Alving
(corrected)

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June 18, 1958

Dr. Alf S. Alving
Department of Medicine
The University of Chicago School of Medicine
Chicago, Illinois

Dear Doctor Alving:

I greatly appreciated your sending me the manuscript of your paper on "Some Genetic Aspects of Primaquine-Sensitive Hemolytic Anemia" which you presented at the meeting of the American College of Physicians in Atlantic City. I have reviewed the manuscript with great interest and am returning it herewith.

I am also enclosing a copy of my own manuscript which has been submitted to the Annals of Internal Medicine. I would be particularly interested in knowing if I have quoted accurately the work done by you and your associates. I would appreciate having the manuscript returned eventually but there is really no hurry about this.

I have often said that the work done in recent years by you and your associates on drug-induced hemolytic anemias forms one of the most exciting chapters in the history of hematology. I shall continue to follow~~ing~~ your work with the greatest of interest and I do hope that we shall have frequent opportunities to compare notes on our explorations of the red cell.

With many thanks and kindest personal regards,

Sincerely yours,

Larry

Lawrence E. Young, M.D.
Professor of Medicine

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HEMOLYTIC DISORDERS: SOME HIGHLIGHTS OF TWENTY YEARS OF PROGRESS [1,2,3]

Lawrence E. Young, M.D., F.A.C.P.
Rochester, New York

(1) Presented at the Thirty-Ninth Annual Session of the American College of Physicians, Atlantic City, New Jersey, May 1, 1958.

(2) From the Department of Medicine, The University of Rochester School of Medicine and Dentistry, and the Medical Service of the Strong Memorial Hospital.

(3) Certain of the studies summarized in this report were aided by grants from the Department of the Army, Office of the Surgeon General, and from the Public Health Service.

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During the past twenty years there have been remarkable advances in our understanding of hemolytic disorders and in our ability to detect, differentiate and treat these conditions. In few other areas of medicine has progress been so rapid or so clearly attributable to the application of modern biochemical and biophysical methods to the study of the cell. In reviewing some of the recent progress in this field I have chosen to comment chiefly on observations which have added especially to our understanding of the structure, cytochemistry and metabolism of the red cell. I shall cite examples illustrating the point that some of the most common and fascinating hemolytic disorders can probably be attributed in large part to abnormalities in synthesis of protein--hemoglobin protein, enzyme protein, or antibody protein.

All of us who have become enamored of the red blood cell agree with Dr. Eric Ponder that it is the product of unusually fine "biological engineering.[1] It is not the inert bag of hemoglobin that we thought it was when I first studied physiology. Although the mature mammalian red cell lacks a nucleus and is incapable of reproduction, it is very much alive and has a remarkably complex structure and metabolism. Since it is the most easily sampled of all cells, it is natural that we should turn to it for some lessons in cellular physiology, despite the fact that it has certain peculiarities.

(Figure 1.)

Structure of the Red Blood Cell

I know of no really satisfactory visual model of the structure of the red cell, but Figure 1, which I have modified considerably from a drawing by Ponder[2]

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will suffice. At least it shows that the normal mature human erythrocyte is biconcave and that the molecules of protein and lipid in the outer layers have an orderly arrangement. The list of constituents of the red cell given in this figure is by no means complete. We shall be particularly concerned with the hemoglobin molecules and with certain of the enzymes and substrates involved in glycolysis.

It should be pointed out that in addition to the structural proteins there are approximately forty enzymes thus far identified in the normal human red cell. The exact manner in which the enzymes and other molecules are distributed throughout the cell is not known. There is good evidence, however, that the hemoglobin molecules and other molecules close to the surface have a rather orderly arrangement whereas those in the interior of the cell have a more disordered, but not entirely disordered, arrangement.[3]

(Figure 2.)

Figure 2 shows a portion of the surface layer according to Ponder's concept.[4] The lipid molecules, that is, phospholipid, cholesterol, fatty acids and neutral fat, are represented by round-headed rectangles in a position perpendicular to the surface of the cell, while the protein molecules are pictured as being wrapped around the cell "like string around a ball." The circles at the top of the diagram represent a layer of albumin which may be adherent to, or a part of, the outer surface of the cell. As we look at this diagram, we should bear in mind that many of the proteins, both structural proteins and enzyme proteins, probably have a spiral or helical molecular structure. I hope that this illustration will assist in our effort to visualize the red cell and its constituents in terms of molecules, but we must realize that this diagram is greatly over-simplified. The numerous blood group substances, for example, are among the many substances

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not shown here but known to be present in the outer layers of the cell.

Metabolism of the Red Blood Cell

Some of the known enzymes of the human red cell are listed in Table 1. We shall be particularly interested in those involved in glycolysis. Some of these enzymes may be non-essential remnants of the cell's nucleated life, but many of them are known to be active in the metabolism of the mature red cell.

(Insert Table 1.)

The energy derived from glycolysis is used in a number of ways and it is now appreciated that the very life of the cell depends on an adequate supply of energy in the form of high energy phosphate bonds.[4,5] A large share of the energy is apparently used in ion transport and in maintaining concentration gradients. The sodium and potassium gradients between the cell and blood plasma have been most extensively studied. Reduction of methemoglobin also requires energy and there are still other requirements that have not been thoroughly investigated. It seems possible, for example, that the shape of the cell and the maintenance of integrity of the structural proteins and lipids may depend upon energy derived from glycolysis.

HEMOLYTIC DISORDERS

During the past fifteen years we have come to appreciate that much understanding can be gained by classifying hemolytic disorders as in Table 2. This classification is based largely on cross-transfusion studies of the early and middle 1960's.[6,7,8,9] Intrinsically abnormal red cells from patients with sickle cell anemia, hereditary spherocytosis or nocturnal hemoglobinuria, for example, were shown to disappear rapidly from the circulation of normal recipients. On the other hand, normal red cells usually survived normally after transfusion into patients with any

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of these diseases. Normal red cells were rapidly destroyed when transfused into patients in whom extracorpuscular agents, such as antibodies, were involved in the destruction of the patient's own red cells.

(Table 2)

Intracorpuscular Abnormalities

Hemoglobinopathies

Several of the best known intracorpuscular abnormalities are genetically determined and the patterns of inheritance are well established. Recent studies of the red cells in these conditions have done much to clarify the manner in which genes produce their amazing and sometimes disastrous effects. Work on sickle cell anemia has been especially fascinating and has already pinpointed ~~the~~ a abnormality within the hemoglobin molecule.

Pauling, Itano, Singer and Wells[10] first showed in 1949 that all of the hemoglobin molecules in sickle cell anemia are abnormal, while red cells from patients with sickle cell trait, the heterozygous condition, contain a mixture of normal, or hemoglobin A, molecules and the abnormal hemoglobin S molecules. Whether or not there are other abnormalities involved in sickling and hemolysis of sickle cells remains to be determined. Thus far, no other abnormalities of apparent significance have been described.

During the past year Dr. Vernon Ingram[11,12] of the University of Cambridge reported a tedious and brilliantly executed study in which he separated by electrophoresis and chromatography the peptides yielded from the hemoglobin S molecule

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by systematic digestion with trypsin. The abnormality in hemoglobin S was shown to be confined to a single peptide unit, No. 4. Within this peptide a valine unit occupies the place normally occupied by glutamic acid in the 7th position of the sequence of nine amino acids, as indicated in Table 3. A glutamic acid unit has a negative electrical charge while a valine unit is electrically neutral, hence the difference in net electrical charge and in electrophoretic mobility of the two peptides and in fact of the whole hemoglobin molecules.

(Table 3)

Ingram's colleague, Hunt, found that in hemoglobin C the abnormality was also confined to the amino acid in the 7th position in the No. 4 peptide, with replacement of a glutamic acid unit by a lysine unit instead of a valine unit as in hemoglobin S.[12] This finding correlates with the genetic evidence that production of hemoglobin C is due to a mutation in the same part of the chromosome causing the production of hemoglobin S. Fortunately, hemoglobin C disease is much less common and less disabling than sickle cell disease but in the homozygous form it is nevertheless a hemolytic disorder. Cells containing only hemoglobin C do not undergo sickling. The mechanism of their destruction is by no means clear, despite the precise characterization of the abnormal hemoglobin molecule.

It is indeed remarkable that in sickle cell anemia a change of one amino acid in three hundred in the hemoglobin molecules is associated with the sickling phenomenon and may therefore be importantly involved in the hemolytic and thrombotic processes with which the possessor of hemoglobin S is afflicted, [redacted]. It is also amazing that the responsible gene affects hemoglobin synthesis so delicately and so regularly that all but one of the three hundred amino acids in the molecule are present

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in the normal position. How can a gene produce such a deviation in structure of hemoglobin or of any other protein molecule? At this point we must consider the earlier life of the red cell when it still had a nucleus containing chromosomes.

(Figure 3)

The most recent contributions of the biochemists show that chromosomes are composed of a number of constituents including deoxyribonucleic acid (DNA), histone, and a non-histone lipoprotein. Functionally, the DNA is probably the most important of these, since recent studies on bacterial transforming factors and bacteriophage, as well as studies of mammalian cell nuclei, indicate strongly that DNA is the genetic material of the cell.[13,14,15]

DNA is a fibrous substance which on a molecular basis is thought to consist of two long chains or strands of nucleotides running in opposite directions and twining about each other (Figure 3). The two chains are cross-linked by the hydrogen-bonded nucleotide base pairs, adenine-thymine and guanine-cytosine. The arrangement of the bases is such that wherever adenine occurs in one of the DNA strands, thymine must occur in the opposite strand, which is hydrogen-bonded to the adenine in question. A similar relation exists between guanine and cytosine.

Crick[13] likens the DNA molecule to a long winding staircase, with the nitrogenous bases in the position of stairtreads. It seems likely that each type of DNA molecule has a particular order of arrangement of its bases and that this order somehow determines the order of arrangement of amino acids in corresponding proteins which are being synthesized under control of the gene composed of the particular kind of DNA in question.[12,13] The properties of any given protein are in turn, to a considerable extent at least, attributable to the specific sequence of its amino acids. The control

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of protein synthesis by the gene, or DNA in question, may actually be mediated through ribonucleic acid (RNA) in the cytoplasm of cells.[13,14,15,16] RNA probably also has a helical structure. The configuration of RNA, or more specifically, the arrangement of its nitrogenous bases, may be controlled by DNA and may in turn control the arrangement of amino acids in proteins undergoing synthesis within the cytoplasm. It should be understood, however, that the exact role of RNA in protein synthesis and the relationship between RNA and DNA are by no means established.[14,17,18,19]

The recent work on sickle cell hemoglobin constitutes a landmark in the advancement of genetics. The work of Ingram[11,12] is, in fact, the first and best example of the manner in which a mutant human gene, or altered DNA molecule, may (? through the agency of RNA) produce a minute but highly significant change in the arrangement of amino acids in a molecule of protein under construction. This demonstration would seem to be the ultimate in identification of genetically determined biochemical lesions. In sickle cell disease, as in so many other diseases recently subjected to intensive study, the biochemist has had the last word.

Drug-Induced Hemolytic Anemia

Another milestone in our understanding of the red blood cell and its destruction is the fascinating series of investigations on hemolytic anemia induced by primaquine and aniline derivatives such as sulfanilamide, naphthalene, phenacetin, acetanilid, para-amino-salicylic acid, and Furadantin. Susceptible persons are mostly Negroes whose red blood cells have been shown by Carson, Flanagan, Ickes and Alving,[20] and by Gross and Marks,[21] to be deficient in activity of the enzyme, glucose-6-phosphate dehydrogenase. Beutler, Dern and Alving have shown that incubation of such red

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blood cells with acetyl phenylhydrazine results in the appearance of abnormally large numbers of intracellular inclusions called Heinz bodies[22] and in a marked decrease in content of reduced glutathione in the cells.[23] The glutathione stability test has been utilized by Beutler,[23] Childs et al,[24] Szeinberg et al,[25] and by Cross and Marks,[21] to detect persons susceptible to development of this form of hemolytic anemia.

The older cells in the circulation are most susceptible to hemolysis in such persons, presumably because they are most deficient in enzyme activity. Since younger cells are resistant to hemolysis by this mechanism, hemolysis tends to be self-limited. Dern, Beutler and Alving[26] have shown, moreover, that the red cells remaining in the circulation after hemolysis due to sulfanilamide or acetanilid are relatively insensitive to administration of primaquine.

Although there are other biochemical abnormalities in such red cells,[27] available evidence suggests that the "basic" defect is probably the deficiency in dehydrogenase which is genetically determined, quite likely by a sex-linked gene,[21,24,28] that is, by a gene in the X-chromosome. The deficiency in dehydrogenase and in reduced glutathione is of no consequence to the red cell unless the cell is exposed to certain substances, such as the drugs mentioned, which presumably have an adverse effect on the cell's metabolism. Normal red cells, on the other hand, are unaffected by exposure to similar quantities of the drugs.

Favism, or acute hemolysis following ingestion of fava beans, may be associated with metabolic abnormalities similar to or possibly identical with those found in the drug-induced cases.[24,25] Zinkham, Lenhard and Childs[29] have demonstrated a

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deficiency of dehydrogenase activity in red cells from patients with favism, and Childs and associates[24] have obtained abnormal results in glutathione stability tests on red cells from persons in two Greek families afflicted with favism. The results of their studies on these families suggest, but do not prove, sex-linkage of the metabolic abnormality. Favism is most common among Greeks, Sards,[30] Sephardic Jews[31] and certain other Mediterranean stocks including Italians, but there are no reported data on its occurrence among Negroes. It now seems possible that the apparent rarity of favism among Negroes may be due to lack of exposure of Negroes to fava beans rather than lack of inherited susceptibility. At any rate, we now realize that when hemolytic reactions occur after use of certain drugs or other substances, a genetically determined basis should be suspected, especially if the reactions occur most frequently in particular racial groups.

Motulsky[32] makes the point that such reactions should be regarded as "models for demonstrating the interaction of heredity and environment in the pathogenesis of disease." It is, in fact, difficult to conceive of better models. It should also be appreciated that the deficiencies in these red cells could not have been demonstrated until recently, when suitable chemical methods became available. We can expect that many inherited biochemical abnormalities of various types of cells will be demonstrated in research laboratories during the next two decades. It seems reasonable to predict that much of the future progress in our understanding of disease will be derived from the same general type of biochemical and genetic study recently executed so precisely at the University of Chicago,[20,22,23,26,27,28] Johns Hopkins,[24,29] Columbia,[21] Stanford,[21] and at the Government Hospital in Tel-Hashomer, Israel,[25,31] by use of red cells from patients with hemolysis induced by drugs or fava beans.

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Hereditary Spherocytosis

Another inherited hemolytic disorder which has been under intensive study in recent years is hereditary spherocytosis, formerly known as congenital hemolytic anemia. This condition is inherited as a mendelian dominant with widely varying penetrance or expression of the responsible gene, and is characterized by the presence of spherocytes or abnormally thick red cells in the circulation.

The immature red cells in the circulation of affected persons have normal shape; the sphering or increase in thickness/diameter ratio occurs only when the red cell has become mature. In this disorder as in many other hemolytic states, immature red cells seem to enjoy some degree of immunity to destructive processes. Perhaps such immunity is due to differences in metabolism in the immature cell, but this possibility will require further study in each of the hemolytic disorders under consideration.

Anemia and jaundice are promptly, completely and permanently relieved by splenectomy in nearly all cases of hereditary spherocytosis despite persistence of the abnormal shape of the red cells. These features of hereditary spherocytosis have been recognized for many years.[15,33] What, then, is the role of the spleen in this disorder?

Whipple[34] suggested in 1941 that spherocytes might be readily trapped within the splenic pulp because the abnormal thickness of the cells would make difficult their escape through slit-like openings between the pulp and the venous sinusoids. Ham and Castle[35] in 1940 had found that spherocytes incubated in vitro at body temperature underwent lysis more rapidly than normal red cells. They postulated that changes

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occurring in spherocytes while stagnating within the spleen might be similar to the changes observed during in vitro incubation and might be largely responsible for hemolysis in spherocytic states.

Studies employing transfusion and perfusion by Dacie,[36] Emerson et al,[37] Weisman et al,[38] and in our laboratory,[39] have subsequently demonstrated that spherocytes are indeed readily trapped within the splenic pulp. Within that site they undergo still more sphering and more rapid increase in osmotic fragility than do normal transfused or perfused red cells which are found in the pulp in relatively small numbers during such experiments. Moreover, the normal human spleen, or spleen in persons with non-hemolytic disorders, appears to be capable of trapping spherocytes as readily as the spleen in a person with spherocytosis.[38,39] In this condition the abnormality is clearly within the red cell rather than the spleen, but the spleen provides environmental factors necessary for hemolysis of the defective cells.

When samples of sterile defibrinated blood are incubated at body temperature for 48 hours or longer, the degree of spontaneous autohemolysis of red cells from patients with hereditary spherocytosis is usually much greater than that of normal red cells. Selwyn and Dacie[40] showed that addition of glucose to spherocytic blood markedly inhibited such autohemolysis. We have obtained similar results in our laboratory and have found that addition of mannose or the nucleosides adenosine, inosine or guanosine also inhibits hemolysis of incubated red cells from patients with hereditary spherocytosis.[41] It seems likely that these additives protect the spherocytes by helping to maintain energy production from glycolysis above a critical level. Jaffe and associates[42] reached similar conclusions by measuring the capacity of purine ribosides to enhance osmotic resistance of normal red cells after short periods of incubation.

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During the past five years Prankard, Altman, Tabechian and associates in our laboratory have studied abnormalities of carbohydrate metabolism in hereditary spherocytes by incubating the red cells with P^{32}-labelled orthophosphate and measuring the rate of incorporation of P^{32} into the various organic phosphate esters. The phosphorus-containing fractions of trichloracetic acid extracts of the red cells were separated by paper chromatography, and radioactive and chemical phosphorus measured in each fraction. There was an abnormally small flux of P^{32} into adenosine triphosphate and 2,3-diphosphoglycerate and an abnormally large initial flux into the inorganic phosphate fraction inside the spherocytes. Motulsky and associates[45] have obtained similar results. These abnormalities persisted after splenectomy and were largely corrected in the majority of cases by incubating the red cells with adenosine. Lack of the corrective effect of adenosine was encountered in all affected members of four families and may point to a variant of some significance in this disorder which was previously thought to be a single disease.[43,46]

The relationship of the disturbed carbohydrate metabolism to the shape of the cells and to the hemolytic process remains to be clarified. Our work to date has provided more questions than answers. It is possible that the inherited abnormality is one of structure, which in turn might account for the results obtained in the studies on metabolism and on autohemolysis. A more attractive hypothesis, however, is that the sphering and ultimate hemolysis of the red cells are related in some manner to derangement in the energy-yielding reactions of glycolysis, which in turn may be due to deficiency in activity of one or more enzymes. Our most recent observations[44] lend support to this hypothesis, but much more study of this problem is needed.

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Spherocytes may at least provisionally be regarded as having a metabolic handicap which becomes clearly manifest when they are trapped in the spleen or when they are removed from the circulation and incubated in the laboratory at body temperature. In either case these red cells undergo rapid sphering and lysis. If certain sugars or nucleosides are added to the incubating cells, hemolysis is markedly inhibited, perhaps because the supposed metabolic handicap may thereby be overcome. Once the spleen is removed from these patients, the red cells have more continuous access to plasma constituents and have normal or only moderately reduced life span despite persistency of the inherited abnormalities.

It seems possible that hereditary spherocytosis may prove to be another example of abnormal or deficient protein synthesis, more specifically a deficiency in synthesis of glycolytic enzyme protein due to a mutation in the responsible gene or DNA molecule (or through the agency of RNA). This condition may prove to be analogous in certain respects to the genetically determined deficiency in glucose-6-phosphate dehydrogenase found in red cells of persons with drug-induced hemolytic anemia. In the latter condition, the drug is the environmental factor needed to cause hemolysis. In hereditary spherocytosis the splenic trap provides an environment conducive to hemolysis of the inherently defective cells.

Extracorpuscular Agents

Let us turn now to consideration of hemolytic processes due to extracorpuscular factors. In this group of disorders the red cells are presumably normal when delivered to the circulation from the bone marrow but are destroyed in one way or another by extracorpuscular agents. Of the many known hemolytic agents, only antibodies will be considered because advances in our understanding of erythrocyte-antibody relationships have been especially rapid during the past twenty years.

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Interest in antibody-induced hemolysis was rekindled by the observations of Dameshek and Schwartz in 1938.[47]

Antibody-Induced Destruction of Red Cells

Studies on the capacity of isoantibodies anti-A, anti-B, anti-Rh, anti-Kell, anti-Duffy, anti-Lewis, etc., for initiating destruction of red cells in vivo have lagged somewhat behind studies on in vitro behavior. It is already clear, however, that in the presence of specific antibodies, red cells may be destroyed by any one of several different mechanisms or by several different mechanisms operating simultaneously. Certain antibodies are capable of rapidly lysing red cells intravascularly with the aid of complement, presumably in much the same way as red cells are lysed by such antibodies in vitro. These same antibodies, especially anti-A and anti-B from certain individuals, are the ones most capable of promoting phagocytosis of red cells by leukocytes or macrophages in vitro, intravascularly, in the spleen and in other portions of the reticuloendothelial system. The observations of Doan, Wright and associates,[48] Wasastjerna,[49] and Swisher and Dale[50] on phagocytosis in the spleen, and by Zinkham and Diamond[51] and Bennin and Schwartz[52] on in vitro erythrophagocytosis are especially interesting.

Jandl, Jones and Castle[53] found that red cells sensitized or coated with the incomplete Rh antibody, anti-D, were sequestered chiefly by the spleen. Under these circumstances the spleen appears to serve as a "passive filter" and sequestration may be enhanced by the rouleaux-producing globulins of plasma. On the other hand, tagged group B red cells transfused by these investigators to a group A recipient with complete anti-B agglutinins in the circulation were sequestered chiefly in the liver. The mechanisms by which sequestered red cells are lysed within the spleen

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or liver are not yet [illegible]; leukocytes may be [illegible] associates[54] in our laboratory have found disturbed intermediary metabolism of [illegible] carbohydrate in red cells sensitized in vivo with certain antibodies, but the significance of this disturbance in relation to the lytic process remains to be determined.

Autoimmune Hemolytic Disease

Of the hemolytic states involving antibodies, one of the most fascinating and most studied is autoimmune hemolytic disease, a form of acquired hemolytic anemia associated with autoantibodies; that is, antibodies or antibody-like substances reacting with the affected person's own red cells. Presence of autoantibodies on the red cells or in the serum is demonstrated by use of techniques, such as the antiglobulin (Coombs) test,[55] developed during the past fifteen years in the course of studies on isoantibodies, especially Rh antibodies. The mechanisms by which autoantibodies destroy red cells appear to be the same as those just enumerated for isoantibodies.[51,54] The relative importance of the several hemolytic mechanisms can be expected to vary considerably from case to case and from time to time in the same case, depending upon the quantity and characteristics of the autoantibody.[9]

It should be emphasized that in most cases autoantibodies, like most of the known isoantibodies, are incapable of hemolyzing either autogenous or normal human red cells in vitro in the presence of complement. They may be regarded as "potential lysins", however, since certain autoantibodies may hemolyze normal red cells treated with enzymes such as trypsin, and they may also hemolyze the abnormal red cells from persons with nocturnal hemoglobinuria.[9] Many observations of the past decade support the conclusion that the body contributes importantly, and in ways that are not yet understood, to the destruction of red cells initiated

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by antibodies.[47,49,[illegible]-56,57] In vitro systems provide only hints regarding the [illegible] mechanisms that may operate in vivo. Especially mysterious is the sphering of [illegible] red cells produced by certain antibodies, auto-, iso- and hetero-, over a period of about 4 to 24 hours after transfusion of incompatible plasma.[47,56-60] This phenomenon has not yet been satisfactorily reproduced in vitro.

Whatever the mechanisms of hemolysis may be in autoimmune hemolytic disease, hemolysis subsides in most cases after administration of ACTH or corticosteroids so that splenectomy can now be reserved for the more refractory cases.[61,62] The steroids may inhibit formation of autoantibodies or they may somehow interfere with destruction of red cells in the presence of such antibodies. The exact mechanisms of action of steroid hormones in this disorder, as in many others, remain to be determined.

Experience in the past fifteen years has revealed that about forty per cent of patients with autoimmune hemolytic anemia have an underlying disease, most frequently lymphoma, lymphocytic leukemia, or diffuse collagen disease.[61-63] In fact, presence of autoantibodies may be the first indication of an underlying disorder. Use of the Coombs test has helped to reveal the long-term picture of autoimmune hemolytic disease and associated disorders in much the same manner as the use of the Wassermann test helped to reveal the full story of syphilis during the earlier years of this century.[64]

Striking similarities have become apparent between idiopathic thrombocytopenic purpura and idiopathic autoimmune hemolytic disease.[65,66] Both appear to be associated with a form of autoimmunization. Both occur more commonly in

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females. Both are frequently relieved by administration of ACTH or corticosteroids, and in some cases by splenectomy but relapse is a constant threat in both disorders. Both may occur simultaneously or sequentially in the same patient. Leukopenia may also occur simultaneously or sequentially with this form of hemolytic anemia,[64] but the mechanisms responsible for leukopenia seem currently to be less clear than those demonstrated in thrombocytopenic patients by Evans et al,[65] Harrington et al,[66] and by Stefanini and Dameshek.[67]

It seems to me that autoimmune hemolytic disease may be best understood if regarded as a disorder resulting chiefly from synthesis of abnormal proteins, an aberration that may be comparable in some respects to that observed in multiple myeloma[68] and in disseminated lupus.[69] Just as the characteristics of the myeloma proteins vary from patient to patient, so do the characteristics of autoantibodies.[9] Patients with autoimmune hemolytic disease, like those with lupus, readily produce immune isoantibodies such as anti-Rh, anti-Kell, anti-Duffy, when transfused with normal red cells.[9] Moreover, they frequently produce cold-precipitable- or cryo-proteins.[64] Certain portions of the protein-forming system of the body seem to undergo a mysterious change. Where does this occur? Available evidence indicates that certain of the most radiosensitive cells of the reticuloendothelial system produce not only antibodies, but also cryoproteins and probably other abnormal proteins found in autoimmune hemolytic disease, multiple myeloma and disseminated lupus.

The microsomes, which are fragments of the endoplasmic reticulum in the cytoplasm of many types of cells, contain protein and ribonucleic acid, the RNA to which I previously referred as a likely mediator of the control of DNA on synthesis

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of hemoglobin and or enzyme protein within the immature red cell. Recent work points to RNA as a template, or to use Zamecnik's[70] term, a "printing press" controlling arrangement of amino acids in the synthesis of protein molecules. In autoimmune hemolytic disease, the tiny printing presses in the antibody-forming cells seem to respond to antigens in the patient's own red cells and in transfused normal red cells which previously evoked no response. Changes occurring in the cytoplasmic RNA of the reticuloendothelial cells may thus result in manufacture of various types of autoantibodies, irregular isoantibodies and perhaps other abnormal proteins such as cryoglobulin. We do not know how such changes in RNA might come about, how they might be related, if at all, to chromosomal DNA, and what change, if any, might occur in the antigenicity of the red cells in this disease. The possible role of cytoplasmic RNA outside the microsomes may also have to be considered.[19] Nevertheless, it seems possible that changes in configuration and/or function of RNA molecules, particularly in the microsomes, of the cells in question could be responsible for the synthesis of the various abnormal proteins found in the autoimmune hemolytic disorders.

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Conclusion

As we survey recent advances in our understanding of hemolytic disorders, it is apparent that much of the progress is due to appreciation of the role of disturbed protein synthesis--hemoglobin, enzymes and antibodies. It becomes clearer each month that protein synthesis is indeed a central problem in biology, and the hemolytic disorders serve admirably to illustrate this point.

Much of the progress in our understanding of hemolysis can also be attributed to the growing appreciation of the fact that the red cell is a complex, highly organized, living cell, a cell from which we can learn many lessons if we give it the attention it deserves. As each year passes we can understand more fully the meaning of the statement made by Lord Dawson[71] in 1931 that "the disease hemolytic anemia has an interest beyond itself."

Abstract (for interlingua)

Recent advances in our understanding of four types of hemolytic disorders are reviewed: (1) hemoglobinopathies, (2) hemolysis induced by drugs and fava beans, (3) hereditary spherocytosis and (4) autoimmune hemolytic disease.

The observations cited support two general conclusions:

A. Some of the most common and fascinating hemolytic disorders can probably be attributed in large part to abnormalities in synthesis of protein--hemoglobin, enzymes and antibodies.

B. Much of the progress in our understanding of hemolysis is due to appreciation of the fact that the red blood cell is a complex, highly organized, living cell.

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Table 1.

Enzymes Demonstrated in human Erythrocytes

Glycolytic enzymes	Catalase
Hexose-mono-phosphate shunt enzymes	Urease
Phosphatases	Arginase
Acetyl cholinesterase	Proteases
Glyoxalase	ATP-ase
Carbonic anhydrase	Methemoglobin reductase
Glutathione reductase	Purine nucleoside phosphorylase
Pyrophosphatase	Adenosine deaminase
	Myokinase

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Table 2.

Classification of Hemolytic Disorders

Intracorpuscular abnormalities
- Hereditary (e.g. hemoglobinopathies, spherocytosis, elliptocytosis, thalassemia major)
- Non-hereditary (e.g. nocturnal hemoglobinuria)

Extracorpuscular "agents"
- Spleen; antibodies; chemical, physical, infectious agents

Mixed types
- Both intracorpuscular abnormalities and extracorpuscular agents involved

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Table 3.

Arrangement of Amino Acids in Peptide No. 4 of Hemoglobin Molecules (Ingram[11, 12])

Hemoglobin A	Hemoglobin S	Hemoglobin C
Histidine	Histidine	Histidine
Valine	Valine	Valine
Leucine	Leucine	Leucine
Leucine	Leucine	Leucine
Threonine	Threonine	Threonine
Proline	Proline	Proline
Glutamic acid	Valine	Lysine
Glutamic acid	Glutamic acid	Glutamic acid
Lysine	Lysine	Lysine

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Explanation of Figures

Figure 1. Visual model of normal human red blood cell, viewed from cut surface. Molecules of lipid are represented by bars and molecules of protein by dots. The sizes of the bars and dots are diagrammatic. Molecular size is indicated more accurately in Figure 2.

Figure 2. Model of red cell membrane, reprinted from Ponder[1] by courtesy of Scientific American. Round-headed rectangles represent lipids of all types (cholesterol, phospholipid and fatty acids). Large shaded circles containing smaller circles are protein bundles cut in cross section. Circles at top represent a layer of albumin.

Figure 3. Model of DNA structure, reprinted from Crick[13] by courtesy of Scientific American.

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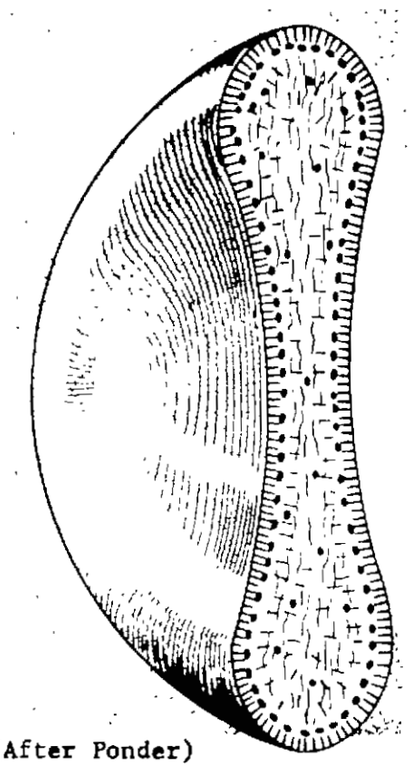

(After Ponder)

SOME COMPONENTS OF HUMAN ERYTHROCYTE

LIPID

STRUCTURAL PROTEIN

BLOOD GROUP SUBSTANCES

HEMOGLOBIN

PROTOPORPHYRIN

COPROPORPHYRIN

GLYCOLYTIC SYSTEM

GLUTATHIONE

ENZYMES (40)

VITAMINS

MINERALS

WATER

Fig 1

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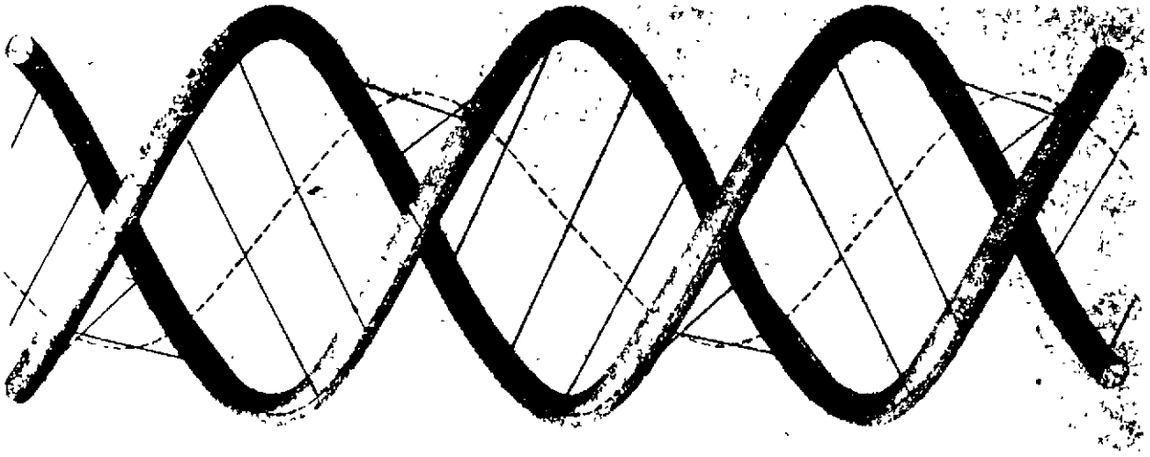

Fig 3

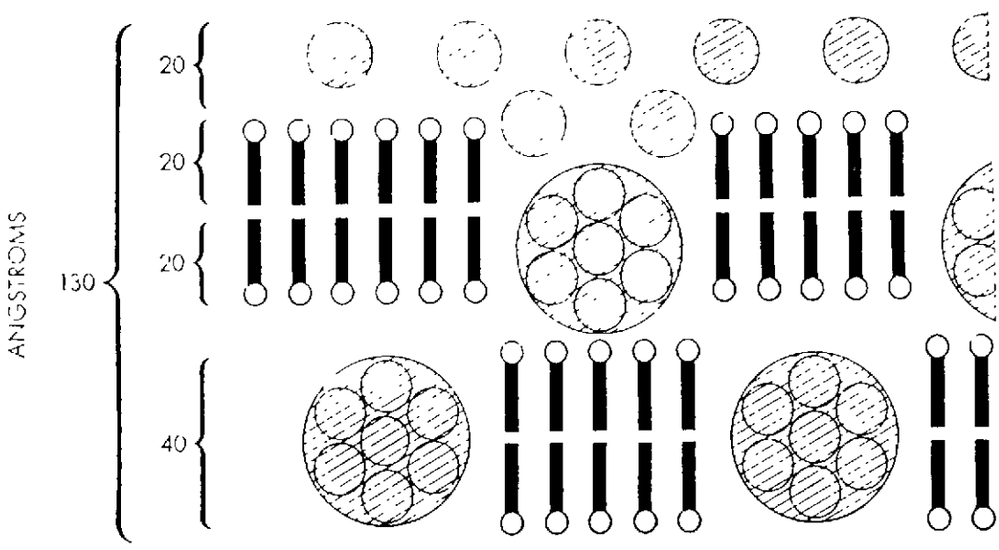

Fig 2

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