The
PHYSIOLOGICAL BASIS
of
MEDICAL PRACTICE

A TEXT IN APPLIED PHYSIOLOGY

By

CHARLES HERBERT BEST

C.B.E., M.A., M.D., D.Sc. (Lond.), F.R.S., F.R.C.P. (Canada)

Professor and Head of Department of Physiology, Director of the Banting-Best Department of Medical Research, University of Toronto

and

NORMAN BURKE TAYLOR

V.D., M.D., F.R.S. (Canada), F.R.C.S. (Edin.), F.R.C.P. (Canada), M.R.C.S. (Eng.), L.R.C.P. (Lon.)

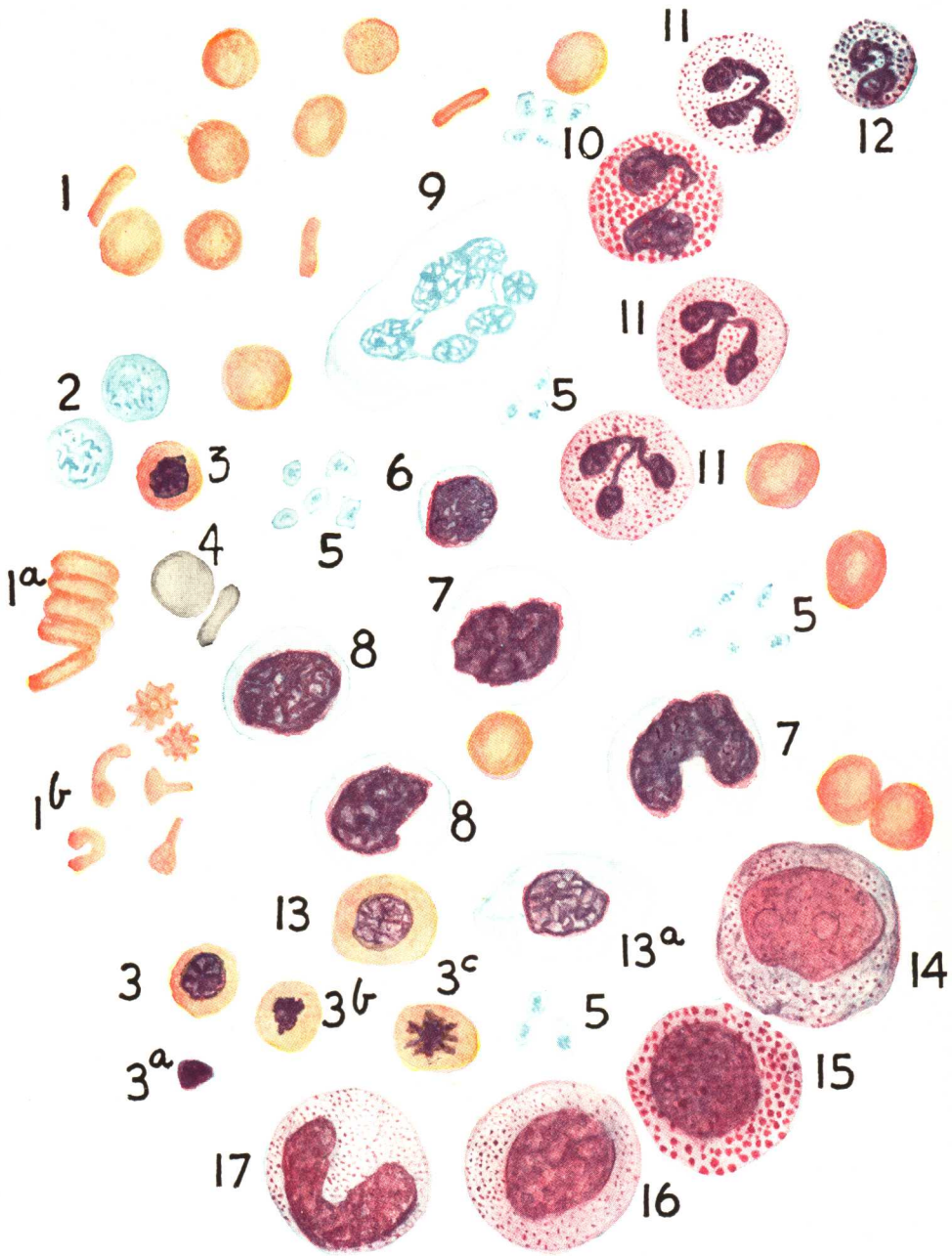
Professor of the History of Medicine and Medical Literature, University of Western Ontario, London, Canada; formerly Professor of Physiology, University of Toronto

Fifth Edition

BAILLIÈRE, TINDALL & COX, LTD.

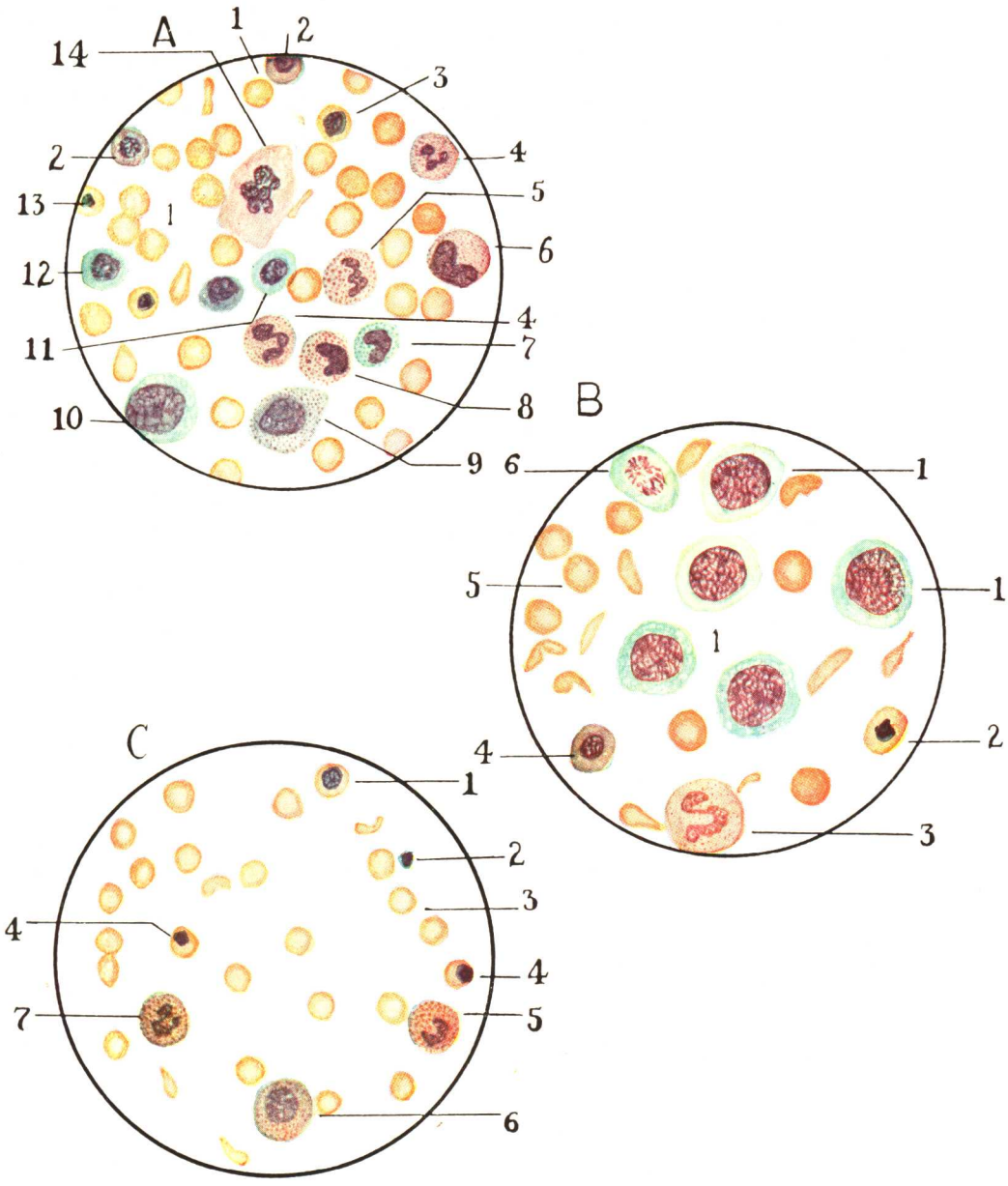
LONDON

1950



NORMAL BLOOD AND MARROW CELLS

1 Erythrocytes
1a Erythrocytes in rouleau
1b Deformed cells (poikilocytes) crenated forms
2 Reticulocytes stained with dilute solution of cresyl blue
3 Early normoblasts
3a Extruded nucleus
3b Late normoblast
3c Normoblast in mitosis
5 Platelets
6 Small lymphocyte
7 Monocytes
8 Large lymphocytes
9 Megakaryocyte
10 Eosinophil leucocyte
11 Neutrophil leucocytes
12 Basophil leucocyte
13 Polychromatophil erythroblast
13a Hemocytoblast
14 Megaloblast
15 Eosinophil myelocyte
16 Neutrophil myelocyte
17 Neutrophil metamyelocyte



Samples of bone marrow obtained by sternal puncture

A. Normal

1. Erythrocytes
2. Erythroblasts
3. Early normoblast
4. Neutrophil leucocyte
5. Eosinophil leucocyte
6. Neutrophil metamyelocyte
7. Basophil metamyelocyte
8. Eosinophil metamyelocyte
9. Neutrophil myelocyte
10. Myeloblast
11. Hemocytoblast
12. Lymphocyte
13. Late normoblast
14. Megakaryocyte

B. In pernicious anemia

1. Megaloblasts
2. Late normoblast
3. Giant neutrophil leucocyte
4. Erythroblast
5. Erythrocytes (macrocytes)
6. Megaloblast in mitosis

C. In microcytic anemia due to iron deficiency

1. Early normoblast
2. Erythrocytes (microcytes)
3. Extruded nucleus from normoblast
4. Late normoblasts
5. Eosinophil leucocyte
6. Neutrophil leucocyte

PREFACE TO THE FIFTH EDITION

The period that has passed since the publication of the last edition has been one of lively research and unusually productive; it is notable for important advances in many fields of medical science. In order to bring the text up to date its expansion has proved unavoidable. This will be regretted by many; others will deplore omissions. But an earnest effort has been made toward a critical selection of the material to be included, and, wherever feasible, accounts of recent work have been given space at the expense of other sections of the text embodying older material and which, it has been thought, could, with more justification be omitted. A very considerable proportion of the added pages has been taken up by new illustrations which number more than a hundred. Many other figures have been redrawn.

The authors have received many letters relating to some or other statement in the book; the criticisms, comments and suggestions which have been so kindly offered are most cordially welcomed. These letters seem to display an interest in the welfare of the book which has been a source of satisfaction and pleasure to us; they have been of much assistance in the preparation of this edition. We are also most grateful to many of our friends and colleagues who have sent us reprints of their articles; it is hoped that even greater numbers will be received for use in the preparation of the next edition. Since one of the authors has transferred to the staff of another university, and in order that it may be known to whom letters or reprints should be addressed, it has been thought advisable that the parts of the text originally written by this author and revised by him in succeeding editions should be shown. His responsibility has, therefore, been indicated by initials at the heads of sections.

The type for this edition, as for the last, has been entirely reset, an undertaking which, though it entails a greater labor of proof-reading, ensures maximal legibility of the printed word.

The assistance of Miss Joan Lailey in the preparation of manuscript for the press is most gratefully acknowledged. To Mrs. Dorothy Spicer who prepared copy for the later chapters, arranged the bibliography and read a part of the galley proof, and to Mrs. Kate Sheldon who has corrected proof, we also offer our thanks.

N. B. T.

PREFACE TO FIRST EDITION

Physiology is a science in its own right and the laboratory worker who pursues his researches quite detached from medical problems need offer no apology for his academic outlook. Indeed some of the most valuable contributions to medical science have been the outcome of laboratory studies whose applications could not have been foreseen. Nevertheless, we feel that the teacher of physiology in a medical school owes it to his students, whose ultimate interest it must be conceded is in the diagnosis and treatment of disease, to emphasize those aspects of the subject which will throw light upon disorders of function. The physiologist can in this way play a part in giving the student and practitioner a vantage point from which he may gain a rational view of pathological processes.

We have endeavored to write a book which will serve to link the laboratory and the clinic, and which will therefore promote continuity of physiological teaching throughout the pre-clinical and clinical years of the under-graduate course. It is also hoped that when the principles underlying diseased states are pointed out to the medical student, and he is shown how a knowledge of such principles aids in the interpretation of symptoms or in directing treatment, he will take a keener interest in physiological studies. When such studies are restricted to the classical aspects of the subject, apparently remote from clinical application, the student is likely to regard them only as a task which his teachers in their inscrutable wisdom have condemned him to perform. Too often he gains the idea, from such a course, that physiology is of very limited utility and comes to believe that, having once passed into the clinical years, most of what he has "crammed" for examination purposes may be forgotten without detriment to his more purely medical studies. Unfortunately, he does not always realize at this stage in his education how great has been the part which physiological discoveries have played in the progress of medicine, and that the practice of today has evolved from the "theories" of yesterday.

Many physiological problems can be approached only through animal experimentation. Advances in many fields, most notably in those of carbohydrate metabolism, nutrition, and endocrinology, bear witness to the fertility of this method of research. On the other hand, many problems can be elucidated only by observations upon man, and physiology has gained much from clinical research. The normal human subject as an experimental animal possesses unique advantages for many types of investigation; and in disease, nature produces abnormalities of structure and function which the physiological laboratory can imitate only in the crudest way. Within recent years the clinical physiologist, fully realizing these advantages and the opportunities afforded by the hospital wards, has contributed very largely to physiological knowledge. In many instances, clinical research has not only revealed the true nature of the underlying process in disease, but has cast a light into some dark corner of physiology as well; several examples of clinical investigation which have pointed the way to the physiologist could be cited. In the last century, knowledge of the processes of disease was sought mainly in studies of morbid *anatomy*; biochemistry was in its infancy and many of the procedures now commonly employed for the investigation of the human subject had not been devised. Today, the student of scientific medicine is directing his attention more and more to the study of morbid *physiology* in his efforts to solve clinical problems. This newer outlook has borne fruit in many fields. It has had the beneficent result of drawing the clinic and the physiological and bio-

chemical laboratories onto common ground from which it has often been possible to launch a joint attack upon disease. We feel that this modern trend in the field of research should be reflected in the teaching of medical students, and have therefore given greater prominence to clinical aspects of the subject than is usual in physiological texts.

In order to understand the function of an organ it is usually essential to have a knowledge of its structure. For this reason we have followed the plan of preceding the account of the physiology of a part by a short description of its morphology and, in many instances, of its nerve and blood supply. The architecture and functions of the central nervous system are so intimately related that some space has been devoted to a description of the more important fiber tracts and grey masses of the cerebrum, cerebellum and spinal cord.

We wish to thank our colleagues in physiology, biochemistry and anatomy whom we have drawn upon on so many occasions for information and advice; without their generous help the undertaking would have been an almost impossible one. We are also deeply grateful for the unstinted assistance which we have received from our friends on the clinical staff, several of whom have read parts of the text in manuscript or in proof. We wish especially to acknowledge our indebtedness to Professor A. M. Wynne, who has written the section on the oxidizing systems of living cells, to Dr. J. K. W. Ferguson for his collaboration in the preparation of Chapter 33, and to Professor C. B. Weld and Dr. E. T. Waters whose stimulating criticisms and sound counsel have been invaluable.

Finally, we wish to thank our secretaries, Miss Mabel Cory and Miss Dudley Martin, who have spent so many tedious hours in preparing the manuscript for the press, in checking the references and in compiling the index.

C. H. B.
N. B. T.

October 15, 1936

CONTENTS

SECTION I. THE BLOOD AND LYMPH

SECTION II. THE CIRCULATION OF THE BLOOD

SECTION I. THE BLOOD AND LYMPH

By N. B. T.

CHAPTER 1

THE PHYSIOLOGICAL PROPERTIES, PHYSICAL CHARACTERS AND COMPOSITION OF THE BLOOD

Outline of the Functions of Blood

In animals (Metazoa) whose bodies are composed of many cells the blood serves those purposes, which for unicellular organisms (Protozoa) are carried out by the fluid medium, the salt or fresh water, which surrounds them and bathes their surfaces. For example, an organism such as the amoeba acquires oxygen by diffusion directly from the environment into the interior of the cell. Similarly the carbon dioxide diffuses outwards. The processes of nutrition and the excretion of the products of the cell's metabolism are accomplished in a manner equally simple. Food is taken in through the cell membrane either in solution or as particulate matter, and waste products pass into the surrounding medium. Other requirements of this organism, such as the maintenance of an optimum temperature and the proper degree of moisture, are dependent on the immediate environment.

The elemental needs of each cell in a multicellular form from the most primitive type to the highest vertebrate are the same as for the unicellular organism; yet in the evolution of the higher forms the cells composing their bodies have become farther and farther removed from immediate contact with the outside world. Myriads of cells have become packed together, and the deeper ones could not possibly satisfy their needs after the direct and simple fashion of the unicellular forms. The more primitive multicellular types overcame the difficulty by the development of canal systems which opened upon their exteriors and through which the ocean waters flowed freely in and out, bringing oxygen and aliment to the more deeply lying cell and bearing carbon dioxide and other excretory products away. This, the first attempt at a circulation, was an open one. As higher forms evolved the circulation became closed and the waters of the environment no longer flowed and ebbed through the body. No longer could the interchange of the respiratory gases and the absorption of nutriment be carried out in this direct and simple way. Yet the vessels of this closed circulatory system were filled with a fluid which took the place of and fulfilled the duties of the watery environment of the more primitive types. The blood and other body fluids may be looked upon as that environment which has become enclosed within the bodies of the higher forms, and has undergone certain modifications in its composition to meet the requirements of the more specialized cells which it bathes.

The similarity between the compositions of sea water and blood which has been stressed by the researches of Macallum lends support to these views on the evolution of the blood.[1] This brief account will also serve as an introduction to a consideration of the functions of the body fluids, since their duties are to satisfy in the same way as did their prototype, the requirements of the individual cells.

(1) *Respiratory.* The transport of oxygen from the air in the lungs to the tissues, and of carbon dioxide from the tissues to the lungs.

(2) *Nutritive.* The conveyance of food materials, glucose, amino acids and fats from the alimentary canal to the tissues.

(3) *Excretory.* The removal of waste products of metabolism, e.g., urea, uric acid, creatinine, etc.

(4) *The maintenance of the water content of the tissues.* Though the blood itself is contained within vascular channels a constant interchange of fluid through the vessel walls takes place. This fluid which has left the blood vessels and come into direct contact with the tissue cells is known as the tissue or interstitial fluid. It closely resembles the blood fluid in chemical composition. Through the medium of the transuded fluid the final stage in the transportation of oxygen and food materials to the tissues and the first stage in the journey of CO_2 and waste products from the tissues are made.
(5) *To regulate body temperature.* The body owes its ability to regulate its temperature (ch. 54) largely to the water of the blood and tissue fluids. Water possesses

[1] Sea water of today differs from blood serum in having a total salt concentration of about 3 per cent, a much higher concentration of magnesium and a lower concentration of potassium. But Macallum points out that the sea water of the geological period when the ancestors of mammalian forms adapted themselves to a terrestrial life was probably closely similar in its inorganic composition to blood serum.

three qualities which fit it pre-eminently to fulfil this purpose.

(a) The *specific heat*[2] of water is considerably higher than that of any other liquid or solid. On account of this great heat storage power of water, sudden changes of body temperature are avoided and even a cold-blooded animal such as the frog has, due to this purely physical quality, some ability to maintain a relatively constant body temperature gainst transient fluctuations in environmental temperature. A man of average weight develops 3000 Calories in 24 hours. This amount of heat is capable of raising the temperature of his tissues (which are mostly water) only about 32°C. Heat elimination (radiation, etc.) is able to keep pace with heat production and the body temperature varies but slightly within normal limits. But it has been pointed out by L. J. Henderson that if the tissues had the low heat storage capacity (spec. heat) of most substances, an amount of heat equal to 3000 Calories would raise the temperature of the tissues and fluids of the body by from 100°–150°C.

(b) *High conductivity.* The thermal conductivity of water is greater than that of any other ordinary liquid. The advantage of this in the dissipation of heat from deeply situated regions of the body is obvious.

(c) *High latent heat of evaporation.* More heat is required for the vaporization of water than for that of an equivalent amount of any other liquid. 1 cc. of water requires about 0.6 Calories for its vaporization. This figure is 50 per cent higher than that of water's closest competitor. Fluid is being constantly lost from the body through evaporation from the lungs and skin. A large amount of heat is lost in the process (ch. 54).

These physical properties of water which make it ideal as a heat regulating medium are enhanced by other purely *physiological factors.* The mobility of the blood, and the readiness with which it may be quickly redistributed in the body, combined with the unique physical properties of the fluid itself, render it so highly efficient as a regulator of body temperature. The blood may in a moment be brought from deeper to superficial regions and spread out in fine vessels over a broad area just beneath the skin, and in this way will greatly increase the radiation of heat. At another instant, in order that heat may be conserved, the fluid is drained from the surface areas and collected in the deeper parts of the body—internal organs, muscles, etc.

(6) *Protective and regulatory.* The blood and lymph contain certain chemical substances of a complex nature, antitoxins, lysins, and other antibodies, which are the basis of the body's defence against injurious agents of various kinds. The circulating fluids are also the vehicle by which the hormones of the different ductless glands are brought into direct contact with the cells of the tissues.

[2] The specific heat of a substance is defined as the number of calories required to raise 1 gram of the substance one degree Centigrade.

The Composition of Blood

The blood is a highly complex fluid in which solid elements are suspended—the *corpuscles or blood cells.* Its specific gravity is from 1.050 to 1.060 and its viscosity from 5 to 6 times that of water. If blood is centrifuged before it has had time to clot, or if clotting is prevented by special means (p. 116), the solid elements are thrown down and separated from the fluid portion. The latter is called the *plasma* and contains *proteins,* as well as many organic and inorganic substances in solution —nutritive and excretory materials, antibodies and hormones, and other substances of an unknown or imperfectly known chemical constitution. The specific gravity of plasma is normally around 1.027 but varies with the protein concentration. The cells constitute about 46 per cent of the volume of human blood, the plasma 54 per cent. Small variations above or below these values are commonly met with.

The specific gravity of a small sample of blood or of plasma may be measured by the method of Phillips, Van Slyke and associates. A series of small bottles is set up containing copper sulfate solutions varying by small equal increments (0.004) in specific gravity. A drop of blood or plasma is allowed to fall from the tip of a medicine dropper into each of a number of the bottles whose solutions are within the expected specific gravity range of the blood or plasma sample. The tip of the medicine dropper should be held about 1 cm. above the surface of the solution. The drop of blood or plasma, upon entering the solution, becomes coated with a film of copper proteinate and remains suspended, neither rising nor falling for a few seconds, if it is of the same specific gravity as the solution; thus, since the specific gravity of the solution is known, that of the blood or plasma is indicated (Fig. 1).

In the following table are given the constituents of the blood, grouped upon a physiological basis.

Whole blood:
- *A. Cells:*
  - (1) Red corpuscles or erythrocytes
  - (2) White corpuscles or leucocytes
  - (3) Platelets or thrombocytes
- *B. Plasma:*
  - (1) *Water,* 91 to 92 per cent
  - (2) *Solids,* 7 to 9 per cent
    - (a) *Proteins,* 7 per cent. Serum albumin, serum globulin and fibrinogen.[3]

[3] Plasma from which the fibrinogen has been removed through clotting (ch. 12) is spoken of as serum.

(b) *Inorganic constituents*, 0.9 per cent. Sodium, calcium, potassium, magnesium, phosphorus, iodine, iron, copper, etc.

FIG. 1. Description in text. (After Phillips and Van Slyke, redrawn).

(c) *Organic constituents* (other than (a) and (d)). Non-protein nitrogenous substances, (urea, uric acid, xanthine, hypoxanthine, creatine and creatinine, ammonia and amino acids) neutral fats, phospholipids, cholesterol, glucose.

(d) *Internal secretions, antibodies and various enzymes, amylases, proteases, lipases, esterases, etc.*

INORGANIC CONSTITUENTS

The concentration of the plasma in the various inorganic materials is given in table 1.

It will be noted that the plasma is relatively rich in sodium and calcium but poor in potassium and magnesium whereas in the cells conditions are reversed. The cells show a relatively high concentration in potassium and magnesium, but are lacking in calcium and have a low concentration of sodium (human). In the blood of some species sodium is absent or present only in traces. Except for a minute amount of iron in the plasma, this element is confined to the red cells and the greater part of it is attached to the hemoglobin molecule (ch. 6). It has been suggested that the small quantity of non-hemoglobin iron in the erythrocyte is bound loosely with the lecithin of the cell stroma (p. 9).

Phosphorus

Phosphorus exists in blood in four main forms. One of these is *inorganic phosphorus* (orthophosphate). The three other phosphorus fractions are in *organic* combination and are as follows.

a. *Ester phosphorus*, e.g., diphosphoglycerate, adenosinetriphosphate, hexose phosphates, glycerophosphate.

b. *Lipid phosphorus*, e.g., the phosphatides lecithin, cephalin, sphingomyelin.

c. *Nucleic acid phosphorus.*

TABLE 1

Inorganic constituents of plasma, red cells and whole blood, milligrams per 100 cc. average values

	SODIUM	POTASSIUM	CALCIUM	MAGNESIUM	CHLORINE	IODINE	IRON	COPPER	PHOSPHATE	SULFATE	TOTAL BASE CC. N/10 NaOH
Plasma	340	20	10	2.7	370		0.2				160
Cells	20	410	0	6.0	190		100.0				
Whole blood	190	220	5.2	4.0	250	0.01	50.0	0.1	3.0	2.0	

The concentrations of these various inorganic constituents are also commonly expressed as milli-equivalents (m.equ.) per liter. Thus serum contains 100 mgm. of calcium per liter. The molecular weight of Ca is 40.07. So being divalent its milli-equivalent is 20.03. The concentration of calcium in serum is therefore $\frac{100}{20.03} = 4.9$ milli-equivalents per liter. Sodium is monovalent and has a molecular weight of 23; serum therefore contains $\frac{3400}{23} =$ 147.8 m.equ. per liter.

According to Kay the nucleic acid phosphorus in normal human blood is negligible. It is derived from the nuclei of white cells and the reticulum of the reticulocytes. In abnormal blood containing a large number of leucocytes, reticulocytes or nucleated red cells this fraction may however constitute a considerable proportion of the total phosphorus.

The inorganic phosphorus (3 mgm. per 100 cc.) is according to most observers about equally distributed between cells and plasma. The quantity of organic phosphorus in blood is many times greater than the inorganic. In whole blood it amounts to from 35 to 40 mgm. per 100 cc. and the greater proportion of this is in the cells.

The inorganic and ester fractions are extracted from blood by the precipitation of the proteins with trichloracetic acid and filtering. The phosphorus contained in the filtrate is spoken of as the acid soluble phosphorus. Upon extraction of blood with alcohol-ether the lipid phosphorus is obtained. The phosphorus of blood is therefore separable into two classes.

(1) *The acid soluble which includes*
   (a) Inorganic phosphorus
   (b) Ester phosphorus
(2) *Alcohol-ether soluble*, i.e., lipid phosphorus.

} organic phosphorus

The ester, or organic acid-soluble phosphorus is obtained by determining the total acid soluble P and subtracting from it the inorganic phosphorus. Of the ester phosphorus, all of which is intracellular, about one-quarter is hydrolyzable by bone phosphatase (ch. 60). The hydrolyzable portion is mainly adenosinetriphosphate, and the non-hydrolyzable part mainly diphosphoglycerate. Since the nucleic acid phosphorus is negligible in normal blood, the acid soluble + the alcohol-ether soluble phosphorus equals the total phosphorus as determined by wet-ashing.

In the following table is given the distribution of inorganic, ester and lipid phosphorus in normal blood.

Phosphorus in whole blood

Milligrams per 100 cc., average figures

1. Total Phosphorus	40
2. Total acid soluble—90 per cent in cells	27
3. Inorganic—in cells and plasma	3*
4. Ester (2–3)—practically all in cells	24
5. Lipid (1–2)—in cells and plasma	13

The phosphorus compounds of the blood and tissues play an important role in maintaining the electrolyte equilibrium within the red cells and in regulating the acid base balance. Diabetic acidosis, for example, and the acidosis induced by the ingestion of ammonium chloride, are accompanied by increased excretion of phosphorus in the urine and a pronounced reduction of the organic acid-soluble phosphorus in the blood cells. Reverse changes occur in alkalosis; the reduction in the chloride of the blood following pyloric obstruction, and the alkalosis caused by over-breathing are associated with a reduction in the urinary excretion of phosphates and an increase in the inorganic and ester phosphorus of the blood. In renal insufficiency, the inorganic phosphorus in the plasma and cells and the ester phosphorus (diphosphoglycerate) in the cells are greatly increased. The inorganic and ester phosphorus are reduced in rickets but a rapid increase accompanies the healing process. The inorganic phosphorus is diminished after the injection of insulin and in hyperparathyroidism (ch. 60). In anemias associated with high reticulocyte counts and in leukemia, the concentration of ester phosphorus in the blood is increased. The inorganic phosphorus is increased in some forms of tetany.

* In infants and young children, the inorganic phosphorus is from 1 to 3 mgm. per cent higher than it is in adults.

ORGANIC CONSTITUENTS

Plasma proteins

The concentration of total protein in the plasma and the proportions of the three fractions—*albumin*, *globulin* and *fibrinogen*—vary from species to species but under ordinary conditions of health remain relatively constant between individuals of the same species.

Serum globulin can be separated into two fractions—*euglobulin* and *pseudoglobulin*—by "salting out"; or into three fractions—α, β and γ-*globulins* —by electrophoresis. The euglobulin is thrown out of solution by saturation with NaCl, half-saturation with $MgSO_4$, or one-third saturation with $(NH_4)_2SO_4$; it is insoluble in water. The pseudoglobulin is not "salted out" by NaCl but is thrown down by saturation of its solution with $MgSO_4$ or half-saturation with $(NH_4)_2SO_4$. It is soluble in water.

α, β and γ-globulins have isoelectric points of 5.1, 5.6 and 6.0, respectively. It is questionable whether these fractions are distinct chemical entities. It is more probable that they are merely artificially produced as a result of the methods of treatment employed. In other words, it is likely that serum globulin is a single large molecule which is split into two or three separate parts by laboratory manipulation. Yet however this may be, the gamma-globulin is more intimately associated with antibody production, and undergoes an increase in many acute and chronic infections.

Pseudoglobulin contains 85 per cent alpha-globulin and 15 per cent gamma-globulin, whereas, euglobulin contains less alpha but more of beta and gamma globulins.

The several electrophoretic[4] fractions of plasma protein are not pure; all contain lipid and carbohydrate material combined probably as prosthetic groups. The albumin fraction also contains bilirubin (ch. 41). It has been estimated that at least 50 per cent of the lipid and carbohydrate content of serum is bound to the albumin and gamma-globulin fractions. Other substances, e.g. calcium, phosphorus, sulfonamide drugs and the dye T-1824 (p. 17) are bound to the albumin fraction.

Fibrinogen has been isolated and prepared in crystalline form. X-ray diffraction studies indicate that its molecule is structurally similar to such fibrous proteins as collagen and myosin (see p. 623). The molecular weights of the plasma proteins are given in Chapter 36.

Protein fractions in human plasma

FRACTIONATION BY ELECTROPHORESIS	*grams/100 cc.*	FRACTIONATION BY SALTING OUT WITH SODIUM SULFATE	*grams/100 cc.*
Total protein	6.03–6.72	Total protein	6.0–8.0
Albumin	3.32–4.04	Albumin	4.3–5.0
Total globulin	2.23–2.39	Total globulin	1.1–3.1
Alpha globulin	0.79–0.84	Euglobulin	0.1–0.4
Beta globulin	0.78–0.81	Pseudoglobulin	1.0–2.7
Gamma globulin	0.66–0.70		
Fibrinogen	0.34–0.43	Fibrinogen	0.2–0.3
Albumin/globulin ratio	1.00	Albumin/globulin (A/G) ratio	1.50

In some animals the globulin is equal to or exceeds the albumin. Of the three fractions fibrinogen is always in lowest concentration and it is considerably lower in human plasma than in that of some animals (e.g., 0.58, 0.72, 0.60 gram per 100 cc. in dog, cow and goat respectively).

The total plasma protein can be calculated from the specific gravity of the plasma by means of line charts, or by using the formula $P = K (S - A)$, where P is the plasma protein in grams per 100 cc., S the specific gravity and K and A are constants with values of 364 and 1.006, respectively. Thus, if the specific gravity is 1.026, the protein in grams per 100 cc. is 7.28 (364 (1.026–1.006)).

The values of total protein and of the different fractions in human plasma are given in the table above.

PATHOLOGICAL VARIATIONS IN CONCENTRATION.

The several protein fractions of plasma may change in value independently of one another, and either with or without alteration in the quantity of total protein; in several pathological states the albumin and globulin fractions may change in opposite directions, i.e. a fall in albumin accompanied by a rise in globulin.

The fibrinogen concentration is increased in *pregnancy* and *menstruation*, in *tissue injury* of various kinds, in *parathyroid overdosage*, *acute infections*, *malaria* and several other conditions. This fraction is markedly reduced in animals after hepatectomy or severe liver damage and in several diseases involving the liver. In rare instances it is congenitally considerably below normal or absent.

In *hemorrhage* a loss of all fractions of plasma protein occurs, their concentrations are also diminished as well, since the blood volume is at first made good by the passage of a saline solution or one of low protein concentration from the tissue spaces into the blood stream. In extensive *burns*, on the other hand, especially during the following few days, all fractions are reduced as a result of the leakage of blood fluid from the denuded surface and into the tissues in the region of the burned area; but since the lost fluid is usually relatively low in its content of protein, the protein concentration of the plasma tends towards an increase. In *cirrhosis of the liver*, *chronic hepatitis* (depressed synthesis by liver), *chronic infections*, the albumin fraction is reduced.

In *nephrotic* and *nephritic conditions* (due to loss of albumin in the urine) and in severe *malnutrition* (owing to the low intake of the necessary amino-acids for protein synthesis) the albumin fraction is also reduced. As a result of the diminished concentration of albumin, the oncotic pressure of the plasma tends to fall, less water is held in the vessels and, as a consequence, the plasma volume is reduced. As a consequence of these changes, the globulin, though not raised absolutely, shows increased concentration. In any condition asso-

[4] The usual method used today in electrophoresis (i.e. the migration of charged particles in an electric field to cathode or anode) of protein in a suitable buffer solution and other colloidal systems is that carried out with the apparatus of Arn Tiselius, in which the moving boundaries formed between the protein and buffer solutions are recorded graphically by optical methods. The different proteins of serum are separable upon the basis of the rates and direction of movement of their boundaries. The most rapidly moving boundary is that of the smaller albumin molecule. Alpha, beta and gamma-globulins have much slower rates but of the three the alpha fraction has the fastest rate, and the gamma globulin the slowest. By ultra-violet photography a characteristic electrophoretic pattern of these boundaries is obtained, which shows a series of peaks corresponding to the individual proteins in the solution. The albumin peak is by far the highest.