis to be the normal state of erythrocytes in this species. It is most interesting that he found sickle-shaped red copuscles only in the oxygenated state whereas CO_2 renders them into round cells of usual appearance. The transformation into sickle cells and reversal into round cells can be carried out at will in vitro by exposing the blood to O_2 and CO_2 respectively. Undritz also found that the sedimentation of the sickle-shaped cells (under O_2) was considerably slower than that of the round ones (under CO_2). The physical properties of this hemoglobin have not been studied so far but they certainly must be different from any of the types of hemoglobin occurring in humans.

Whether drepanocytosis in deer represents a "normal" state, however, must be questioned. O'Roke reported on actual sickle cell anemia with atrophy of the spleen in white-tail deer in the forests of Michigan. The animals may die from this disease.

Recently a new type of hemoglobin has been discovered — provisionally called hemoglobin III — by electrophoretic analysis (Itano and Neel). It is different from N-hemoglobin and S-hemoglobin and seems to be different also from F-hemoglobin. The term *hemoglobin IV* would, therefore, be more appropriate. The structural anomaly of this hemoglobin IV is determined by a gene inherited as a simple Mendelian dominant.

The presence of hemoglobin IV when combined with structurally normal N-hemo-

globin is expressed as an asymptomatic carrier state. The erythrocytes do not sickle but have a high incidence of target cell deformity and increased resistance to hypotonic saline. Although there is no evidence of hemolysis in such individuals their erythrocytes are eliminated with abnormal rapidity from the circulation of normal recipients.

A distinct hemolytic syndrome which is intermediate between the benign sickle cell trait and sickle cell anemia results from the combination of the new hemoglobin with S-hemoglobin. In contrast to classical sickle cell anemia this form of sickle cell disease is characterized by a mild hemolytic anemia with slowly progressive splenomegaly in the absence of cardiac or musculo-skeletal manifestations. In vitro, the erythrocytes sickle like those of sickle cell anemia. The bone marrow shows erythroid hyperplasia, fecal urobilinogen excretion is increased, and the survival time of the erythrocytes in normal recipients is shortened, but in the patients the red cell count and hemoglobin concentration are only slightly depressed. Reticulocytosis is slight and icterus is not observed. Whereas in sickle cell anemia both parents are expected to have the sickle cell trait, only one parent of these individuals shows sickling, while the nonsickling parent is a carrier of the hemoglobin IV. The new syndrome does not appear to be identical with that resulting from the simultaneous presence of the sickling gene and the thalassemia gene.

The homozygous state with respect to this new hemoglobin has not yet been identified but may well be some already recognized atypical form of chronic hemolytic anemia. This is the summary of the investigations of Kaplan, Zuelzer and Neel concerning the clinical manifestations of the abnormal hemoglobin IV.

Occasionally cases of hereditary anemia are observed which do not fall into any group of commonly recognized types. Thus a familial anemia was reported by Mills and associates which was interpreted as result of a *hereditary defect in hemoglobin synthesis.* They came to the conclusion that the passage of iron between nucleus and cytoplasm of normoblasts is impaired in these cases resulting in faulty hemoglobin synthesis. Expression of this disorder is the " piling up " of iron within the normoblasts in the form of siderotic granules. After maturation of these normoblasts the cells with the iron containing inclusion bodies are known as siderocytes. They are destroyed soon after reaching the circulation. They are poor in hemoglobin but rich in iron to give an increased rate of red cells iron turnover. Grueneberg described a similar type of transitory siderocytic anemia in infantile mice, with bony flexures of the tail and some spotting on belly, feet and tail. It had been found that this syndrome is caused by a recessive gene.

Mild familial anemia has been reported associated with dysplastic erythropoiesis characterized by *erythroid multinuclearity* in the bone marrow (Wolff and von Hofe). Another type of mild anemia, obviously of genetic origin, was associated with an unusual type of "crenation"; the deformed erythrocytes showed irregularly spaced, large and coarse projections on their surface. K. Singer and associates (1952) termed this abnormality " acanthrocytosis " (linguistically correct would be " *acanthocytosis* ") which means thorny red cells. It has been found in the offspring of consanguinous marriages. The affected persons had been suffering from celiac disease in early childhood and later developed a progressive atypical neuropathy with ataxia, resembling Friedreich's hereditary ataxia. Retinitis pigmentosa may or may not accompany this syndrome. Acan-

thocytosis is due to an abnormal recessive gene whose normal allel controls the normal architecture of the red cell (Singer et al. 1952).

An even more extensive genopathy is the basis of the so-called *Fanconi's syndrome.* The bone marrow is hypoplastic and less viable from birth and later becomes victim of constitutional abiotrophy. This congenital hypoplastic anemia may affect several members of a family. The constitutional (genetic) nature of such an abiotrophy is substantiated by the fact that the hypoplasia of the marrow may be only one of a number of congenital anomalies such as microcephaly and other skeletal deformities, congenital heart disease, strabismus, deafness, testicular hypoplasia, microphthalmos and others (Estren et al.; Levy; Silver et al.). In one instance such a refractory anemia was associated with excessive hemolysis (Dacie and Gilpin). It is remarkable that congenital absence or deformity of one or both thumbs has been observed in several of the cases of Fanconi's syndrome. This seems to indicate a chromosomal relation of the genes ruling over the development of the bone marrow and of the thumbs, either due to pleiotropism of one gene ot to linkage of several genes. Patients with Fanconi's syndrome have a peculiar pigmentation of the skin.

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SUMMARY

The concept and definition of constitutional pathology. Genetic erythropathies such as constitutional spherocytosis, leptocytosis, ovalocytosis and drepanocytosis and their relation to hemolytic clinical syndromes are discussed. Sickle cell trait, sickle cell anemia, and sickle cell disease have to be distinguished as clinical manifestations of drepanocytosis. They represent a special variety of a « status degenerativus » (Bauer). Four genetic types of human hemoglobin have so far been identified that differ from each other by their molecular architecture and chemical reactivity. Several constitutional abnormalities of erythropoiesis other than those just mentioned are discussed: a hereditary defect in hemoglobin synthesis; erythroid multinuclearity; acanthocytosis; Fanconi's syndrome of hypoplasia and abiotrophy of the bone marrow as another variety of a status degenerativus.

SOMMARIO

Concetto e definizione della patologia costituzionale. Vengono discusse le eritropatie genetiche quali la sferocitosi, la leptocitosi, l'ovalocitosi e la drepanocitosi ed i loro rapporti con le sindromi cliniche emolitiche. L'anomalia falciforme, l'anemia falciforme e la malattia falciforme devono essere distinte come manifestazioni cliniche della drepanocitosi. Esse rappresentano una speciale varietà dello « stato degenerativo » (Bauer). Quattro tipi di emoglobina umana sono stati finora identificati dal punto di vista genetico, i quali si distinguono per l'architettura molecolare e per la reattività chimica.

Parecchie altre anomalie costituzionali dell'eritropoiesi vengono discusse: le sintesi dell'emoglobina ereditariamente difettosa, la « erythroid multinuclearity », l'acantocitosi, la sindrome d'ipoplasia e di abiotrofia del midollo osseo di Fanconi che viene considerata come un'altra varietà dello « stato degenerativo ».

RÉSUMÉ

L'idée et la définition de la pathologie constitutionnelle. Les érythropathies génétiques comme sphérocytose, leptocytose, ovalocytose et drépranocytose constitutionnelles et leur relation avec des syndrômes hémolytiques sont discutées. L'anomalie en faucille, l'anémie en faucille et la maladie en faucille doivent être distinguées comme manifestations cliniques de la drépanocytose. Elles représentent une variété spéciale de « l'état dégénératif » (Bauer). Quatre types génétiques d'hémoglobine humaine ont été identifiés jusque maintenant qui se distinguent par leur architecture moléculaire et par leur réactivité chimique. Plusieurs autres anomalies constitutionnelles de l'érythropoièse sont discutées: synthèse d'hémoglobine défectueuse héréditaire; « erythroid multinuclearity »; acanthocytose; Fanconi's syndrôme d'hypoplasie et d'abiotrophie de la moëlle osseuse comme une autre variété de l'état dégénératif.

ZUSAMMENFASSUNG

Begriffsbestimmung und Definition der Kontsitutionspathologie. Genetische Erythropathien wie Spherocytosis, Leptocytosis, Ovalocytosis und Drepanocytosis und ihre Beziehung zu hämolytischen klinischen Syndromen werden besprochen. « Sickle cell trait », Sichelzellanämie und Sichelzellkrankheit müssen unterschieden werden als klinische Aeusserungen der Drepanocytose. Sie stellen eine spezielle Varietät des « Status degenerativus » (Bauer) dar. Bisher wurden vier genetische Typen menschlichen Hämoglobins identifiziert, die sich voneinander durch die molekulare Architektur und chemische Reaktivität unterscheiden. Mehrere andere konstitutionelle Anomalien der Erythropoiese ausser den eben erwähnten werden besprochen: hereditärer Defekt der Hämoglobinsynthese; Mehrkernigkeit der Erythroblasten; Akanthocytose; Fanconi's Syndrom einer Hypoplasie und Abiotrophie des Knochenmarks als eine andere Varietät des Status degenerativus.