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PATHOGENESIS AND CLASSIFICATION OF DYSPROTEINEMIA

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## PATHOGENESIS AND CLASSIFICATION OF DYSPROTEINEMIA

Following is the translation of an article by Prof. I. A. Oyvin (Krasnodar) entitled "Patogenez i Klassifikatsiya Disproteiniy" (English version above) in Klinicheskaya Meditsina (Clinical Medicine), Vol. 38, No. 7, July 60, pages 13-21.<sup>7</sup>

From the Chair of Pathological Physiology of Kuban Medical Institute

During the past 15 years, thanks to the development of new methods of investigation (electrophoresis in its various modifications and in combination with other methods, ultracentrifugation, labeling of proteins with isotopes, immunochemical and chemical methods, etc.), many new data have been obtained on the protein composition of the blood plasma and its disturbances. The isolation of various protein components from the plasma and their study contributed to the improvement of diagnostics (general myelomatosis, macroglobulinemia, etc.), to the clarification of the pathogenesis and the development of methods of treatment (hypogammaglobulinemia, hemophilia, etc.), and to the procurement of data on the rate of synthesis and disintegration of various plasma proteins, their quantity, and the metabolism between aqueous spaces in healthy and diseased organisms.

The complexity of the protein composition of plasma and the multiformity of its disturbances prompted the development of a special terminology and classification. Apitz (1940) introduced the term "paraproteinemia" for the designation of the presence of abnormal proteins in the plasma. Wuhrman (1945) suggested the term "dysproteinemia" for the impairment of correlations between the basic protein fractions of plasma. (He retained the term "paraproteinemia" in the sense which Apitz attached to it.) Wuhrman and Wunderly (1957) have distinguished dysproteinemia and paraproteinemia in normal, hypo-, and hyper-proteinemiae. According to Homburger and Petermann (1949), the deviations of protein plasma composition from the norm (euproteinemia) are as follows: hyper- and hypo-proteinemia, dysproteinemia, and paraproteinemia. Gross (1956)

distinguishes three types of disturbances: (1) pseudodysproteinemia (dilution of the blood or of its protein concentration), (2) dysproteinemia (changes in the proportionalities between protein fractions in normal, hypo-, and hyperproteinemia), and (3) paraproteinemia. Waldenström (1957) also divides the plasma protein disturbances into three types: (1) congenital dysproteinemia, (2) essential dysproteinemia, (3) symptomatic dysproteinemia (transitory changes of protein composition).

We consider it expedient to designate as "dysproteinemia" any quantitative and qualitative deviation of plasma protein composition from europroteinemia, i.e., from the norm. Hypo- and hyperproteinemia, as well as paraproteinemia, must be regarded as particular instances of dysproteinemia. The changes in the concentration of various protein components are to be designated, as generally accepted, with prefixes "hyper" and "hypo." For example, hypergammaglobulinemia, hypoproteinemia, etc. Prefixes "a" and "an" are to be avoided, since the protein component in the plasma is practically never completely absent; in the most pronounced cases only a marked decrease in concentration is observed.

Various clinical forms of dysproteinemia can be generalized within the suggested pathogenetic classification which, of course, like any classification is somewhat schematic, but includes all the mechanisms known at present which lead to disturbances of the blood plasma protein composition (see page 14 of Source).

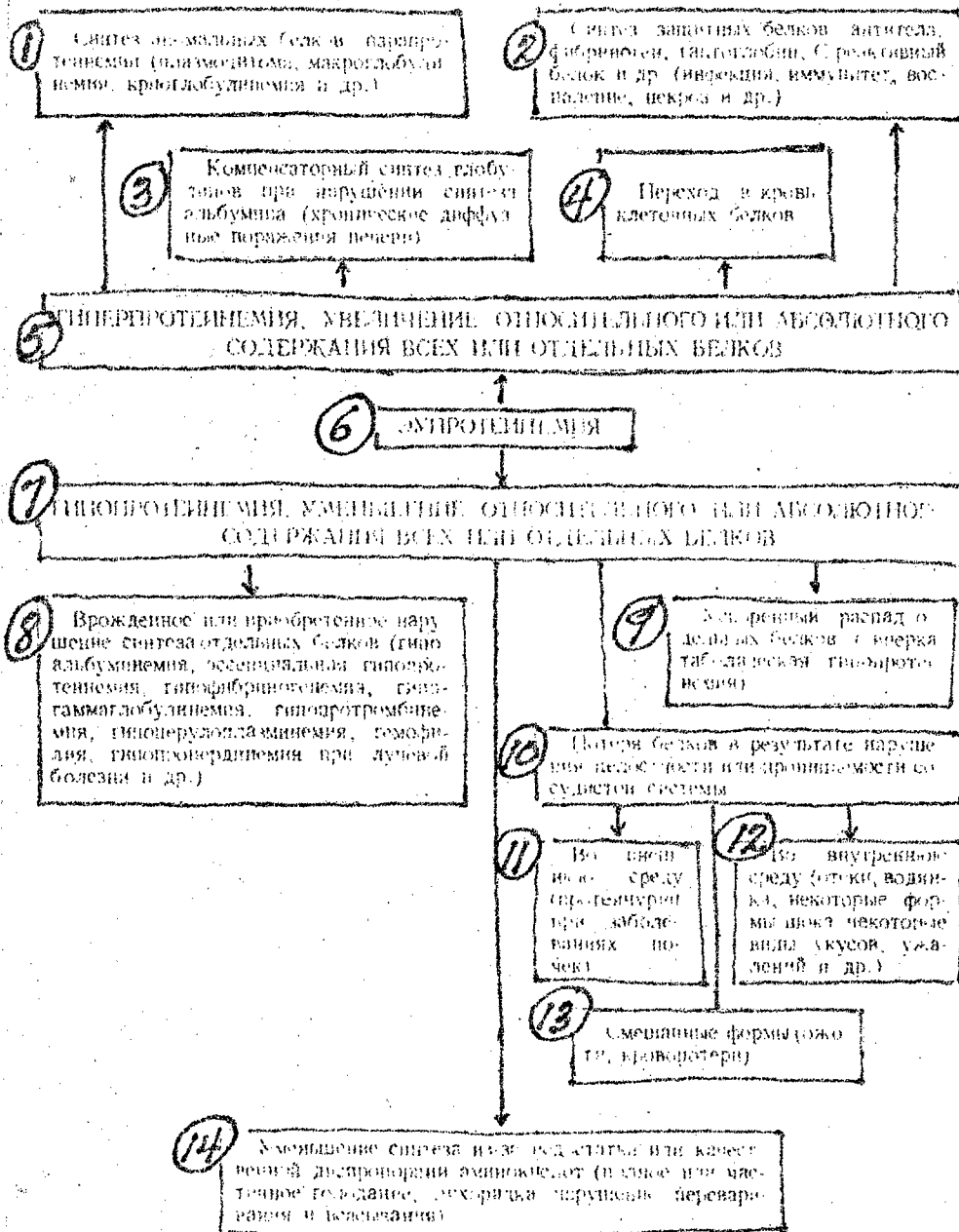
Hyperproteinemia, -- increase of absolute or relative content of total or individual proteins

This group includes the following types of dysproteinemias: (a) paraproteinemia (presence of abnormal proteins); (b) increased formation of proteins of a protective character; (c) increased formation of globulins, as a manifestation of a compensatory reaction for the impaired formation of albumin; (d) transition of cellular proteins into the blood.

Paraproteinemias. Plasmocytoma (general myelomatosis, myeloma disease), characterized by marked disturbances of blood protein composition has been studied in detail in recent years (Wuhrman, Wunderly, Hugentobler, 1949; Osserman and Leilar, 1955; Z. N. Ivanova, 1955; S. I. Ryabov, 1956; Putnam, 1957; V. V. Akkerman and V. P. Moyseyeva, 1958; etc.).

Characteristic of plasmocytoma is the presence of an abnormal globulin fraction in the patient's blood serum, distinguished by electrophoretic homogeneity. According to their mobility, myelid proteins approximate most frequently gamma-globulins (gamma-plasmocytoma), less frequently beta-

### К. КЛАССИФИКАЦИЯ ДИСПРОТЕИНЕМИИ



Key on next page

### Classification of dysproteinemiae

- ① Synthesis of abnormal proteins -- paraproteinemiae (plasmocytoma, macroglobulinemia, cryoglobulinemia, etc.)
- ② Synthesis of protective proteins -- antibodies, fibrinogen, haptoglobin, C-reactive protein, etc. (infection, immunity, inflammation, necrosis, etc.)
- ③ Compensatory synthesis of globulins in impaired albumin synthesis (chronic diffuse affections of the liver)
- ④ Transition of cellular proteins into the blood
- ⑤ Hyperproteinemia, increase of the relative or absolute content of total or individual proteins
- ⑥ Euproteinemia
- ⑦ Hypoproteinemia, decrease of the relative or absolute content of all or individual proteins
- ⑧ Congenital or acquired impairment of synthesis of individual proteins (hypoalbuminemia, essential hypoproteinemia, hypofibrinogenemia, hypogammaglobulinemia, hypoprothrombinemia, hypoceruloplasminemia, hemophilia, hypoproperdinemia in radiation sickness, etc.)
- ⑨ Accelerated disintegration of individual proteins (hyper-catabolic hypoproteinemia)
- ⑩ Loss of proteins as a result of the impairment of wholeness of permeability of the vascular system
- ⑪ Into the external medium (proteinuria in kidney diseases)
- ⑫ Into the internal medium (edema, dropsy, some forms of shock, some forms of bites, stings, etc.)
- ⑬ Mixed forms (burns, loss of blood)
- ⑭ Diminished synthesis due to insufficient quantity or qualitative disproportion of amino acids (complete or partial starvation, fever, impairment of digestion and absorption)

globulins (beta-plasmocytoma), and still less frequently alpha-globulins. Abnormal proteins belong to glycoproteids. In the case of a gamma-plasmocytoma described by us (I. A. Oyvin, M. Ya. Basok and V. I. Oyvin, 1951a) the content of gamma-globulins reached 54.3% of the total quantity of protein, and in the case described by Z. N. Ivanova - it reached 79.3%. As a rule, in plasmocytomas hyperproteinemia is present (the protein concentration in the serum reaches 14 to 17%) with normal albumin concentration. The pathogenesis of dysproteinemia in plasmocytomas is explained by the impaired functioning of plasma cells in the lymph nodes, spinal marrow and spleen, which commence to produce abnormal proteins instead of the usual gamma-globulins and antibodies.

In a number of cases, plasmocytomas in the blood of patients reveal globulins in soluble at low temperatures which

have been named, as per Lerner, cryoglobulins. In gamma-plasmocytoma, the cryoglobulins enter into the abnormal gamma-globulin fraction. Cryoglobulins are not present in the blood of healthy people, but can be detected in the blood of people with the most diverse diseases, mainly of inflammatory character (Lerner, et al, 1947; Putnam, 1955; Rice, 1956; Demulder, V. K. Kozhina, 1957; V. V. Bakanskaya, 1958; etc.).

In plasmocytomas macroglobulins are encountered in the blood serum which are characterized by molecular weights on the order of  $10^6$ . Macroglobulins are very similar to the normal gamma-globulins of human serum in their immunochemical properties. They may be detected in the serum in diseases of the liver, for instance, in infectious hepatitis, alcoholic cirrhosis (Biserte, 1955; Hartman et al., 1956; Korngold and van Leeuwen, 1957; Sandor, 1958; etc.). Waldenström (1952) described macroglobulinemia as an independent disease, different from plasmocytoma. According to M. S. Dul'tsin and Yu. I. Loriye (1958), macroglobulinemia should be related to the paraproteinemic reticulosis group.

There are indications in the literature of a number of other anomalies of the serum protein composition. There have been described appearances of additional alpha-, beta-, and gamma-globulin fractions in the blood sera of experimental animals and patients suffering from various diseases (Blazius and Seitz, 1950; Franklin et al., 1951; T. S. Paskhina, 1955; Knedel, 1957; V. K. Kozhina 1957, V. V. Bakanskaya, 1958; etc.).

It is necessary to point out that the designation of supplementary peaks on electrophoregrams is often conditional. Orientation according to mobility, especially in paper electrophoresis, does not always permit determination of the true nature of the supplementary fraction.

Increased formation of proteins of a protective character. The formation and properties of protective proteins as antibodies has been thoroughly studied. In rabbits sensitized with egg protein or horse serum, there appear in the blood antibodies with the mobility of usual gamma-globulins (Tiselius and Kabat, 1939; I. A. Oyvin, V. I. Oyvin and V. I. Somin, 1951; Richter, 1952). The majority of antibodies possess the electrophoretic mobility of gamma-globulins (Boyd, 1958, Yuz, 1958, A. Ye. Gurvich, 1955; M. A. Rozhdestvenskaya, 1955; etc.); the gamma-globulins of human serum are not homogeneous (the molecular weight varies between 150,000 and 300,000) but represent a mixture of various antibodies (Jane-way and Gitlin, 1957). Apparently, normal gamma-globulins, i.e., those not related to antibodies, do not exist in general. Gamma-globulins are formed outside the liver, in the plasma cells, and their number increases only during antigenic

irritation.

A number of antibodies differ from gamma-globulins in their electrophoretic mobility (Anders, 1944; Deutsch et al., 1946; Brattsten et al. 1955; Humphrey and Porter, 1957; Jane-way and Gitlin, 1957; etc.). In infectious processes there is generally an increase in the concentration of gamma-globulin in the blood as the result of formation of antibodies. However, in some infections (pneumococcus sepsis) the gamma-globulin concentration in the blood diminishes (Bruton, 1952). It is necessary to point out that in dysentery in humans and in experimental dysentery in rabbits there is an increase in the alpha-globulin concentration while the gamma-globulin content remains the same. It has been demonstrated by means of specific adsorption of agglutinins that these are contained in the alpha<sub>2</sub>-globulins of the serum of dysentery patients and in the alpha<sub>2</sub>- and beta-globulin fractions of rabbits infected with dysentery (V. I. Oyvin and L. S. Koretskaya, 1954, 1957; V. I. Oyvin and D. M. Khashimov, 1954; V. I. Oyvin et al., 1957; I. I. Balashova, 1959).

In inflammation in humans, dysproteinemia is characterized by hypoalbuminemia and hyperglobulinemia resulting from increased contents of alpha<sub>2</sub>- and gamma-globulins in the plasma. The fibrinogen concentration in the plasma also increases (Wuhrman and Wunderly, 1957; Schultz, 1953; Odental, 1958). The total protein concentration may be normal or even somewhat increased in chronic inflammatory processes. Changes in the protein composition of the blood serum are revealed in the inflammatory processes in the lungs and pleura, in polyarthritis of various origins, and in dermatitis and other diseases of inflammatory character (Röckl and Jaroschka, 1953; Jackson et al., 1953; Krupp et al., 1954; Ropes et al., 1954; B. S. Kasavina and V. Z. Gorkin, 1955; A. A. Nizov, 1956; M. V. Bavina, 1956; T. M. Trofimova, 1958; etc.). In particular, we elicited hypoalbuminemia and increased concentrations of alpha- and gamma-globulins in the sera of pneumonia, rheumatism and nephritis patients (I. A. Oyvin et al., 1951a).

In inflammation there is an increase in the content of mucoprotein-haptoglobin in the serum. The haptoglobin content in the blood of healthy individuals varies 30 to 190 mg% and in inflammatory and degenerative processes it reaches 1,000 mg-% (Jayle et al., 1955; Newman et al., 1959). Haptoglobin in electrophoresis migrates with the alpha<sub>2</sub>-globulin fraction, constituting about 20% of this fraction (Newman, 1957). The increase in the alpha<sub>2</sub>-globulin fraction in humans during the development of inflammatory processes is due only to the increased content of haptoglobin; the concentration of the non-haptoglobin part of alpha<sub>2</sub>-globulin does not change, as a rule, (Jayle et al., 1955). It is possible that the increased

concentration of alpha<sub>2</sub>-globulin observed in myocardial infarct patients (Pollak, 1956; V. M. Zaytsev, 1957, 1958; Wang He-Pin, 1958; etc.) is also connected with the increase in the haptoglobin content.

In active inflammatory and necrotizing processes, there appears in the blood serum a C-reactive protein, which disappears after the patient's recovery. Apparently the C-reactive protein, like haptoglobin, is a protective protein, but its biological significance remains obscure. Much literature has been devoted to the diagnostic significance of the C-reactive protein (F. L. Bukh, 1958).

In inflammation the disintegration of albumin is accelerated (Whipple, 1956; M. S. Surovikina, 1959). A hypoalbuminemia develops which can be regarded as a nonspecific reaction of the organism, in which the latter responds to all excessive stimuli, as a rule, by reduced albumin synthesis. The increased globulin concentration in the blood in inflammation attests to the prevalence of processes of synthesis over disintegration. The increases alpha<sub>2</sub>-globulin concentration can be explained, as mentioned above, by the increased haptoglobin formation. The increased gamma-globulin concentration, manifested in septic as well as in aseptically inflammation, apparently, represents the result of formation of specific and nonspecific (anamnestic) antibodies. The possibility of increased formation of gamma-globulin as a compensatory reaction of the organism to hypoalbuminemia is not excluded (see below).

Compensatory synthesis of globulins in hypoalbuminemia. Luetcher, and after him Longworth and many other researchers (Grey and Barron, 1943; Sterling and Ricketts, 1949; Antonaci, 1955; Bharucha and Rao, 1957; etc.), demonstrated that the development of hepatic cirrhosis is characterized by hypoalbuminemia and marked increases in the gamma- and at times beta-globulin fractions of the patients' blood serum. Analogous data were obtained in our laboratory by V. K. Kozhina (1957) who found, in cirrhoses of a mixed type, hyperproteinemia, hypoalbuminemia, a decreased albumin-globulin ratio, and an increase in the relative and absolute contents of gamma- and beta-globulin.

In correspondence with the literature data (Grey and Barron, 1943; Martin, 1946; Kunkel and Ahrens, 1949; Ricketts and Sterling, 1949; etc.) I. A. Oyvin, M. Ya. Basok and V. I. Oyvin (1951b) discovered in Botkin's disease a regular decrease in the albumin concentration and an increase in the relative and absolute content of beta- and gamma-globulin in the serum. Identical data were obtained by V. K. Kozhina (1956), M. G. Denisova (1956), Ye. N. Gerasimov and S. R. Belous (1958), etc. Analogous changes in the protein blood

serum composition were elicited in our laboratory by Ye. P. Smolichev (1954) in experiments on rabbits in experimental affection of the liver with carbon tetrachloride.

The pathogenesis of dysproteinemiae in the aforementioned liver conditions is complex. In cirrhosis, hepatitis, and experimental liver affections the basic cause of hypoalbuminemia is the diminished synthesis of albumin resulting from the morphological impairment of the liver. Upon the development of portal stasis and ascites, two additional factors leading to hypoalbuminemia appear: (1) the selective transition of albumin from the blood and tissue fluid into ascites; (2) the diminished formation of albumin due to the impaired entry of amino acids into the liver from the gastrointestinal canal. The retarded rate of albumin disintegration in liver cirrhosis (Sterling, 1951) can be regarded as an adaptive reaction of the organism, induced by the reduced intensity of albumin synthesis and directed toward its conservation. The increased content of beta-globulin in patients' serum is connected with high concentration of lipids, in particular cholesterol. Hence the beta-globulin concentration is higher in liver pathology, as well as in other diseases such as severe forms of diabetes. The most typical phenomenon in liver affections is the increase in the gamma-globulin concentration in the serum. In contrast to this, in mechanical jaundice the content of gamma-globulin in the serum is normal as a rule. This fact prompted I. A. Oyvin, M. Ya. Basok and V. I. Oyvin (1951b) to suggest the determination of gamma-globulin in patients serum for the differential diagnosis of infectious and mechanical jaundices.

According to the data of V. K. Kozhina (1957), in liver cirrroses of mixed nature the albumin concentration in the serum decreases on the average by 1.3 gm-% while the concentration of beta-and gamma-globulin increases by 1.9 gm-%. The excessive formation of globulin leads to hyperproteinemia. According to Martin and Davis (1955), in chronic hepatitis without ascites the quantity of protein circulating in the vascular system increases (on the average by 1.35 gm/kg at the expense of globulin, despite the diminished quantity of circulating albumin (0.53 gm/kg). The increase in the quantity of globulin, calculated from the oncotic  $\sqrt{\text{osonotic?}}$  pressure, corresponds to the decrease in the quantity of albumin. An analogous regularity is observed in the experimental liver affection. According to Ye. P. Smolichev (1954), the decreased concentration of albumin in rabbit's serum (by 0.6%) corresponds to the increase in globulin concentration (by 1.3 gm-%). Hyperproteinemia in these tests was the result of excessive formation of globulins. An absolute increase in the gamma-globulin content is revealed even in

heliotropic toxicosis and atrophic cirrhosis of the liver during the ascites stage, despite pronounced hypoproteinemia (V. K. Kozhina, 1956, 1957). Were dysproteinemia in these diseases the result only of a selective transition of albumin into the ascitic fluid, the hyperglobulinemia would have a relative, not an absolute character. However, in chronic liver affections of a diffuse character hypergammaglobulinemia is most pronounced, and is in all cases combined with hypoalbuminemia.

As is known, the oncotic pressure of albumin is approximately two and a half times as great as the oncotic pressure of globulin. The decrease in albumin concentration in the blood serum in chronic liver affections is accompanied by an increase in the globulin concentration almost twice the albumin decrease. One cannot regard this as an accidental phenomenon. In liver impairments conditions are created for excessive synthesis of gamma-globulins which apparently are formed, under normal and pathological conditions, outside the liver (Robert and White, 1949; Miller et al, 1954). The gamma-globulin synthesis is aided by the diminished utilization of amino acids for the formation of albumin, as well as by the development of collateral circulation in portal hypertension, as a result of which the amino acids often bypass the liver. In infectious hepatitis, synthesis of specific gamma-globulin may take place, and in noninfectious liver affections nonspecific gamma-globulins may be formed. The formation of excessive quantities of globulins in liver pathology can be regarded as an adaptive reaction of the organism, which helps to a certain extent to compensate for hypoalbuminemia and to maintain the constancy of the oncotic pressure of the blood and, consequently, the state of aqueous equilibrium between the blood and tissues. Statements to this effect are not new in the literature (Wuhrman and Wunderly, 1947; I. A. Oyvin et al, 1951b, 1954).

The reduced concentration of prothrombin, proconvertin and Ac-globulin in the blood of patients suffering from liver affections is explained by the reduced synthesis of these proteins in the liver.

Changes in the blood serum protein composition occurring with insufficient cardiac circulation are characterized by hypoalbuminemia and hyperglobulinemia. Along with insufficiency of blood circulation of the second and third degrees, I. A. Oyvin, M. Ya. Basok and V. I. Oyvin (1951a) detected in a number of patients hypoalbuminemia and increased concentration of alpha<sub>2</sub> and gamma-globulins. Analogous data were obtained also by other researchers (Zsoter and Pinter, 1954; Luteroti, 1955; etc.).

The pathogenesis of dysproteinemia in heart diseases and circulatory disturbances is complex. In edemas the protein composition of the blood may be affected by the selective transition of protein from the blood into the edematous fluid. Increased concentration of alpha<sub>2</sub>- and gamma-globulins may be the result of an inflammatory process (endocarditis). However, the increase in the gamma-globulin concentration in chronic cardiac insufficiency is connected basically with impaired functioning of the liver. The greater the duration of the cardiac disease, the more marked are the congestive phenomena of the liver, and the more pronounced are hypoalbuminemia and hypergammaglobulinemia. Apparently, in these cases hypergammaglobulinemia also has an adaptive function -- to partially compensate for the hypoalbuminemia and to lower the oncotic pressure of the blood.

Transition of cellular elements into the blood. Concerning the relation of dysproteinemia to the entry into the blood of proteins from disintegrating cells, under pathological conditions, little is known; nevertheless, it should be taken into consideration (Yuz, 1958).

Hypoproteinemia -- a decrease in the relative or absolute content of proteins. This group of impairments includes dysproteinemias resulting from the following causes: (a) congenital or acquired impaired synthesis of individual plasma proteins; (b) accelerated disintegration of individual plasma proteins; not compensated for by a corresponding acceleration of synthesis; (c) decrease in the intensity of synthesis of plasma proteins due to a lack of amino acids in the undisturbed mechanisms of synthesis; (d) loss of plasma proteins as a result of impairment of the wholeness or permeability of the vascular system.

Congenital or acquired impaired synthesis of individual proteins. The changes in the protein composition of the blood are generally secondary effects of the basic disease. However, primary dysproteinemia also occurs, as a result of the disturbance of the mechanism of protein synthesis.

The symptom most characteristic of dysproteinemia is hypoalbuminemia. The synthesis of albumin is much more susceptible to impairment than is the synthesis of other protein fractions. The excessive influence of any environmental factor leads to hypoalbuminemia. Hyperalbuminemia has not been described. In rare instances there is observed an essential hypoproteinemia accompanied by long-lasting disturbances that may result in the development of edema. Hypoproteinemia may be accompanied by hypoalbuminemia (Schonenberg, 1954). A case of complete analbuminemia has been described (Kaller, 1958).

In recent years it has been established that the cause of various types of hemophilia lies in the insufficient content in the plasma of the antihemophilic globulins A, B, and C, the impaired synthesis of which is of congenital origin.

In a number of diseases (myxedema, lipoid nephrosis, etc.) the concentration of the copper-containing alpha-globulin of the plasma, ceruloplasmin is reduced. The absence of ceruloplasmin in the plasma is characteristic of hepato-lenticular degeneration which, in accordance with this symptom, may be classed with the large group of congenital syndrome of impaired synthesis of individual plasma proteins (Steinbuch, 1958).

Agammaglobulinemia or, more correctly, hypogammaglobulinemia, was first described as an independent disease by Bruton in 1952. At the present time three forms of hypogammaglobulinemia are distinguished: (a) a transitory form, in newborn infants; (b) a congenital form, in male children, (c) an acquired form, in individuals of both sexes.

During the first half year after birth, there is a decrease in the concentration of gamma-globulins in the blood. The low level of gamma-globulins is maintained during the second half of the year, but subsequently the concentration rises as a result of the fact that the gamma-globulins begin to be synthesized in the organism. Toward the fourth year, the gamma-globulin concentration reaches the level characteristic of an adult organism.

The gamma-globulin content in the blood of hypogammaglobulinemia patients varies from zero to 40 mg-% (normal content: 0.6 to 1.5 gm-%) (Gitlin, 1956; Good and Zak, 1956). The patients show a markedly reduced resistance to infection (pneumococcus and staphylococcus). The respiratory tract (pneumonia) is affected most frequently, but recurrent otitis, ethmoiditis and meningitis may also be observed. The hypogammaglobulinemia syndrome is characterized by the impairment of antibody formation.

The low content of gamma-globulins in patients' blood is not connected with the accelerated disintegration of gamma-globulins in the organism. The impaired synthesis of gamma-globulins leads to their reduced concentration in the blood and to the appearance of symptoms of hypogammaglobulinemia. The causes responsible for the impaired synthesis have not been clarified sufficiently. In hypogammaglobulinemia of the spinal cord and lymphatic nodes there is an almost complete absence of plasmic cells where gamma-globulins are synthesized. Immunization of healthy individuals induces a marked increase in the number of plasmic cells, but has almost no effect on the plasmic cell count in hypogammaglobulinemia patients (Good, 1955; Jeschal, 1956). Systematic administration of gamma-glob-

ulin solutions to these patients, or administration of antibiotics, increases their resistance to infection (Zbar et al, 1956).

Accelerated disintegration of individual plasma cells. In recent years, thanks to the development of clinical methods of determining the biological half-life of plasma proteins, anomalies in the durabilities of individual blood proteins have come to light. Apparently, accelerated albumin disintegration may cause hypoalbuminemia. For instance, in one patient a five-day half-life of albumin was observed; three patients with idiopathic (hypercatabolic) hypoproteinemia had albumin half-life periods of 6.6 to 7.4 days. In healthy individuals the albumin half-life period lasts 9 to 23.9 days (Thorn et al., 1956; Schwartz, 1959).

Decrease in rate of synthesis of plasma proteins. Total and partial starvation (including avitaminosis) are characterized by hypoalbuminemia. Apparently, hypoalbuminemia, in exhausting, febrile diseases is related to a negative nitrogen balance in patients. A decreased utilization of amino acids as a result of the impairment of digestion and absorption in the gastrointestinal tract also leads to the development of hypoproteinemia. In all above-mentioned conditions the albumin synthesis is the first to be impaired, and therefore the albumin-globulin ratio is always reduced (Zeldis, et al., 1945; Chow, et al., 1945; Fritz, 1954; etc.).

Proteins losses resulting from impairment of wholeness or permeability of the vascular system. Among these dysproteinemias are forms frequently encountered in the clinic. The loss of proteins may take place into the external medium (proteinuria in kidney diseases) or into the internal medium (exudation, transudation). Mixed forms are possible; the loss of proteins may take place into the external medium only (external hemorrhages), into the internal medium only (internal hemorrhages), or simultaneously into external and internal medium (hemorrhages, burns). The development of disturbances of capillary permeability is characterized by a selective transition of individual serum protein fractions, initially the albumin fraction, into the tissue fluids, body cavities or urine, and has a marked effect on the protein composition of the plasma. The origin of hypoproteinemia and hypoalbuminemia in kidney diseases has been thoroughly studied. In nephrosis, the albumin-globulin ratio in the blood serum may be as low as 0.3, while in the urine it rises to 8 or 10 (selective elimination of albumin). Studies in recent years have shown that the development of dysproteinemia in kidney diseases cannot be explained by proteinuria alone. In nephrotic syndromes of children and adults one ob-

serves impairments in the rate of synthesis, and disintegration of the plasma albumin (Blaht et al., 1955; Gitlin, 1957; McFarlan, 1958; Schwartz, 1958). This indicates the complexity of the pathogenesis of dysproteinemiae in proteinuriae.

The impairment of capillary permeability, accompanied by selective transition of individual plasma proteins into tissue fluids and body cavities via excessive transudation and exudation, may lead to the emergence of dysproteinemiae. Thus, Iwata et al. (1958) in examining 200 patients with exudates and transudates, discovered regular impairments of the protein plasma composition (hypoalbuminemia, hyperglobulinemia and hyperfibrinogenemia). However, the development of an intensive transudation or exudation is often the result of cardiac insufficiency, cirrhosis of the liver, inflammation, etc., which may themselves lead to dysproteinemia. For example, in cirrhosis of the liver the transition of proteins into the ascitic fluid aggravates dysproteinemia, but is not the cause of this condition.

The relation of the removal of proteins from the vascular stream to the origin of dysproteinemia is seen more clearly in the case of pulmonary edema. I. I. Islamov (1954) in our laboratory induced the development of toxic edema in the lungs of dogs. The animals died within 15 to 45 minutes. Up to 70% of the protein and up to 90% of the total fluid present in the blood outside of the erythrocytes prior to the development of edema, passed into the edema fluid. Relatively more albumin than globulin passed into the edema fluid, which led to a change in the albumin-globulin ratio. However, in such a rapidly developing process it is impossible to account for the emergence of dysproteinemia only by the transition of proteins into the edema fluid. Owing to the existence of a dynamic balance between blood proteins and tissue fluid, there is observed a simultaneous transition of proteins from the tissue fluid into the blood and from the blood into the lungs. On the average, during the experiment, 26 percent fluids and nine percent protein passed from the tissues into the blood, counting the quantities which passed into the edema. Thus, the protein composition of the blood, in the development of edema, represents the result of two opposite processes -- the passage of protein in both directions between the tissues and the blood.

Changes in capillary permeability may not lead to dysproteinemia in cases where only an increase, but not an impairment, of capillary permeability takes place. Under these circumstances there is only an increase in the rate of transfer of plasma proteins into the tissue fluid. If the proteins are not retained in the tissues, they are returned rapidly to the body by the lymph flow. As a result, only the rate of ex-

change of proteins between the intravascular and extravascular spaces is accelerated, and the protein composition of plasma may remain constant.

The results of studies by V. V. Bakanskaya (1957) may serve as an example; in our laboratory he investigated the protein composition of blood and lymph in dogs during a pentose shock. Together with a drastic reduction of the arterial pressure, increase in the flow of lymph in the thoracic duct and in the protein concentration in the lymph were observed. However, the protein concentration in the blood serum and the protein composition of the serum and lymph showed no change.

In burns there is a development of hypoproteinemia, hypoalbuminemia and relative hyperglobulinemia. The origin of dysproteinemia in burns is complex. In addition to the effect of the selective loss of proteins into the external medium, there is the important transition of proteins from the vascular bed into the tissues, owing to the increased total permeability of the capillaries -- a fact established in our laboratory by V. V. Bakanskaya (1956, 1959) in experimental burns. Undoubtedly, the inflammatory reaction is also effective.

Lowered hydrostatic pressure due to loss of blood leads, according to the Sterling mechanism, to the immediate transfer of the tissue fluid into the vascular bed. The studies of N. A. Gorbunova (1957, 1959) in our laboratory demonstrated that following the removal of 25% of the circulating blood, the volume of circulating plasma in dogs is virtually restored within 30 minutes, and after 120 minutes it even exceeds the initial figures. When 40% of the blood is removed, the plasma volume is still low after 30 to 60 minutes, but is completely restored after 120 minutes. The volume is restored by passage of the fluid and protein from the extravascular tissue space into the vascular bed. However, the flow rate of the fluid is considerably higher than that of the protein. Therefore, hypoproteinemia develops following loss of blood, despite the pressure of the normal quantity of circulating protein in a number of instances. In dogs the protein composition of the blood serum does not change during the first few hours following loss of blood. This is explained by the fact that the proportionality between the protein fractions of the protein which enters the vascular system is similar, on the average, to that of the blood.

#### Conclusion

The most characteristic manifestation of dysproteinemia is hypoalbuminemia. The synthesis of albumin is more easily

impaired than is the synthesis of other fractions. Under pathological conditions, the albumin-globulin ratio may only decrease. Dysproteinemiae occurs most frequently as the result of the impairment of albumin synthesis, the selective loss of individual proteins, the synthesis of protective proteins, or the compensatory synthesis of globulins in hypoalbuminemia. Less frequently, dysproteinemia appears as the result of synthesis of anomalous globulins or of congenital or acquired impairments in the synthesis of individual protein components of plasma.

The pathogenesis of impaired blood protein composition in various diseases is complex, and generally a number of mechanisms of impairment and restoration are involved.

The restoration of the blood protein composition proceeds comparatively easily in cases where the mechanisms of protein synthesis are not impaired. In other cases the dysproteinemiae are protracted.

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