There is no general agreement about the best therapy of myxoedema coma. It is common practice to give thyroxine in doses of 0·05 mg daily by mouth combined with triiodothyronine 20 μg twice daily by intramuscular injection together with hydrocortisone hemisuccinate 50 mg twice daily (in case of adrenal failure). Assisted respiration may be required if there is carbon-dioxide retention or hypoxaemia. Infections, cardiac failure, or arrhythmias should be treated vigorously and cardiac monitoring is desirable. The body temperature should be slowly raised to normal, using a "space blanket" and heating pads if necessary, in a warm room.

References

[1] Gull, W. W., *Transactions of the Clinical Society of London*, 1874, 7, 180.
[2] Ord, W. M., *Medico-Chirurgical Transactions*, 1878, **61**, 57.
[3] Haliburton, W. D., *Journal of Pathology and Bacteriology*, 1893, **1**, 90.
[4] Hall, R., Amos, J., and Ormston, B. J., *British Medical Journal*, 1971, **1**, 582.
[5] Hedley, A. J., Hall, R., Amos, J., Michie, W., and Crooks, J., *Lancet*, 1971, **1**, 455.
[6] Evered, D. C., and Hall, R., *in preparation*, 1972.
[7] Lowrey, R., and Starr, P. J., *Journal of the American Medical Association*, 1959, **171**, 2045.
[8] Gordin, A. G., Heinonen, O. P., and Lamberg, B. A., European Thyroid Association Abstracts, Berne, 1971.
[9] Bastenie, P. A., Neve, P., Bonnyns, M., Vanhaelst, L., and Chailly, M., *Lancet*, 1967, **1**, 915.
[10] Bastenie, P. A., Vanhaelst, L., and Neve, P., *Lancet*, 1967, **2**, 1221.
[11] Bastenie, P. A., Vanhaelst, L., Bonnyns, M., Neve, P., and Staquet, M., *Lancet*, 1971, **1**, 203.
[12] Vanhaelst, L., Neve, P., Chailly, M., and Bastenie, P. A., *Lancet*, 1967, **2**, 800.
[13] Fowler, P. B. S., and Swale, J., *Lancet*, 1967, **1**, 1077.
[14] Fowler, P. B. S., Swale, J., and Andrews, H., *Lancet*, 1970, **2**, 488.
[15] Ormston, B. J., *et al.*, *Lancet*, 1971, **2**, 10.
[16] Dingle, P. R., *et. al.*, *Clinical and Experimental Immunology*, 1966, **1**, 277.
[17] Levy, R. I., *Lipids and Heart Disease*, p. 66. Amsterdam, Excerpta Medica, 1968.
[18] Rifkind, B. M., *British Journal of Hospital Medicine*, 1970, **4**, 683.
[19] Murphy, B. P., *Journal of Laboratory and Clinical Medicine*, 1965, **66**, 161.
[20] Sterling, K., Bellabarba, D., Newman, E. S., and Brenner, M. A., *Journal of Clinical Investigation*, 1969, **48**, 1150.
[21] Hall, R., Anderson, J., and Smart, G. A., *Fundamentals of Clinical Endocrinology*, London, Pitman, 1969.
[22] Cotton, G. E., Gorman, C. A., and Mayberry, W. E., *New England Journal of Medicine*, 1971, **285**, 529.
[23] Smith, R. N., Taylor, S. A., and Massey, J. C., *British Medical Journal*, 1970, **4**, 145.

Scientific Basis of Clinical Practice

The Red Cell

G. W. G. BIRD

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Almost everyone knows that the human red blood cell is a circular biconcave disc consisting of a solution of haemoglobin contained within a membrane, and that its function is to give oxygen to and remove carbon dioxide from the tissues. Not everyone knows that this oddly shaped cell is the site of considerable dynamic activity. The red cell is a veritable microcosm, with surprisingly many enzymes, proteins, lipids, carbohydrates, and electrolytes all vigorously taking part in maintaining its integrity, shape, and function.

In man and many other animals the red cell has no nucleus and therefore does not conform to the strict definition of a biological cell. Nevertheless, the red cell is accepted not only as a cell but as a model cell which has been studied in considerable depth.

During its life span of about 120 days, the red cell travels 175 miles in its prodigious task of delivering oxygen to the tissues.[1] In the average person in the resting state about 250 ml of oxygen is inspired every minute, taken up by the red cells, and given up to the tissues. A red cell spends only 780 milliseconds in a pulmonary capillary in a resting person, yet complete oxygenation takes place in the first third of that time. During activity the rate of oxygen transfer is greatly increased. The process is aided by the vast surface area of the total red cell mass, which has been estimated at about 3,000 square miles.

The biconcave discoidal shape of the mature red cell is adapted to this function of gas transfer. The surface area of the red cell is larger than the minimal area needed to enclose its volume, which would be provided if the red cell were a simple sphere. In the narrow channels of the microcirculation, where oxygen is given up, more red cells can be accommodated in a given volume of blood than would be possible if the cells were spherical. The cell membrane is elastic and therefore distortable; this property aids the movement of the red cell in the microcirculation.

The presence of haemoglobin within rather than outside the red cell is advantageous for various reasons. By providing bolus flow rather than laminar flow it avoids a stagnant layer of flow along the capillary wall. Haemoglobin is isolated from the general metabolic pool, preventing rapid turnover; the half-life of intracellular haemoglobin is 120 days, as against 3 hours and 20 minutes for free haemoglobin. Furthermore, intracellular haemoglobin is kept in close proximity to the red cell enzymes involved in oxygen transport.

Measurements of red cells *in isotonic media* show that the average red cell is 8·4μ in diameter, 2·4μ thick at the periphery, and 1μ thick at its narrowest part.

Red Cell Membrane

The red cell membrane is not just an inert barrier between the plasma and the red cell contents; it is a dynamic structure of some depth (70-80 Å) and intricate organization. It consists of an outer hydrophilic layer of proteins, glycoproteins, and glycolipids; a central hydrophobic layer of α-helical protein, cholesterol and phospholipids; and an inner hydrophilic layer of proteins and glycolipids. The lipid molecules of the central layer are radially orientated, with their polar (hydrophobic) groups facing outwards and their hydrocarbon chains inwards.

According to Zahler[2] the membrane is not a continuous structure but is an aggregate of a number of cylindrical sub-

Regional Blood Transfusion Service, Birmingham B15 2SG
G. W. G. BIRD, M.B., F.R.C.PATH.

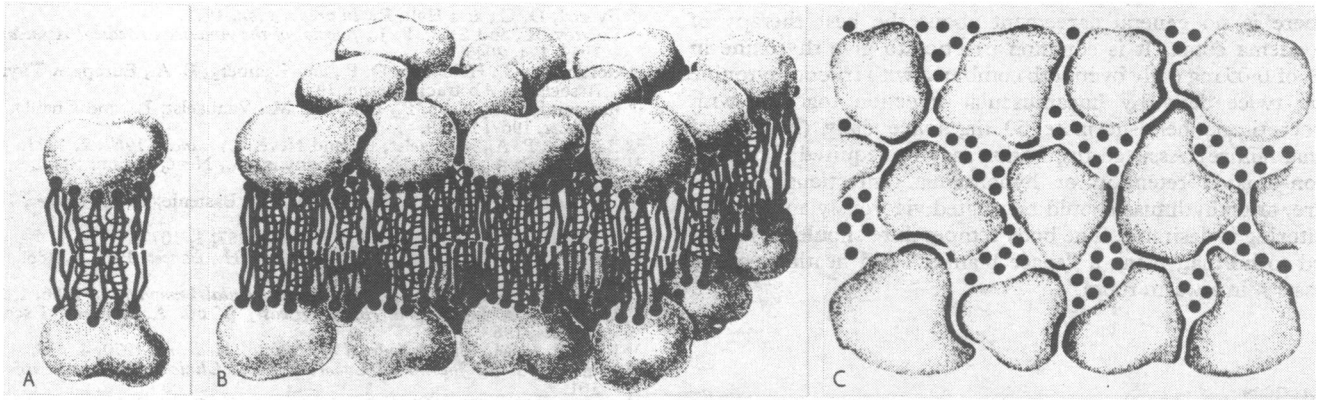

FIG. 1—Speculative structure of the red cell membrane according to Zahler[3] showing regions of the membrane mosaic in which penetrating proteins are predominant: (a) single subunit; (b) aggregates of subunits; (c) view of membrane surface from on top. (Reproduced by the kind permission of author and publisher.)

units each consisting of a central hydrophobic α-helical region with a hydrophilic region above and below. Zahler's interpretation of red cell membrane structure (Fig. 1b) brings to mind a comfortable spring mattress. The space between the subunits is filled with lipids. Water is able to diffuse through the cell membrane along channels suited to this purpose. The passage of water through the cell membrane is not a simple matter of osmosis as was once believed; it is exceptional for cells to be in osmotic equilibrium with their environment. The red cell membranes are in fact permeable to potassium and sodium ions.

The red cell behaves in respect to water and electrolytes "like a leaking ship kept steady with pumps".[3] The cell has an active water transport system, which pumps water out of the cell or prevents it from entering. Potassium ions tend to leak out and sodium ions to leak in; the metabolic pump works against osmotic gradients to extrude the latter and retain the former. The energy for this process is derived from the anaerobic conversion of glucose to lactic acid.

Blood Groups

One of the most important attributes of the red cell membrane is the presence of blood-group characters on its surface. Over a hundred blood-group antigens have been distinguished and three-quarters of them assigned to fifteen genetically distinct systems.[4] Accurate identification of blood groups is fundamental to safety in blood transfusion.

The most important blood group system is ABO, in which *A* and *B* genes act on a preformed substrate H, the product of an independent gene *H*, to produce the A and B antigens, respectively. The *H* gene acts on a precursor glycolipid or glycoprotein substrate which terminates in an oligosaccharide chain which has the structure:
β-galactose-(1-3) or (1-4)-N-acetylglucosamine-(1-3)β-galactose---.

The primary product of a blood group gene is an enzyme, a glycosyltransferase, which attaches the characteristic end sugar to a substrate formed by the sequential addition of the appropriate sugars by other transferases. Each transferase is specific not only for the sugar it adds but also for the substrate and the type of chemical linkage. The product of the *H* gene is a fucosyltransferase which adds L-fucose, in α-linked (1-2) position, to the terminal β-galactose of the precursor chain. The product of an *A* gene is N-acetyl-D-galactosaminyltransferase which adds N-acetyl-D-galactosamine, in an α-linked (1-3) position, to the H chain; the product of a *B*-gene is a D-galactosyltransferase which adds D-galactose, in an α-linked (1-3) position, to the H chain. The biosynthetic steps in the formation of the A and B characters are shown in Fig. 2.

Group O cells are rich in H because there are no *A* or *B* genes to utilize H-substance. In the very rare "Bombay" blood group (H-negative) there is no *H* gene and therefore no fucosyltransferase to act on the precursor material. "Bombay" blood therefore lacks not only H but also A and B, even in the presence of *A* or *B* genes, because the enzymes produced by these genes have no substrate on which to act. The subject is reviewed by Morgan and Watkins.[5]

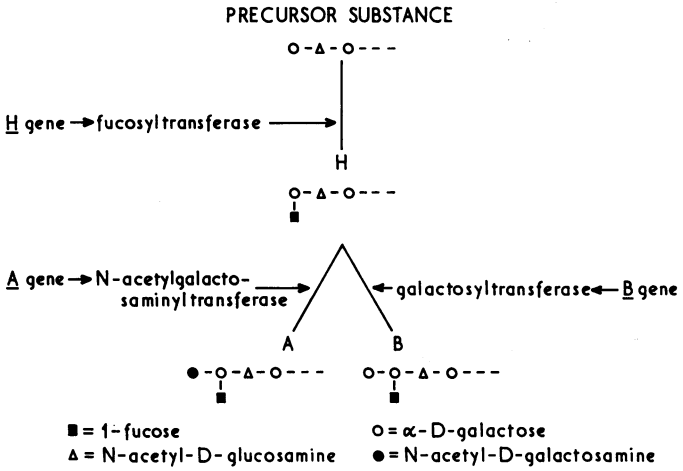

FIG. 2—Biosynthetic steps in the formation of the A and B blood groups.

The biosynthetic pathways relevant to the other blood group systems are yet to be fully elucidated.

N-acetylneuraminic (Sialic) Acid

An important carbohydrate constituent of the red cell membrane is N-acetylneuraminic acid (NANA). It is largely responsible for establishing the negative charge of red cells and therefore in maintaining their separate state. NANA also forms part of the structure of the human blood-group antigens M and N. When red cells are deficient in NANA their M and N antigens are destroyed or depressed; some types of NANA-deficient red cells are polyagglutinable—that is, they are agglutinated irrespective of blood group by a variable number of sera. This type of polyagglutination may be due either to the exposure of a latent antigen T by microbial neuraminidase (an enzyme which specifically detaches NANA) or to a red-cell antigen receptor Tn of mysterious origin. Tn-polyagglutination may be associated with haemolytic anaemia, leucopenia, and thrombocytopenia.[6]

An Antigen Carrier

The antigens of all human blood group systems except the Lewis group are an intrinsic part of the structure of the red cell membrane. The Lewis system, however, is primarily

an antigen system of the tissue fluids. Red cells acquire their Lewis antigens by adsorption from the plasma.

The red cell is in fact prone to acquire a variety of passenger antigens—for example, bacterial polysaccharides, penicillin, and other substances—so that they become agglutinable by sera which contain antibodies to the adsorbed substance. Certain substances are sometimes deliberately attached to red cells to provide a convenient haemagglutination test for the presence of antibody. In a positive indirect Coombs test, for example, red cells which have been exposed to incomplete blood-group antibody globulin are agglutinated by antiglobulin serum. Protein antigens are sometimes coupled to red cells by various devices—for example, thyroglobulin to red cells previously treated with tannic acid, so that thyroglobulin antibody can be demonstrated by haemagglutination.

Clinical Importance of Blood Groups

Besides their obvious importance in blood transfusion, blood groups are of significance in certain clinical conditions. Blood-group incompatibility between mother and fetus may cause fetal haemolytic disease. If a mother (X-negative) lacks a hypothetical red cell antigen X which is carried on the red cells of her fetus (X-positive), which has inherited the antigen from its father, she may develop anti-X antibodies if, at or near term, fetal red cells enter her circulation. If she becomes immunized in this way (or by transfusion of X-positive blood), and subsequently bears an X-positive fetus, her anti-X antibody may cross the placental barrier and destroy the X-positive red cells of her fetus so that, at birth or shortly thereafter, her child may show the signs of haemolytic disease of the newborn. The antibody most commonly responsible for haemolytic disease in many parts of the world, including Britain, is anti-D, an antibody of the Rhesus blood-group system.

Some curious associations of blood groups with disease have been recorded. Paroxysmal cold haemoglobinuria, a complication of syphilis or certain viral infections, is due to a red cell autoantibody, known as the Donath-Landsteiner antibody, which has a specificity within the P blood-group system.

There is strong statistical evidence to show that cAncer of the stomach is more common in persons who are group A, and duOdenal ulcer in those who are group O. (The capital letters in the disease names are intended as an aide memoire.) Group O non-secretors are in fact more liable than secretors to duodenal ulcer. Women on the contraceptive pill are more likely to develop thromboembolic disorders if they are of group A.[7]

Abnormally Shaped Red Cells

The relationship between volume, diameter, and thickness of the red cell may be changed, as in the spherocyte, the leptocyte, and the elliptocyte.

The spherocyte is a red cell which is more spherical than normal. Spherocytes are formed in conditions of capillary stasis, deranged osmosis, or from deficiency of plasma antisphering factor. There are also two clinically important forms of spherocyte. One is the spherocyte of hereditary spherocytosis; the other is the acquired spherocyte, which is produced by the action of red cell antibody, and is therefore seen in conditions such as haemolytic disease of the newborn, particularly when it is caused by ABO blood-group antibodies, and in autoimmune haemolytic anaemia. The osmotic fragility of the red cell or its capacity to haemolyse in hypotonic saline solution depends on the ratio of its surface area to its volume; the greater the ratio the greater the additional volume that can be accommodated within the cell. The osmotic fragility of spherocytes is increased because a relatively small additional volume causes the cells to rupture.

The leptocyte is the opposite of a spherocyte. It is a pale flat cell with more surface area per unit of volume than a normal cell, and it is therefore abnormally resistant to rupture in hypotonic saline solution—that is, its osmotic fragility is decreased. In stained blood films the leptocyte may appear as a ring of haemoglobin with an unstained centre, or there may also be a central stained area, in which case the leptocyte is known as a target cell. Target cells are found in haemoglobinopathies, liver diseases, and after splenectomy.

The elliptocyte is an elliptical or oval red cell characteristic of an inherited red cell anomaly, elliptocytosis. In the normal red cell, there is a greater concentration of cholesterol in the periphery than in the concavity, a property on which the shape of the normal red cell may depend.[1] But elliptocytes have a greater than normal concentration of cholesterol at the ends of the cells.

Poikilocytes or irregularly shaped red cells are seen in all severe anaemias. Stomatocytes or cells with eccentric slit-shaped pallor and not central circular pallor are seen in various haemolytic anaemias. Irregularly contracted cells may be seen in microangiopathic and other haemolytic anaemias; cell fragments (schistocytes) or cells with spiny projections (Burr cells) may also be seen. Sickle cells will be described in a future article in this series.

Crenated red cells are sometimes seen in blood films; they are usually artifacts produced by shrinkage of red cells in hypotonic media. A persistent form of gross red cell crenation known as acanthocytosis is a feature of a rare congenital disorder, abetalipoproteinaemia. Membrane cholesterol is increased and lecithin decreased. Similar cells, known as spur cells, with raised cholesterol and normal lecithin levels may occur in liver disease.

Intraerythrocytic Bodies

The cytoplasm of the red cell may contain various indigenous and foreign bodies, some of which are known as "inclusions" (Table I). Heinz-Ehrlich bodies are of special significance. They appear only for a few days after assault by a drug; it is therefore important to look for them as soon as drug toxicity is suspected. They are usually seen in persons with glucose-6-phosphate dehydrogenase deficiency, but may also be seen in patients with normal red-cell-enzyme levels. The Heinz bodies associated with the unstable haemoglobins are thought to be due to precipitation of mutant β-chains after they have lost their haem groups.[8]

TABLE I—*Structures Observed within Red Cells*

	Structure(s)	Remarks
Immature red cells	Nucleus	Up to late erythroblast stage
	Reticulum	In reticulocytes—supravital staining
	Basophil punctation (stippling)	Same significance as reticulocytes or polychromasia
	Cabot's rings	Nuclear remnants
	Howell-Jolly bodies	Nuclear remnants
	Siderocytes	Non-haematin iron pigments. A few may be seen in mature cells
	Pappenheimer bodies	Iron-containing granules—also seen in mature cells
Mature red cells	Malaria parasites	
	Schüffner's dots	In cells parasitized by *Plasmodium vivax* or *P. ovale*
	Maurer's dots	In cells parasitized by *P. falciparum*
	Bartonella bacilliformis	In Oroya fever
	Heinz-Ehrlich bodies	Caused by some toxic substances. Supravital staining (refractile bodies in unstained films)
	Haemoglobin C crystals	Hb C Disease
	"Inclusion bodies"	Hb H Disease—precipitated denatured Hb H.
	"Inclusion bodies"	Unstable haemoglobins—e.g., Hb Zurich. Thought by many to be Heinz-Ehrlich bodies

Haemolysis

Haemolysis or the loss of haemoglobin from red cells may result, in unfavourable osmotic conditions, in distention of the "pores" of the cell membrane, so that haemoglobin escapes like water through a sprinkler. In other conditions the red

cell may be perforated and burst like a balloon, so that haemoglobin escapes at a single gap.

Many haemolytic mechanisms and agents are known; one of the most important of these is complement, which is not a single substance but consists of many enzymes and proteins which operate in a definite order after activation brought about by the combination of antibody with a red cell antigen. Holes (diameter 80-100 Å) are ultimately produced in the cell membrane, so that haemoglobin is released.

Formation and Destruction of Red Cells

About 3 million red blood cells are normally broken down per second.[9] Since, in a healthy person, the total number of red cells remains within normal limits, about 3 million red cells must be produced every second. When this balance is disturbed and compensatory haemopoiesis is no longer effective, the haemoglobin level is reduced. Anaemia may therefore arise either from reduced production (dyshaemopoietic anaemia) or increased loss of red cells (post-haemorrhagic anaemia, haemolytic anaemia).

The production of red cells is regulated by an erythrocyte stimulating factor, erythropoietin, present in plasma. Another stimulus to red cell production is anoxaemia.

In red cell maturation a primitive precursor cell, derived from endothelium, becomes successively a proerythroblast; early, intermediate, and late normoblast; reticulocyte; and finally an erythrocyte or mature red cell. The process of maturation involves a decrease in size, shrinkage, and disappearance of the nucleus, and the progressive acquisition of haemoglobin.

The assumption that all red cells live for about 120 days is probably valid in a general sense; there is evidence, however, that some cells may have a relatively short life span and that there may be some random destruction of red cells irrespective of their age.[10] Surprisingly little is known about the physiological mechanism for the removal of effete red cells.

Red cells are as old as their enzymes. Ageing cells become progressively deficient in the enzymes necessary for deriving energy from glucose. The cells then burst or succumb to osmotic lysis, fragmentation, or erythrophagocytosis. Most of the iron released from the haemoglobin of broken down cells is reclaimed by the bone marrow for haemoglobin synthesis. The globin is degraded and the products returned to the amino-acid pool; the pigment portion is converted ultimately to bilirubin.

Haemolytic Anaemias

Pathological or enhanced destruction of red cells, which may arise from a plethora of causes, gives rise to haemolytic anaemia. Harris and Kellermeyer[11] give an elaborate classification of haemolytic anaemias; a less comprehensive classification is given in Table II.

Whereas haemolytic anaemias due to extracorpuscular factors are caused by direct damage to the red cell membrane, the cause of increased haemolysis in the intracorpuscular disorders is not always clear. Some of the latter are disorders of membrane permeability—for example, hereditary spherocytosis, a "small-hole" defect, and paroxysmal nocturnal haemoglobinuria, a "large-hole" defect.[12] The hereditary nonspherocytic haemolytic anaemias are disorders of glycolytic enzymes, essential to cell metabolism.[13,14]

According to Jacob,[15] the membrane protein in hereditary spherocytosis does not form normal aggregates, so that the red cells cannot assume a normal shape, and are instead spherocytic, rigid, and relatively fragile. In paroxysmal nocturnal haemoglobinuria the red cells are peculiarly sensitive to lysis by complement at pH 6·8. Haemoglobinuria is most pronounced at night, because a fall in plasma pH occurs during sleep. Blood group anomalies—for example, Rh_{null} disease[16] or persistent mixed-field polyagglutination[6] may manifest mild haemolytic anaemia.

The microangiopathic haemolytic anaemias form an interesting group which includes thrombotic thrombocytopaenic purpura and the haemolytic-uraemic syndrome.

TABLE II—*Brief Classification of Haemolytic Anaemias*

I		INTRACORPUSCULAR ANOMALIES
	(*a*)	*Inherited*
		Hereditary spherocytosis
		Elliptocytosis
		Stomatocytosis
		Hereditary nonspherocytic haemolytic anaemia, e.g. glucose-6-phosphate dehydrogenase deficiency.
		The haemoglobinopathies
		Erythropoietic porphyria
		Rh_{null} disease
	(*b*)	*Acquired*
		Paroxysmal nocturnal haemoglobinuria
		Persistent mixed-field polyagglutination
II		EXTRACORPUSCULAR FACTORS
	(*a*)	*Due to antibodies*
		Haemolytic disease of the newborn
		Haemolytic transfusion reaction
		Autoimmune haemolytic anaemia
	(*b*)	*Not due to antibodies*
		Due to chemical poisons, e.g. naphthalene
		Burns
		Due to infections, e.g. malaria
		Microangiopathic haemolytic anaemia
III		BOTH INTRA- AND EXTRACORPUSCULAR FACTORS
		Glucose-6-phosphate dehydrogenase deficiency and the effect of certain therapeutic substances, e.g. primaquine, vitamin K
		Lead poisoning
		Unstable haemoglobins

Aspects of Red Cell Metabolism

Red cell glucose is converted to lactic acid by the nonoxidative Embden-Meyerhof pathway, with production of potential energy in the form of adenine triphosphate (ATP). Oxidative metabolism occurs through the pentose-phosphate pathway, also known as the hexose-monophosphate shunt: glucose is converted to carbon dioxide with production of energy in the form of reduced nicotinamide adenine dinucleotide phosphate (NADPH), a substance which is important for protecting red cells against the oxidative stresses of substances such as primaquine. Glucose-6-phosphate dehydrogenase is required for the formation of NADPH; a deficiency of this enzyme makes red cells vulnerable to haemolysis by primaquine or other substances.

Besides ATP other phosphate compounds are generated during red cell metabolism. The red cell contains much larger amounts of 2,3 diphosphoglyceric acid (DPG) than other cells. The affinity of haemoglobin for oxygen varies inversely with the concentration of DPG. DPG therefore regulates the transport of oxygen by haemoglobin—not by making haemoglobin take up more oxygen but by making it give up its oxygen more readily.

Red Cell Preservation

Knowledge of red cell metabolism is essential to a clear understanding of methods used in red cell preservation. Blood for transfusion is collected into an anticoagulant solution which contains glucose (dextrose). The solution is known as acid citrate dextrose (ACD). When sodium citrate alone was used as an anticoagulant the shelf life of stored blood was 7 days; the addition of glucose increased it to 21 days.

Conditions of storage must be optimal for the conversion of glucose to ATP; the post-transfusion survival of red cells is correlated to their ATP content. The consumption of red cell glucose at 4°C is at least 30 times slower than at 37°C. Blood for transfusion is therefore stored at 2-6°C.

Recently there has been a move in support of using citrate phosphate dextrose (CPD) as an anticoagulant for blood transfusion purposes. Blood collected into CPD has an initial pH of 7·2 as against 7·0 for blood in ACD; the higher pH reduces the damage to the red cell membrane known as the "lesion of collection." Blood collected into CPD maintains its ATP level better than ACD blood, so that it has a shelf life of 28 days. Furthermore, CPD blood stored for 7 days has twice as much DPG as ACD blood.

Hence CPD might be a better anticoagulant for blood for transfusion than ACD. It is yet to be determined however whether a relatively low DPG-level in blood for transfusion is of clinical importance. However, an increase in the shelf life of stored blood may have advantages, particularly in hospital blood banks in which there is a relatively slow turnover of blood.

Some purine nucleosides when added to anticoagulant solutions increase ATP concentration and consequently the shelf-life of stored blood and the post-transfusion survival of stored cells. An ACD-adenine solution, in which blood for transfusion is stored for up to 35 days, is used in Uppsala.[17]

Storage of blood in the frozen state has been extensively studied. Krijnen *et al.*,[18] suspend packed cells from ACD blood in 20% (w/v) glycerol and then freeze the cells in liquid nitrogen at −196°C. Blood may be stored in this way for years. When required for transfusion the cells are thawed at 40°C, washed in 16% sorbitol and 0·9% sodium chloride. The 24-hour post-transfusion survival of the cells is over 90%.

Frozen blood has several advantages. It is leucocyte-free and devoid of hepatitis virus. It is particularly valuable for storing patients' own cells for subsequent transfusion in connexion with transplant surgery, in which it is important to avoid cytotoxic incompatibility of lymphocytes, or when the patient has a very rare blood group and has developed antibodies against the red cells of almost everyone else.

When blood of a rare group has been kept in reserve at 2-6°C and has not been used, it can be rejuvenated by the addition of inosine[19] and then stored in the frozen state.

Conclusion

Large volumes have been written on the red cell, and indeed on haemolysis alone. The foregoing account is but a brief essay on a vast and fascinating subject. Further details may be obtained from various monographs[20 21 11] from contributions to recent symposia,[22 23] and from the July and October 1970 numbers of *Seminars in Heamatology*.

This article is based on a lecture given in the Birmingham course under the title "The Scientific Basis of Clinical Practice" (see B.M.J., 27 November 1971, p. 510).

References

1 Harris, J. W., and Kellermeyer, R. W., *The Red Cell*. Cambridge, Mass., Harvard University Press, 1970.
2 Zahler, P., in *Modern Problems of Blood Preservation*, ed. W. Spielmann and S. Siedl, p. 1-13. Stuttgart, Fischer, 1970.
3 Cameron, G. R., *New Pathways in Cellular Pathology*, London, Arnold, 1956.
4 Sanger, R., and Race, R. R., *American Journal of Clinical Pathology*, 1971, 55, 635.
5 Morgan, W. T. J., and Watkins, W. M., *British Medical Bulletin*, 1969, 25, 30.
6 Bird, G. W. G., Shinton, N. K., and Wingham, J., *British Journal of Haematology*, 1971, 21, 443.
7 Mourant, A. E., Kopec, A. C., and Domaniewska-Sobczak, K., *Lancet*, 1971, 1, 223.
8 Jacob, H. S., and Winterhalter, K. H., *Journal of Clinical Investigation*, 1970, 49, 2008.
9 *Lancet*, 1971, 2, 475.
10 Mollison, P. L., *Blood Transfusion in Clinical Medicine*, Oxford, Blackwell 1967.
11 Harris, J. W., and Kellermeyer, R. W., *The Red Cell*. Cambridge, Mass., Harvard University Press, 1970.
12 Heimpel, H., in *Modern Problems of Blood Preservation*, ed. W. Spielmann and S. Seidl, p. 42-50. Stuttgart, Fischer, 1970.
13 Grimes, A. J., *British Journal of Haematology*, 1969, 17, 129.
14 Jaffe, E. R., *Blood*, 1970, 35, 116.
15 Jacob, H. S., in *Abstracts of the 13th International Congress of Haematology*, p. 116, Munich, 1970.
16 Sturgeon, P., *Blood*, 1970, 36, 310.
17 de Verdier, C.-H., Åkerblom, O., Garby, L., and Högman, C., in *Modern Problems of Blood Preservation*, ed. W. Spielmann and S. Siedl, p. 93-98, Stuttgart, Fischer, 1970.
18 Krijnen, H. W., de Wit, J. J. F. M., Kuivenhoven, A. C. J., Loos, J. A., and Prins, H. K., *Vox Sanguinis*, 1964, 9, 559.
19 Högman, C. G., and Åkerblom, O., in *Modern Problems of Blood Preservation*, ed. W. Spielmann, and S. Siedl, p. 212-217. Stuttgart, Fischer, 1970.
20 Ponder, E., *Haemolysis and Related Phenomena*, New York, Grune, 1948.
21 Prankerd, T. A. J., *The Red Cell*, Oxford, Blackwell, 1961.
22 *Red Cell Membrane; Structure and Function*, ed. G. A. Jamieson, and T. J. Greenwalt, Philadelphia, Lippincott, 1969.
23 *Modern Problems of Blood Preservation*, ed. W. Spielmann, and S. Siedl. Stuttgart, Fischer, 1970.

For Debate . . .

Folate Deficiency after Anticonvulsant Drugs: An Effect of Hepatic Enzyme Induction?

J. D. MAXWELL, JOHN HUNTER, D. A. STEWART, SIMON ARDEMAN, ROGER WILLIAMS

British Medical Journal, 1972, 1, 297-299

Summary

Serum and red cell folate levels were reduced in 59% and 58% respectively of 75 children with epilepsy attending a residential school. The degree of folate deficiency was significantly related to increased hepatic microsomal enzyme activity, assessed from increased urinary excretion of D-glucaric acid and also correlated with the daily dose of anticonvulsant taken. Anticonvulsant drugs are known to have inducing properties, and since folate is required as a cofactor in drug hydroxylations it is suggested that folate depletion results from increased demand for the cofactor after induction of drug-metabolizing enzymes. As folate deficiency may ultimately limit drug metabolism this hypothesis would explain why blood phenytoin levels decrease and fit control may worsen after correction of folate deficiency in epileptic patients.

M.R.C. Group on Metabolism and Haemodynamics of Liver Disease, King's College Hospital Medical School, London S.E.5

J. D. MAXWELL, M.R.C.P., Honorary Lecturer in Medicine
JOHN HUNTER, M.R.C.P., Research Fellow
D. A. STEWART, B.SC., Research Biochemist
ROGER WILLIAMS, M.D., F.R.C.P., Director and Consultant Physician

Department of Haematology, Edgware General Hospital, Edgware, Middlesex

SIMON ARDEMAN, PH.D., M.R.C.PATH., Consultant Haematologist

Introduction

Anaemia occurring after treatment with anticonvulsant drugs was first reported in 1952,[1] and it is now recognized that the