Essentials of physiology / by F.A. Bainbridge and J. Acworth Menzies.

Contributors

Bainbridge, F. A. 1874-1921.
Menzies, James Acworth, 1869-1921.

Publication/Creation

London : Longmans, Green, 1920.

Persistent URL

https://wellcomecollection.org/works/dyygzq29

License and attribution

This work has been identified as being free of known restrictions under copyright law, including all related and neighbouring rights and is being made available under the Creative Commons, Public Domain Mark.

You can copy, modify, distribute and perform the work, even for commercial purposes, without asking permission.

wellcome collection

Wellcome Collection
183 Euston Road
London NW1 2BE UK
T +44 (0)20 7611 8722
E library@wellcomecollection.org
https://wellcomecollection.org

I. R. H-O

804

22101017706

Digitized by the Internet Archive
in 2019 with funding from
Wellcome Library

https://archive.org/details/b31348610

ESSENTIALS OF PHYSIOLOGY

THE ESSENTIALS OF HISTOLOGY: Descriptive and Practical. By Sir EDWARD SHARPEY SCHAFER, M.D., Sc.D., F.R.S., Professor of Physiology in the University of Edinburgh. With 645 Illustrations, many of which are coloured. 8vo.

THE ESSENTIALS OF MORBID HISTOLOGY, for the Use of Students. By ALBERT S. F. LEYTON, M.A., M.D., F.R.C.P., D.P.H., formerly Professor of Pathology, University of Leeds. With 151 Illustrations, 22 in Colour. 8vo.

THE ESSENTIALS OF CHEMICAL PHYSIOLOGY. By W. D. HALLIBURTON, M.D., F.R.S., F.R.C.P., Professor of Physiology in King's College, London. With Illustrations. 8vo.

LONGMANS, GREEN, & CO.,

LONDON, NEW YORK, BOMBAY, CALCUTTA AND MADRAS

ESSENTIALS OF PHYSIOLOGY

BY

F. A. BAINBRIDGE

M.D. (CANTAB.), D.Sc. (LOND.), F.R.C.P., F.R.S.

PROFESSOR OF PHYSIOLOGY, UNIVERSITY OF LONDON

AND

J. ACWORTH MENZIES

M.A. (DUNELM.), M.D. (EDIN.)

PROFESSOR OF PHYSIOLOGY, UNIVERSITY OF DURHAM

FOURTH EDITION

WITH 194 ILLUSTRATIONS

LONGMANS, GREEN, AND CO.

39 PATERNOSTER ROW, LONDON

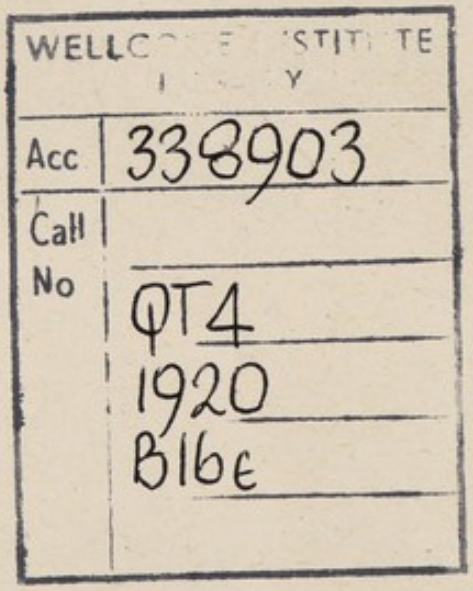
FOURTH AVENUE & 30TH STREET, NEW YORK

BOMBAY, CALCUTTA, AND MADRAS

1920

All Rights Reserved

WELLCOME
LIBRARY
INSTITUTE


WELLCOME INSTITUTE
LIBRARY
Acc
338903
Call
No
QT4
1920
B16e

WELLCOME
HISTORICAL
MEDICAL
LIBRARY

PREFACE

Our object in writing this book has been to bring together in a concise form the fundamental facts and principles of Physiology, primarily with the object of meeting the requirements of the medical student preparing for a pass examination in the subject of Physiology. Considerations of space have led us to exclude as far as possible histological details and descriptions of chemical and experimental methods which form part of each student's laboratory course, and for which separate text-books are used. We have also omitted, for the same reason, all matter of purely historical interest.

In view of the transitional state of anatomical nomenclature, we have, after much consideration, retained the terminology hitherto used in this country, and have inserted the Basle nomenclature in brackets.

While it is impossible to mention all the sources upon which we have drawn, we wish to acknowledge our especial indebtedness to Prof. E. H. Starling, not only for permission to use many figures from his *Principles of Physiology*, but also for advice and information on many points. Our thanks for permission to use figures, which are as far as possible separately acknowledged in the text, are also due to Prof. Sir E. Sharpey Schafer (*Quain's Anatomy* and *Essentials of Histology*), Professor J. N. Langley (*Journal of Physiology*), Dr. M. S. Pembrey (*Practical Physiology*), J. Barcroft, Esq. (*Respiratory Function of the Blood*), Dr. A. Hurst, Dr. Homans, Dr. W. E. Hume, Professor R. Howden (*Gray's Anatomy*), and the Council of the Royal Society. We must also thank the Publishers and others who have kindly supplied us with blocks, namely, Messrs. J. & A. Churchill, Hodder & Stoughton, Macmillan & Co., Ltd., Mr. Edward Arnold, the Cambridge University Press, Messrs. Baird & Tatlock, Ltd., and Messrs. Hawksley.

Finally, we are indebted to Miss F. H. Miller for her unwearying efforts in the production of the original illustrations, and to Messrs. Longmans, Green, & Co. for the great pains they have taken in the reproduction of the figures.

F. A. BAINBRIDGE.
J. ACWORTH MENZIES.

PREFACE TO THE FOURTH EDITION

THE present edition follows so closely on the previous one that no extensive alteration in the text has been necessary, but the opportunity has been taken to revise the whole book thoroughly; to re-write various sections with a view to greater clearness, for example, that on the Brain Stem and that on Enzymes; and to add a number of new figures.

Our thanks are due to Mr. G. Winfield, M.A., for the loan of the preparation from which Fig. 74 was drawn, and for much kind assistance; to Professors Cushny and Plimmer, and to Messrs. Hawksley for the use of blocks; to Messrs. T. P. Collings and Co. for the excellent way in which they have drawn and reproduced the new figures; and to Mr. G. A. Clark, M.B., for his kind help in reading the proof-sheets.

F. A. BAINBRIDGE.
J. ACWORTH MENZIES.

August 1920.

CONTENTS

CHAPTER		PAGE
I.	Introductory	1
II.	Chemistry of the Body	5
III.	Muscle	20
IV.	The Nervous System	
	Section 1. The Neuron	39
	,, 2. The Nerves	44
	,, 3. The Structure of Spinal Cord	55
	,, 4. Conduction in Spinal Cord	59
	,, 5. Reflex Action	66
	,, 6. The Brain Stem	77
	,, 7. The Cerebellum	84
	,, 8. The Fore-Brain	89
	,, 9. The Cerebro-spinal Fluid	109
	,, 10. The Autonomic System	111
V.	The Organs of Sense	
	Section 1. Cutaneous	118
	,, 2. Taste and Smell	125
	,, 3. The Sense of Sight	127
	,, 4. The Sense of Hearing	156
	,, 5. Proprioceptive Senses	168
VI.	The Blood	174
VII.	The Vascular Mechanism	198
	Section 1. General Features of the Circulation	198
	,, 2. The Phenomena of the Normal Heart-Beat	214
	,, 3. The Pulse	230
	,, 4. The Causation of the Heart-Beat	235
	,, 5. The Regulation of the Vascular Mechanism	245
	,, 6. The Lymph	269

CONTENTS

CHAPTER PAGE

VIII. The Respiratory System

Section 1. The Respiratory Movements . . . 27
„ 2. The Chemistry of Respiration . . . 28
„ 3. The Regulation of Respiratory Movements . 29
„ 4. Tissue-Respiration 31
„ 5. The Effect of Changes in Barometric Pressure 31
„ 6. The Influence of the Respiratory Movements on the Circulation 31
„ 7. Muscular Exercise 31

IX. The Digestive System

Section 1. The Nature of Digestion 32
„ 2. Changes in the Food in the Mouth . . 32
„ 3. Deglutition 33
„ 4. Gastric Digestion 33
„ 5. Intestinal Digestion 35
„ 6. Absorption 37
„ 7. The Large Intestine 37

X. Metabolism

Section 1. Methods of Investigation 38
„ 2. The Metabolism of Fat 38
„ 3. The Metabolism of Carbohydrate . . 39
„ 4. The Metabolism of Protein . . . 40
„ 5. Total Metabolism 40
„ 6. The Liver and Spleen 41

XI. The Skin and Animal Heat 41

XII. Food and Diet 42

XIII. The Urinary System

Section 1. The Structure of the Kidney and Composition of Urine 43
„ 2. The Formation of Urine 44
„ 3. Micturition 45

XIV. The Ductless Glands 45

XV. Reproduction 47

Index 48

ESSENTIALS OF PHYSIOLOGY

CHAPTER I

INTRODUCTORY

EVERY living structure is derived, so far as our present knowledge goes, from another living structure, and exhibits certain well-marked features. It takes up non-living material and builds it up in a more or less modified form into its own framework, it has the power of growing up to a certain limit, and it is capable of giving rise to other living organisms like itself. Further, it has the property of irritability, that is, it may be affected by a change in its immediate surroundings which is called a stimulus, and to which it responds by some change in itself, usually movement or secretion. These manifestations of life form the subject-matter of the science of Physiology, which naturally falls into two divisions, Vegetable and Animal. With the former of these, however, we are not here concerned.

The functions of animal life may be studied in their most primitive condition in a unicellular organism, such as amœba. This minute creature may be observed under the microscope to enfold particles of food material, to assimilate what is useful in these particles, and to reject what is useless ; it may be seen to respond to chemical or mechanical stimuli by movement, sometimes contracting into the smallest bulk by becoming spherical, at other times protruding part of its substance and transferring itself, as it were, into the protruded part, thereby changing its position. It may also be observed at a certain stage in its life to divide into two, and each of the young amœbæ so produced grows until it too gives rise in its turn to another generation.

In the higher animals the body is composed of a multitude of cells, and this complexity of structure is accompanied, as in a community of persons, by a specialisation of function whereby certain cells are modified to subserve movement, others to produce

secretions, and so on ; in this way the efficiency of the organism as a whole is increased. In such a community of cells it is clearly of the utmost importance that the various groups should work in harmony, and, to ensure this, they must be linked up by some controlling mechanism.

Two such mechanisms are found in the body : (1) a system of chemical messengers, or *hormones*, and (2) the *nervous system*. The former is the more primitive of the two methods. A hormone is produced in one organ and is carried by the blood to another, exciting or restraining its activity. For example, as the acid contents of the stomach pass into the bowel they lead to the production of a hormone in the intestinal wall. The newly formed substance is taken up by the blood and carried to the pancreas, which it stimulates to secrete the juice required for the next stage of the digestive process. Such a method of communication is comparatively slow, and, where rapidity of transmission is important, the messages are conveyed by the nervous system. The latter, in fact, bears much the same relation to the blood-current as the telegraphic system bears to ordinary letter post. Thus, if a foreign body touches the surface of the eyeball, information of the fact is sent along certain nerve-fibres to the brain, and impulses return to the muscles of the eyelids, causing the lids to close, within a small fraction of a second.

In any living organism the unit of structure is a minute, jelly-like mass known as a *cell*. The simplest organisms consist of a single cell, those which are higher in the scale of life being composed of many cells. Each cell is composed of a semi-fluid material, known as protoplasm, containing a denser circumscribed structure, the nucleus. In some cases a well-defined cell-envelope exists, notably in vegetable cells and in the mammalian ovum, but in many animal cells no definite envelope can be demonstrated, and in these the boundary is probably determined by the condensation of molecules which is known to take place at the surface of colloidal solutions, and which is related to the physical condition known as surface tension.

Protoplasm is semi-transparent, and may be homogeneous in appearance, or may show traces of structure in the form of a network containing hyaline fluid in its meshes. It often contains granules which represent the products of its activity. Such granules are especially seen in secreting cells, and occupy corresponding spaces in the cell-protoplasm. Protoplasm itself varies greatly in composition, but it always contains a large proportion of albuminous substances or proteins.

The *nucleus* is essential to the life of the cell. When a cell is divided into a part which contains the nucleus and a part which

does not, an experiment which may be performed with the larger unicellular organisms, the part separated from the nucleus becomes inactive and dies. Further, when cell-division occurs, the nuclear changes which lead to the formation of two daughter-nuclei precede the division of the protoplasm. The nucleus also differs in chemical composition and in staining reactions from the rest of the cell. It contains a substance called nuclein, which is a compound of nucleic acid with protein. Nucleic acid is distinguished by containing a considerable proportion of phosphorus in its molecule.

In the animal body cells vary in size, shape, and minute structure in accordance with their function. Thus a secretory cell is usually somewhat cubical in shape and contains granules, while many nerve-cells are distinguished by their large size, characteristic branches, and spherical nucleus. Fibres are formed in the body either as a result of the activity of cells, as, for example, the fibres of connective tissue, or by modification of the cells themselves, as is the case with the different kinds of muscle-fibres.

Further, specific cells, or structures developed from cells, are grouped together to form tissues or organs. Examples of the former are connective tissue, bone, and muscle ; of the latter, liver, spleen, and thyroid gland.

In the human body all the tissues and organs subserve, directly or indirectly, the production of movement, whether that takes the form of locomotion, work, speech, or writing. The nervous and muscular tissues are the master tissues of the body, the remaining tissues and organs being designed for their protection and nutrition. The bony skeleton forms a framework which is necessary for the carrying out of movements, and which shields the brain and other important structures from injury. The skin is also protective in function, and with the eye, ear, and other sense-organs it receives impressions from the outer world which are of service in determining the bodily activities. The digestive tract converts insoluble food substances into soluble bodies, which are then absorbed into the blood. The circulatory system conveys the blood to all the cells and tissues of the body so that they receive nourishment. The blood also receives from the cells and tissues the waste products formed by their activity and carries these to the lungs and kidneys, by which they are excreted. In addition to excreting one of the waste products, carbonic acid, the lungs take up oxygen from the air and convey it to the blood, from which it passes to the cells and tissues. Further, in addition to the glands which secrete the digestive and other juices, there are in the body certain glands whose

function it is to produce various hormones. All these subsidiary systems are only of importance in that they serve to sustain the muscular and nervous structures. The muscular system, in its turn, is to be looked upon as the organ of expression of the nerve-centres. The life of the body, therefore, consists ultimately in its nervous activities.

CHAPTER II

THE CHEMISTRY OF THE BODY

The body of an animal is composed of water, organic compounds, and inorganic salts. If the body, or any part of it, be dried at a temperature of 150° C., the loss of weight indicates the amount of water present. If the dried solids be exposed to a high temperature in the presence of oxygen, the organic compounds are all oxidised, and the residue consists of the inorganic matter.

THE INORGANIC SALTS

The chief salts which are found in the body are the chlorides, phosphates, sulphates, and carbonates of sodium, potassium, calcium, and magnesium. Iodine, fluorine, and a few other chemical elements are also present in small amount ; iron enters into the composition of the coloured corpuscules of the blood. Generally speaking, sodium is the base most largely present in the fluids of the body, such as the plasma of the blood, and potassium is that most abundant in the cells and tissues ; while the bones owe their rigidity to the large proportion of calcium phosphate and carbonate which they contain.

The functions of the inorganic salts are various, and are not yet completely understood. Sodium, potassium, and calcium have individually a deleterious effect on muscle and possibly on other cells and tissues ; but in the blood and tissue-fluids they are present in such proportions that they are "physiologically balanced," and have jointly a favourable effect upon muscular contraction, notably upon that of the heart. Sulphates and phosphates are to some extent waste products derived from the breaking down of organic compounds. Phosphates also serve a useful purpose in maintaining the balance between acids and bases in the body by undergoing change from mono- to di-hydrogen phosphate, or the reverse, as occasion requires. The salts as a whole, but especially the chlorides, have,

moreover, important functions depending upon their physical properties (p. 15).

THE ORGANIC COMPOUNDS

The organic constituents of the body fall naturally into two main groups, non-nitrogenous and nitrogenous. The substances comprised in these two groups may be looked upon as fragments of the protoplasm or living material of the cell, for analysis necessarily involves the death of the living structure. It is clear, however, that protoplasm itself is largely composed of nitrogenous material, though it derives much of the energy necessary for its activities from the combustion of the non-nitrogenous compounds.

THE NON-NITROGENOUS SUBSTANCES

These again fall into two groups: (1) those in which the combined oxygen is sufficient to oxidise all the hydrogen of the molecule, and (2) those in which the oxygen is insufficient to combine with the hydrogen of the molecule.

(1) The former group consists of the **Carbohydrates,** and the members of it which occur normally in the body are either hexoses, each of which contains six carbon atoms in its molecule, or are formed by a combination of two or more hexose molecules. Pentoses, with five carbon atoms each, are sometimes found in the urine after the ingestion of grapes or other fruits in which they occur. The carbohydrates commonly found in the body are glucose (dextrose), lævulose (fructose), galactose, lactose, and glycogen. Others occur as constituents of food, *e.g.* cane-sugar and starch. The first three have the formula $C_6H_{12}O_6$, and belong to the group of monosaccharides. Lactose is a di-saccharide, that is, it belongs to a group of substances formed by the condensation of two monosaccharide molecules with the abstraction of a molecule of water.

$$2C_6H_{12}O_6 - H_2O = C_{12}H_{22}O_{11}.$$

Glycogen is a polysaccharide, and is formed by the condensation of a large number of monosaccharide molecules, as in the formula

$$nC_6H_{12}O_6 - nH_2O = (C_6H_{10}O_5)_n.$$

The symbol 'n' may have a very high value. Thus starch is supposed to have the formula $(C_6H_{10}O_5)_{200}$.

The Monosaccharides.—Glucose may be looked upon as th

current carbohydrate coin of the body. It is a soluble crystalline substance, having the formula

$$\begin{array}{l} CH_2OH \\ | \\ (CHOH)_4 \\ | \\ CHO \end{array}$$

It is an aldehyde, and, like other aldehydes, when heated with an alkaline solution of a cupric salt, it reduces the latter with the formation of yellow cuprous oxide. This property of glucose and other "reducing sugars" forms the basis of the tests of Trommer, Fehling, and Benedict. Glucose has also the power of reducing acid solutions of cupric salts, differing in this respect from the reducing sugars belonging to the class of disaccharides. On being heated with phenyl-hydrazine and acetic acid, glucose forms a compound, phenylglucosazone, which crystallises in yellow needles, generally arranged in loose sheaves. Solutions of glucose are decomposed by the action of yeast into carbonic acid and alcohol—

$$\underset{\text{Glucose.}}{C_6H_{12}O_6} = 2\underset{\text{Alcohol.}}{C_2H_6O} + 2CO_2.$$

Further, glucose is dextro-rotatory, that is, its solutions rotate the plane of polarised light to the right.

Lævulose (fructose) and galactose occur in the body in small quantity. The former is lævo-rotatory, the latter dextro-rotatory. Like glucose, they have the property of reducing alkaline solutions of cupric salts, and they also form osazones.

Glucose and galactose are aldehydes and are known as aldoses, while lævulose is a ketone and belongs to the group of ketoses.

$$\begin{array}{l} CHO \\ | \\ H.C.OH \\ | \\ HO.C.H \\ | \\ H.C.OH \\ | \\ H.C.OH \\ | \\ CH_2OH \end{array}$$
Glucose.

$$\begin{array}{l} CH_2OH \\ | \\ CO \\ | \\ HO.C.H \\ | \\ H.C.OH \\ | \\ H.C.OH \\ | \\ CH_2OH \end{array}$$
Lævulose.

$$\begin{array}{l} CHO \\ | \\ H.C.OH \\ | \\ HO.C.H \\ | \\ HO.C.H \\ | \\ H.C.OH \\ | \\ CH_2OH \end{array}$$
Galactose.

The only *disaccharide* which occurs in the body is lactose, the sugar of milk. Two other disaccharides, cane-sugar and maltose,

are of physiological importance, the former being an important food-stuff, the latter an intermediate product in the digestion of starch. Lactose and maltose are reducing sugars, and form characteristic osazones. Each of the three, when boiled with dilute mineral acid, undergoes hydrolysis, the molecule taking up water and being split into two molecules of a monosaccharide.

$$C_{12}H_{22}O_{11} + H_2O = 2C_6H_{12}O_6.$$

The *polysaccharide*, glycogen, occurs chiefly in the liver and muscles as a storage product. Its solution in water differs from that of vegetable starch, which is also a polysaccharide, (1) in that it is more markedly opalescent than that of the latter, and (2) in giving a reddish-brown colour with iodine, whereas vegetable starch gives a blue colour. The polysaccharides do not reduce alkaline solutions of cupric salts. They undergo hydrolysis either when boiled with dilute mineral acid or as the result of the action of enzymes, yielding first polysaccharides of smaller molecule than the starches, called dextrins, and a disaccharide, maltose, and giving as the final product the monosaccharide, glucose.

The first-formed dextrin products of the hydrolysis of the starches are called erythro-dextrins, because they give a red colour with iodine ; the later formed substances are called achroo-dextrins, because they give no colour with iodine. The latter consist of smaller molecules than the erythro-dextrins. The process of hydrolysis of a polysaccharide may be summarised in the equation—

$$(C_6H_{10}O_5)_n + nH_2O = nC_6H_{12}O_6.$$

Inosite.—Inosite is a substance found in muscle and formerly called muscle-sugar. It has the formula $C_6H_{12}O_6 + 2H_2O$, but does not belong to the carbohydrate group, being a benzene derivative. It does not reduce an alkaline solution of cupric sulphate, does not rotate polarised light, and is non-fermentable.

(2) The second group of non-nitrogenous substances, those in which the oxygen of the molecule is insufficient to combine with the hydrogen, consists of the **Fats.** The chief fats found in the body are tristearin, $C_3H_5(C_{18}H_{35}O_2)_3$, tripalmitin, $C_3H_5(C_{16}H_{31}O_2)_3$, and triolein, $C_3H_5(C_{18}H_{33}O_2)_3$. They are compounds of the corresponding fatty acids, stearic, palmitic, and oleic, with the trivalent alcohol, glycerol. Stearic and palmitic acids are saturated compounds, and the former and its esters, being higher in the series than palmitic acid and its esters, have a higher melting-point. Oleic acid is unsaturated, and both the acid itself and triolein have a relatively low melting-point, being fluid at room temperature.

Fats are insoluble in water, but are soluble in ether or in warm alcohol. They are decomposed on heating with alkalies, the fatty acid uniting with the alkaline base to form a soap, and the glycerol being set free (saponification). If a neutral fat, such as pure olive oil, is shaken up with water, the fat becomes broken up into fine globules which run together again when the shaking ceases. If, however, some soap is present, each globule becomes coated with a layer of soap molecules, which so reduce the surface tension between the fat and the water that the globules remain apart. Such a suspension of fat globules is called an emulsion.

Lipoids.—The term lipoids includes a number of substances which resemble fats in being soluble in ether. The commonest of these are lecithin and esters of cholesterol, which are constantly associated in the body, occurring especially in the nervous tissues, in bile, and in the plasma and corpuscles of the blood.

Lecithin is a complex fat and, when boiled with baryta water, it yields two fatty acids, glycerophosphoric acid, and a base, choline, belonging to the group of amines. Lecithin, which contains nitrogen, belongs to the group of phospholipines, which also includes *cephalin* and *sphingomyelin*. Some other lipoid substances found in the brain resemble lecithin in containing nitrogen, but contain no phosphorus.

Cholesterol, $C_{27}H_{45}OH$, is a complex, monatomic alcohol, and is included in the group of lipoids simply on account of its solubilities. It forms colourless, square, flat crystals, often notched at one corner, and gives a red colour with strong sulphuric acid.

Lipoid substances enter into the composition of cell-protoplasm, occurring especially in the superficial layer, or "plasma-skin." This surface layer is less permeable to salts and other substances in watery solution than to water. Substances such as alcohol and alkaloids, which are soluble in oily media, can readily penetrate the cell.

THE NITROGENOUS SUBSTANCES

The nitrogenous substances contained in the body are (1) proteins, which form the greater proportion of the solid constituents of the cells, tissues, and body-fluids, and (2) derivatives of proteins.

The Proteins

The physical properties of proteins are those of colloid substances (p. 18). Some proteins, however, for example egg-albumin and hæmoglobin, the pigment of blood, may be obtained in the crystalline form. Others, such as peptone (which is not a

constituent of the body), are capable of diffusing through an animal membrane.

The molecule of protein is very large ; it contains the elements C, H, N, O, and S in the following proportions :—

C	50·6	to 54·5	per cent.
H	6·5	,, 7·3	,,
N	15·0	,, 17·6	,,
O	21·5	,, 23·5	,,
S	0·3	,, 2·2	,,

Proteins have the power of combining either with acids or with alkalies. When a solution of a protein, such as egg-albumin, is warmed with dilute acid or alkali, it is converted into *metaprotein* and shows changes in its characteristics. The egg-albumin solution is neutral, and is coagulated on heating if salts are present. The metaprotein solution does not coagulate on heating, and gives a precipitate of metaprotein on neutralisation, the precipitate being soluble in excess of either acid or alkali.

If a solution of egg-albumin is subjected to the action of superheated steam, or is boiled for a long time with mineral acid, or is subjected to the action of gastric juice or of pancreatic juice, it undergoes hydrolysis, the albumin taking up water, and the molecule being split up into small molecules. The splitting up occurs in stages, the molecules becoming progressively smaller. After the substance has passed through a metaprotein stage, a series of *hydrated proteins* is formed, the first formed products being called *proteoses* and the later ones *peptones*. The hydrated proteins are soluble in water, and are not coagulated on boiling. Proteoses are distinguished from peptones in that they are precipitated if their solution is saturated with ammonium sulphate, whereas peptones are not precipitated in this way. If the hydrolysis is continued, the peptones are further broken down into substances called *polypeptides*, which do not show protein characteristics, and which consist of groupings of *amino-acids*. By still further hydrolysis these are split into their constituent amino-acids.

Colour Reactions of Proteins.—The proteins give certain colour reactions by which their presence in solutions may be recognised. The most useful of these are the following :—

(1) *The Xanthoproteic reaction.*—Nitric acid is added to the solution and it is boiled. A yellow colour is produced, which changes to orange on cooling and adding ammonia. Many proteins are precipitated by nitric acid, and, in such cases, the colour reaction is shown in the precipitate.

(2) *Millon's reaction.*—An acid solution of mercuric and

mercurous nitrates is added to the solution of protein. A precipitate is formed, and this becomes red when the solution is heated.

(3) *Rose's reaction.*—With dilute copper sulphate and excess of caustic alkali, most proteins give a violet colour, but in the case of proteose or peptone the colour is pink. The pink colour is also given by the substance *biuret.* The reaction is due to the fact that both biuret and proteins contain two —CO—NH— groupings linked together.

(4) *Hopkins' reaction.*—Glyoxylic acid is added to the solution of protein, and then strong sulphuric acid is poured down the side of the tube so as to form a layer at the bottom. A violet colour is produced at the junction of the two fluids.

A trace of formaldehyde may be used instead of glyoxylic acid in the performance of the test.

The xanthoproteic reaction depends upon the presence of the benzene ring in the protein molecule ; Millon's reaction depends upon the presence of a hydroxy-derivative of the benzene ring, contained in the amino-acid, tyrosine ; Hopkins' reaction depends upon the presence of tryptophane. Gelatin, which does not contain either tyrosine or tryptophane, gives none of these reactions.

Classification of Proteins.—The chief proteins found in the body are (1) protamines, (2) histones, (3) albumins, (4) globulins, (5) phosphoproteins, (6) scleroproteins, and (7) conjugated proteins.

(1) *Protamines* are relatively simple substances, are basic in character, and only occur in combination. They are chiefly found, combined with nucleic acid, in the spermatozoa of certain fishes.

(2) *Histones* are also basic in character, and occur in the combined form. An example is globin, the protein constituent of hæmoglobin.

(3 and 4) *Albumin* and *globulin* occur in all cells and in many of the fluids of the body, and are distinguished from each other by their solubilities. Albumin is soluble in water or weak salt solution, and its molecules are aggregated to form a precipitate in a saturated solution of ammonium sulphate. Globulin is insoluble in distilled water, soluble in weak salt solution, and is precipitated in a half-saturated solution of ammonium sulphate. Albumin or globulin in solution, on being heated, undergoes first of all a change which is probably chemical in nature, and is known as *denaturation.* A physical change follows, and consists in the aggregation of the molecules to form a coagulum. The presence

of inorganic salts is favourable to aggregation, but is unfavourable to denaturation. Acids and alkalies, on the other hand, in small amount, favour denaturation but hinder aggregation. A trace of acid assists coagulation of an albumin or globulin solution, because the acid combines with the protein to form a salt. But if the protein is heated with more than the merest trace of acid or alkali, an acid or alkaline solution of metaprotein is obtained, which will not coagulate on heating, but yields a precipitate of metaprotein on neutralisation.

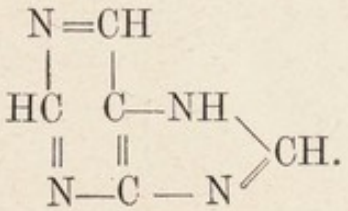
The effect of salts in promoting the coagulation or precipitation of proteins is due to the ionisation of the salt. A solution of protein is really a suspension, and the suspended particles carry an electric charge, which is positive in an acid solution, negative in an alkaline solution. As all the particles carry a similar charge, they will tend to repel one another, but if the charge be reduced, aggregation or coagulation will take place. Hence, in the case of an ionised salt, the effective ion which brings about coagulation is that which carries a charge opposite in sign to that of the protein particles, and thus reduces the charge on these particles. It is found that the effectiveness of an ion is determined by its valency. In the case of acid solutions the trivalent anion of potassium citrate has a greater coagulating power than the divalent SO_4, and the latter again is more effective then the monovalent Cl. So also in alkaline solutions, barium chloride with a divalent kation is more effective than sodium chloride with a monovalent Na ion.

(5) *Caseinogen*, the chief protein of milk, is a *phosphoprotein*, that is, it contains phosphorus combined in its molecule in addition to the five elements common to proteins generally. It is insoluble in water, but soluble in weak alkali, forming a caseinogenate, and is precipitated from its alkaline solution by acetic acid, the precipitate being soluble in excess of the acid. The alkaline solution is not coagulated by heat.

(6) The *Scleroproteins* are distinguished by their relative insolubility. They form the chief constituents of the fibrous and horny structures of the body. Thus, white fibres are mainly composed of collagen, yellow fibres of elastin, and hair, horn, and hoofs of keratin. When collagen is boiled with water it yields gelatin, a substance which is soluble in boiling water, the solution setting to a jelly on cooling. Both elastin and keratin are insoluble in hot or cold water, dilute acids or alkalies, or in alcohol or ether. Keratin is remarkable for the amount of sulphur contained in its molecule.

(7) *The Conjugated Proteins.*—These are nucleoprotein, glucoprotein, and chromoprotein, and each consists of a protein combined with another body called the prosthetic group. *Nucleo-*

proteins are a constant constituent of cell nuclei. They are soluble in water, weak salt solution, or dilute alkalies. They possess acid characters, hence the affinity of nuclear chromatin, which contains nucleoprotein, for basic dyes. A nucleoprotein is a compound of a protein with nuclein, and the latter consists of protein combined with nucleic acid, an organic acid containing phosphorus. If a nucleoprotein is subjected to digestion by gastric juice, an insoluble brownish residue is obtained. This residue consists of nuclein. If the nucleic acid obtained from nuclein is hydrolysed, two substances, adenine and guanine, are constantly found among the products of disintegration. These two bodies belong to the purin group, that is, they may be regarded as derivatives of purin, which has the formula—



Adenine has the formula $C_5H_5N_5$, while *guanine* is $C_5H_5N_5O$. Both these substances, when oxidised, yield uric acid, $C_5H_4N_4O_3$.

In *glucoprotein* the combined body is a carbohydrate radical, often glucosamine ($C_6H_{13}NO_5$), and therefore containing nitrogen ; the glucosamine is split off when the glucoprotein is boiled with mineral acid. It reduces alkaline solutions of cupric salts. Most glucoproteins belong to the group of *mucins*. These are soluble in weak alkalies, they are not coagulated by heat, and they are precipitated by acetic acid, the precipitate being insoluble in excess of the acid.

The best example of a *chromoprotein* is the blood-pigment, hæmoglobin, in which a protein, globin, is combined with an iron-containing body, hæmatin. Hæmoglobin crystallises with comparative ease, and is freely soluble in water.

The Constitution of Proteins

When a protein is acted upon by certain digestive ferments, or is boiled with mineral acid, its molecule is hydrolysed and is split into a large number of smaller molecules belonging to the group of amino-acids. These are the simpler members of the fatty acid series, combined in each case with the NH_2 group. Thus, amino-acetic acid has the formula $CH_2(NH_2).COOH$, and amino-propionic acid is $CH_3.CH(NH_2).COOH$. More complex compounds are formed by the replacement of one H atom of the terminal methyl group by a radical such as phenyl. Some

of the amino-acids which have been isolated from proteins are shown in the following table :—

Acid.	Amino-derivatives.
Acetic, $CH_3.COOH$	Amino-acetic acid (glycine). Methyl-amino-acetic acid (sarcosine).
Propionic, $C_2H_5.COOH$	Amino-propionic acid (alanine). Oxy-amino-propionic acid (oxy-alanine or serine). Phenyl-amino-propionic acid (phenyl-alanine). Oxy-phenyl-amino propionic acid (tyrosine). Indol-amino-propionic acid (tryptophane). Iminazol-amino-propionic acid (histidine). Di-(amino-thio-propionic acid) (cystine).
Valerianic, $C_4H_9.COOH$	Amino-valerianic acid. Guanidin-amino-valerianic acid (arginine).
Caproic, $C_5H_{11}.COOH$	Amino-caproic acid (iso-leucine). Amino-isobutyl-acetic acid (leucine). Di-amino-caproic acid (lysine).

These, and the other amino-acids not included in the table, have both acid and basic properties, the latter depending upon the amino-group (NH_2). Amino-acids can thus become linked together, the CO.OH of one combining with the NH_2 group of another with the elimination of H_2O, the linkage being $-\overset{\overset{O}{\|}}{C}-\overset{\overset{H}{|}}{N}-$. There appears to be no doubt that the protein molecule is formed by the union of a large number of these relatively simple substances in this way. Fischer has succeeded in linking together amino-acids *in vitro*, and has obtained compounds giving the reactions of proteoses.

Each of the three acids, histidine, arginine, and lysine, contains two NH_2 groups. These substances are therefore more strongly basic than the other (mono-amino) acids, and they are spoken of as di-amino-acids or the "hexone bases."

It might be expected that the special characteristics of the individual proteins would be associated with differences in the number and relative proportions of the amino-acids entering into their constitution ; and this is found by analysis to be the case. The first step in such an analysis, after hydrolysis of the protein, is the separation of ammonia by the addition of magnesia and distillation. Next, phosphotungstic acid is added to the residual fluid. This precipitates the di-amino-acids, the amount of which can be estimated by determining the amount of nitrogen present in the precipitate. Lastly, the amount of nitrogen present

in the fluid, after removal of the di-amino-acids, is found, and from this the quantity of mono-amino acids can be calculated.

The following table shows the varying proportions of the amino-acids in certain common proteins :—

	Serum-Albumin.	Egg-Albumin.	Caseinogen.	Gelatin.	Zein.	Gliadin.	Salmin.	Keratin.
Glycine .	0·0	0·0	0·0	16·5	0·0	0·9	0·0	4·7
Alanine .	2·7	8·1	1·5	0·8	9·79	2·7	..	1·5
Serine . .	0·6	..	0·5	0·4	1·02	0·12	7·8	0·6
Phenyl-alanine	3·1	4·4	3·2	0·4	6·55	2·6	..	0·0
Tyrosine .	2·1	1·1	4·5	0·0	3·55	2·4	..	3·2
Tryptophane	present	present	1·5	0·0	0·0	1·0	..	present
Cystine .	2·3	0·2	..	0·0	..	0·45	..	over 10
Amino-valeric acid	..	..	7·2	1·0	..	0·3	4·3	0·9
Leucine .	20·0	7·1	9·35	2·1	19·55	6·0	0·0	7·1
Lysine .	..	2·15	5·95	2·75	0·00	0·0	0·0	1·1
Arginine .	..	2·14	3·81	7·62	1·55	3·4	87·4	4·5
Histidine .	..	..	2·5	0·4	0·43	1·7	0·0	0·6
Proline .	1·0	2·25	6·7	5·2	9·04	2·4	11·0	3·4
Glutamic acid	7·7	8·0	15·55	0·88	26·17	36·5	..	3·7
Aspartic acid	3·1	1·5	1·39	0·56	1·71	1·3	..	0·3

The chief points to notice in the table are that (1) caseinogen contains all the amino-acids except glycine, (2) gelatin contains no tyrosine, tryptophane, or cystine, (3) zein contains no tryptophane, (4) gliadin contains all the amino-acids except lysine, (5) salmin (a protamine) is extremely rich in the diamino-acid, arginine, and (6) keratin contains an unusually large proportion of the sulphur-containing acid, cystine.

The importance of these facts will be appreciated in connection with the study of protein metabolism, when it will be found that the nutritive value of individual proteins depends largely upon the particular amino-acids contained in them. For example, tryptophane is essential for the maintenance of the body, whereas lysine is necessary for growth, while glycine can be synthesised in the body itself.

PHYSICAL PROCESSES WHICH OCCUR IN THE BODY

Ions.—When sodium chloride is dissolved in water its molecules undergo dissociation into sodium *ions*, which are charged with positive electricity, and chlorine ions, which are charged

with negative electricity. Ions are not necessarily the same as atoms, since a solution of sulphuric acid in water contains hydrogen ions and SO_4 ions. Substances which undergo dissociation when in solution are called *electrolytes*, since an electrical current passed through such a solution is conducted by the movement of the ions ; and, owing to the presence of electrolytes in the tissues of the body, these are able to conduct electrical currents. Many substances, however, such as sugar, when dissolved in water do not undergo dissociation, and the dissolved molecules carry no electrical charge.

Diffusion and Osmosis.—When a substance such as sodium chloride is dissolved in water, the dissolved molecules behave like the molecules of a gas ; they are in constant movement and exert pressure upon the walls of the vessel containing them. If, for example, a vessel is divided into two compartments by a vertical membrane, and if one compartment is filled with water and the other with 1 per cent. salt solution, the molecules of salt in their movements will beat upon the membrane ; and if the latter is *permeable* to molecules of salt, they will pass through it into the distilled water until the amount of sodium chloride on the two sides of the membrane becomes equal. This process is known as diffusion, and the rate at which it occurs varies with the percentage of sodium chloride originally present in the solution.

If the membrane allows water but not sodium chloride to pass through it, it is said to be *semi-permeable*, and the pressure exerted by the molecules of salt, as they beat upon the membrane, is called *osmotic pressure* and can be measured in the following manner. A semi-permeable membrane is made by filling the pores of an earthenware cell with silicic acid or copper ferrocyanide ; the cell is filled with 1 per cent. sodium chloride solution, closed by a cork through which passes a tube attached to a mercurial manometer, and immersed in distilled water (fig. 1). Since the molecules of salt cannot pass through the membrane, they exert pressure on the wall of the cell and the surface of the mercury ; water passes through the membrane into the cell, and the mercury is forced downwards in one limb of the manometer and upwards in the other until the difference of height in the two limbs is 5000 mm. Hg. This pressure balances the osmotic pressure exerted by the molecules of salt ; and in raising the column of mercury the salt solution does work. If a 2 per cent. salt solution is used, the osmotic pressure is twice as great.

Similar experiments with other substances show that the osmotic pressure of any substance in solution depends, not upon its nature, but solely on the number of its molecules in solution,

and is proportional, therefore, to the concentration of the solution. A gram-molecule of any substance is its molecular weight in grams. The molecular weight of glucose is 180, and a gram-molecule of glucose is 180 grams. A gram-molecular solution of glucose contains 180 grams in 1 litre, whereas a similar solution of sodium chloride contains 58·5 grams per litre. The two solutions contain the same number of molecules and, if the sodium chloride did not dissociate, their osmotic pressure would be the same. But since sodium chloride does dissociate and each of its ions behaves like a molecule as regards osmotic pressure, the solution of sodium chloride, if completely dissociated, will exert twice the osmotic pressure of the solution of glucose.

It is difficult to measure osmotic pressure in the manner just described, since the membranes are apt to give way and leak ; and indirect methods are usually employed, of which the best is the determination of the freezing-point of a solution. When a substance is dissolved in water, the freezing-point of the water is lowered, the lowering being proportional to the concentration and osmotic pressure of the dissolved substance. The lowering of the freezing-point below 0° C. is expressed by the letter Δ.

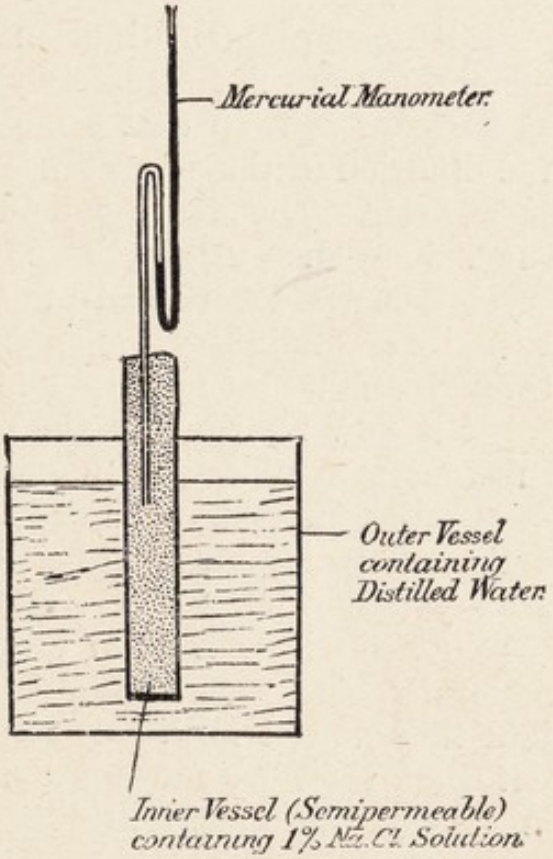


FIG. 1.—Osmometer. (Starling's *Elements of Physiology.*)

When a gram-molecule of any substance is dissolved in 1 litre of water the freezing-point is lowered by 1·87° C., and its osmotic pressure = 17,024 mm. Hg. The osmotic pressure of a substance in solution can be calculated from the formula

$$\text{Osmotic pressure} = \frac{\Delta}{1{\cdot}87^\circ\ \text{C.}} \times 17{,}024\ \text{mm. Hg.}$$

The osmotic pressure of a substance in solution equals the pressure that would be necessary to compress it from the gaseous state (assuming such a state to be possible) to the volume of the solution. A gram-molecule of a gas occupies 22·4 litres. To compress this to a volume of one litre would require a pressure of 22·4 atmospheres. $22{\cdot}4 \times 760 = 17024$.

Solutions which have the same osmotic pressure are said to be *isotonic*, and the tissues in mammals are isotonic with a solution containing 0·9 per cent. sodium chloride in water ; this is known as normal saline solution. When the tissues are immersed in stronger, *i.e. hypertonic*, salt solution, water passes from the tissue into the salt solution by osmosis ; when the salt solution has a lower osmotic pressure than the tissues, it is *hypotonic*, and the tissues take up water from the solution. When they are immersed in an isotonic solution, the tissues neither take up nor lose water.

Both osmosis and diffusion take place in the body, but the membranes are not completely impermeable to substances such as sugar or salt, so that osmosis is soon brought to an end by the diffusion of these substances through the membrane.

Colloids.—The term colloid was originally applied to all substances, such as starch and proteins, which would not form crystals or pass through an animal membrane, in contradistinction to easily crystallisable bodies, such as sugar, which diffuse rapidly through animal membranes and are called crystalloids.

It is now known that the colloidal form is a state in which substances exhibit certain characteristic features, and that a very large number of substances, including metals, may exist in the colloidal form. Further, some colloids, such as hæmoglobin, are crystallisable.

Most colloids consist of very large molecules or aggregates of molecules, and their characteristics depend largely on the fact that they do not form true solutions in water or other solvents, but that their pseudo-solutions consist of particles suspended in a very dilute solution of the colloid. Owing to the size of the particles, colloidal suspensions do not follow the laws of true solution, and they exert only a very small osmotic pressure.

If an electrolyte, such as sodium chloride, is added to a colloidal suspension, the salt concentrates at the surface of each colloidal particle, this process being called *adsorption*. Its occurrence can be readily demonstrated by dipping strips of blotting paper, which is colloidal, into a solution of a dye. The dye accumulates on the particles in the paper, and the latter becomes more deeply coloured than the solution into which it is dipped.

The amount of adsorption is relatively much greater in dilute than in strong solutions of the electrolyte. Its importance lies in the fact that the velocity with which a chemical change takes place varies with the concentration of the interacting substances. If two electrolytes, which can interact, are added to a colloidal solution, they become concentrated on the surface

of the colloidal particles, and at these surfaces the reaction between them will therefore proceed more rapidly than if the colloid were absent.

Solutions of colloids are called *sols* ; in certain circumstances the particles may aggregate into larger masses, forming a precipitate, or the solution may change to a jelly, called a *gel*. An example of this process is the coagulation of protein by heat.

CHAPTER III

MUSCLE

THERE are three varieties of muscle in the body, each consisting of fibres, and described histologically as striped, unstriped, and cardiac muscle respectively. The *striped* fibres form the skeletal muscles. Since the skeletal muscles are used to carry out voluntary movements, striped muscle is often described physiologically as *voluntary* muscle; but this term is not strictly accurate, because striped fibres, as will be seen later, contract at times independently of the will. The *unstriped* fibres are found in the walls of the blood-vessels, digestive tract, uterus, and elsewhere; their contraction is almost invariably independent of the will, the only exception being the ciliary muscle of the eyeball, and they are therefore known as *involuntary* muscle-fibres. *Cardiac* muscle is only found in the heart, and will be described in connection with that organ.

VOLUNTARY MUSCLE

Structure of Striped Muscle.—Striped muscle-fibres are cylindrical in shape; they may be 40 mm. in length, and they vary in diameter from 10 to 100 thousandths of a millimetre (10 to 100 μ). Each is enclosed in a delicate, structureless membrane, the *sarcolemma*, and exhibits many oval nuclei, which in the mammal usually lie immediately under the sarcolemma, but in the frog are scattered throughout the substance of the fibre. The striation consists of alternate dim and clear transverse stripes, the former being doubly refracting, or *anisotropic*, and the latter singly refracting, or *isotropic*, when examined with polarised light. The clear segment is furthur divided into two equal parts by a line running across it, known as Dobie's line or Krause's membrane. When the fibre is fully extended, the dim segment is similarly divided into two parts by a clear line, the line of Hensen.

By histological methods the fibre can be shown to consist

of parallel fibrils, or *sarcostyles*, running longitudinally and separated by a small quantity of a more fluid substance, *sarcoplasm*. Each sarcostyle shows the same bands and lines as the whole fibre, and may be regarded as a series of *sarcomeres*, each of these lying between two adjacent Dobie's lines.

The sarcostyles of the wing muscles of insects are relatively broad, and are easily separated, and Schafer, working with these, has described appearances which give a clue to the processes by which contraction of the fibres is effected. Fine canals run from the clear portion of each sarcomere into the dim segment, terminating close to Hensen's line by blind extremities (fig. 2). When the muscle contracts, the isotropic substance of the clear segment flows into these canals, the sarcomere thus becoming shorter and wider.

When the fibre as a whole is examined in a state of contraction, there is an appearance simulating reversal of the stripes, the dim segment becoming less dim owing to the flow of clear substance into its canals, and the clear stripe appearing darker because sarcoplasm accumulates in greater quantity between the sarcostyles in that region.

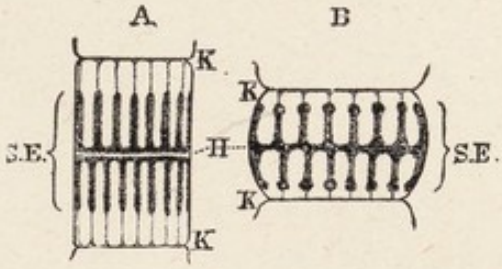


Fig. 2.—Diagram of a sarcomere: A, in a moderately extended condition; B, in a contracted condition; K, K, membranes of Krause; H, line of Hensen. (From Quain's *Anatomy*, by permission of Sir Edward Sharpey Schafer.)

In certain animals, such as the rabbit, some of the muscles are pale and others are red in colour. The pale muscles have the structure just described, whereas the red muscle-fibres contain more sarcoplasm than the pale ones, and their nuclei are scattered throughout the substances of the fibres. The red colour is due to the presence of hæmoglobin in the fibres. The red muscles contract more slowly than the pale muscles, but their contraction is more prolonged. In many animals these two varieties of fibre are found together in the same muscle. All muscles are supplied with nerve-fibres, some of which are motor and end in the muscle-fibres in end-plates, while others are sensory and convey impulses from the muscle to the central nervous system.

Chemical and Physical Characters of Striped Muscle.—Muscle contains about 75 per cent. of water and 25 per cent. of solid substances, of which proteins form 18 to 20 per cent. The other constituents are a small amount of fat, glycogen ($\frac{1}{2}$ to 1 per cent.), inosite, and a number of nitrogenous extractives

including creatine, xanthine, and hypoxanthine; the most important of these is creatine, which forms 0·2 to 0·4 per cent. of the muscle.

At a variable period after death the proteins coagulate, the product being called myosin, and the muscles become rigid and opaque; this condition is known as *rigor mortis*.

The nature of the proteins in living muscle can be studied if coagulation is delayed by cooling the muscle. The muscle is minced at a temperature of 0° C., and is then extracted with ice-cold saline solution (0·9 per cent. NaCl) and filtered; the filtrate contains two proteins, called respectively paramyosinogen and myosinogen. The former is a globulin which coagulates at 47° to 50° C., and constitutes about 20 per cent. of the total protein in muscle. The remaining four-fifths consist of myosinogen, which has the properties of an albumin, though it coagulates at the low temperature of 56° to 60° C. When the solution of these substances is warmed it clots, the proteins being converted into myosin, though the myosinogen passes through a transition stage as soluble myosin, which undergoes heat coagulation at 40° C. In the frog's muscle soluble myosin is present as such in the living muscle. When cooled living muscle is pressed, a fluid is obtained, called muscle-plasma, which contains the proteins of muscle and clots on standing. The coagulation of muscle-plasma can be prevented by the removal of calcium salts, but there is no evidence that it is brought about by a ferment.

Resting muscle is very extensible and can be stretched by applying a weight to it; it is also elastic, and returns completely and rapidly to its original length when the weight is removed.

THE CONTRACTION OF VOLUNTARY MUSCLE

In response to a stimulus a living muscle alters its form, becoming shorter and thicker; this change of form constitutes muscular contraction, and can be very easily studied in the muscles of the frog. For this purpose the gastrocnemius muscle and the sciatic nerve which supplies it are generally used, and are known as a muscle-nerve preparation. The fibres in the gastrocnemius do not run regularly from end to end of the muscle, and, when it is desirable to use a muscle the fibres of which run approximately parallel to one another, the sartorius may be chosen. The normal stimulus to muscular contraction during life is an impulse passing from the central nervous system along the nerve which ends in the muscle-fibres. In a muscle-nerve preparation, the muscle contracts either when it is stimu-

lated directly or when the stimulus is applied to the nerve. Different methods of stimulation may be used, mechanical, chemical, or electrical. Pinching the muscle, for example, causes it to contract. The application of a moderately strong solution of common salt is also effective ; this acts by withdrawing water from the muscle by osmosis, and is not a true chemical stimulus. Ammonia stimulates muscle, but has a destructive action on the nerve. The passage of a constant current through a muscle does not excite contraction, but the making or breaking of the current, or any sudden variation in its strength, acts as a stimulus. Induction shocks are of very short duration, occurring only when the primary circuit of the apparatus is made or broken, and, because of this and of the ease with which their strength can be varied, they are generally used as the most convenient form of experimental stimulus.

It was formerly supposed that, even when the stimulus was applied to the muscle itself, the latter did not respond directly, but contracted because the stimulus acted upon the nerve-fibres running within the muscle. There is no doubt, however, that muscle can be excited to contract independently of impulses reaching it along nerve-fibres (independent irritability of muscle). Curare paralyses the motor endings of nerve-fibres in muscle, and, when it is injected into an animal, stimulation of a motor nerve has no effect upon the muscle, whereas direct stimulation of the muscle causes it to contract.

The changes which take place in a contracting muscle are (1) a change of form and physical condition, (2) an electrical change, (3) chemical changes, and (4) evolution of heat.

Changes in Form and Physical Condition.—When a muscle contracts, it becomes shorter and thicker, but undergoes no change in volume. The shortening may be studied in the muscle-nerve preparation of a frog by fixing the upper attachment of the gastrocnemius muscle and attaching the tendo Achillis by a thread to the short arm of a lever ; the long arm carries a writing point, and a weight can be attached to it if so desired. When the muscle contracts it pulls on the lever, and the movement of the writing point can be recorded on a smoked, revolving drum.

When a single induction shock of suitable strength is applied to the muscle, it responds by a single contraction or twitch. A graphic record of such a contraction is shown in fig. 3.

The contraction lasts about one-tenth of a second in the case of frog's muscle, and the tracing shows three parts, namely, (1) a short latent period, during which the muscle shows no visible change ; (2) a period of shortening of the muscle, whereby the

lever is raised; and (3) a period of relaxation, during which the muscle returns to its former length. The length of the latent period is due partly to the inertia of the lever and recording apparatus. This source of error can be avoided by interposing a muscle between a source of light and a rapidly moving photographic plate; the thickening of the muscle, as it contracts, is photographed, and the interval between the application of the stimulus and the beginning of contraction is measured. This interval, which is only 0·0025 second, represents the true latent period. The relaxation is not an active process, but is due to the weight of the lever pulling the muscle back to its former length; if an isolated muscle lying on mercury, and therefore not subject to any tension, is made to contract, it relaxes very imperfectly.

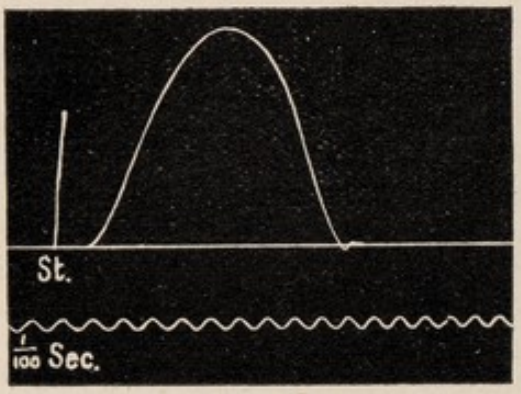


FIG. 3.—Simple muscle twitch.

The vertical line marks the moment at which the stimulus was applied. Below is a time-record, each double vibration representing $\frac{1}{100}$ second.

A certain strength of stimulus is necessary in order to produce any visible shortening of a muscle; a further increase in the strength of the stimulus, beyond this point, causes the muscle to contract more strongly, until finally the contraction becomes maximal. The varying degree of the response of the muscle to varying strength of stimulus is due to the fact that a weak stimulus affects only a few fibres, whereas a strong stimulus throws into contraction a large number of fibres; when all the fibres are stimulated, the shortening is maximal. Each fibre, however, if it contracts at all, gives the maximal contraction of which it is capable for the conditions under which it is placed, whatever the strength of the stimulus. This is known as the "all or none law," and holds good whether the muscle is stimulated directly or through its nerve.

When a muscle contracts, the contraction travels from the point of stimulation in the form of a wave at the rate of 5 to 6 metres per second in mammals and 3 to 4 metres in cold-blooded animals. This rate can be measured by resting two levers on a muscle, one at the middle, the other at one end, and applying a stimulus to the opposite end of the muscle. The lever nearer the stimulated point will rise earlier than the one at the opposite end of the muscle; and, if this interval is measured and the length of muscle between the two levers is known, the

rate at which the wave travels can be calculated. The length of the wave is measured by multiplying the rate at which it travels by its duration at any one point; it varies in frog's muscle from 150 to 300 mm.

Contracting muscle differs from resting muscle in being more extensible and more elastic, that is, it returns to its original length more rapidly than resting muscle when the force stretching it is removed.

Effect of temperature.—A rise of temperature quickens, and a fall of temperature delays, every phase of the contraction (fig. 4). If the muscle is lifting a small load, the lever often

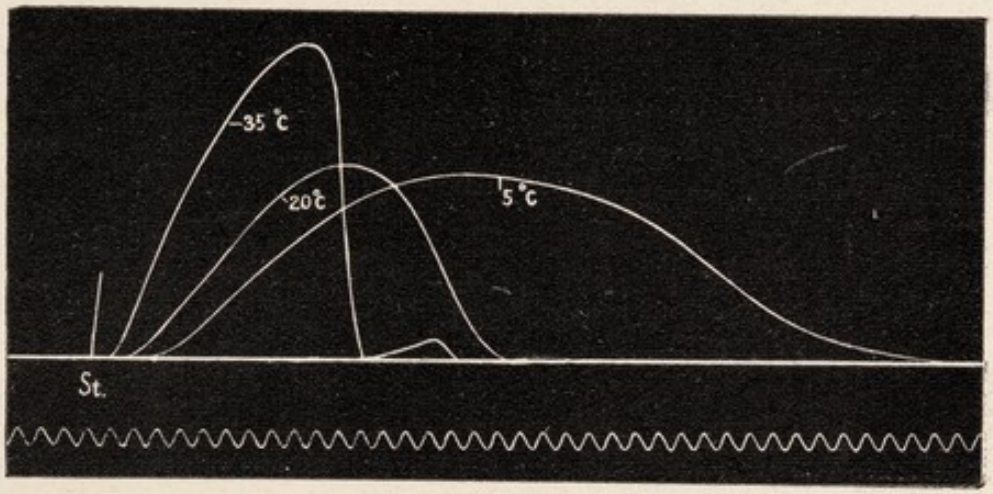


FIG. 4.—Tracing showing the effect of temperature on a simple twitch of the gastrocnemius of the frog. The point of stimulation is the same for each of the three contractions.

rises higher at a high, than at a low, temperature, since the sudden jerk given to the lever by the rapid contraction imparts to it a greater momentum than when the pull on the lever takes place more gradually. On the contrary, when a heavy weight is attached to the lever, a slowly contracting, cooled muscle may be more effective in raising the lever than the rapidly contracting, warmed muscle. These differences are of purely mechanical origin, and the actual force of the contraction for a given load and for the same strength of stimulus remains unchanged between 5° C. and 20° C. Cooling increases the excitability of muscle, and maximal stimuli should therefore be used in studying the effect of temperature on the height of contraction. Prolonged exposure to a temperature of 0° C. destroys the vitality of muscle.

Effect of fatigue.—If a muscle is repeatedly stimulated, the height of the contractions diminishes, and all phases of the contraction, including the latent period, are prolonged; finally

the muscle may fail to contract in response to a stimulus (fig. 5). This condition constitutes fatigue.

Effect of load.—When a weight is attached to the lever, the

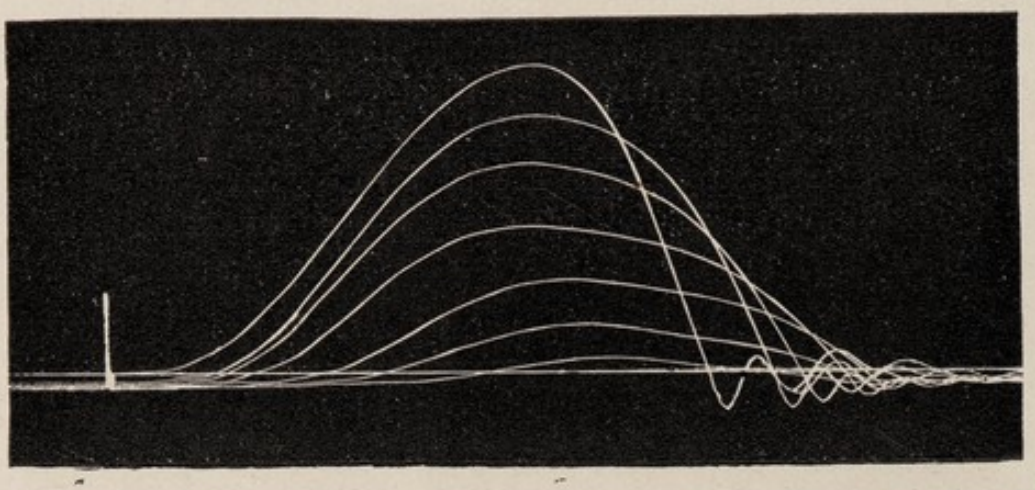


FIG. 5.—Tracing showing the effect of fatigue upon muscular contraction. Every fifteenth contraction is recorded. The muscle was heavily loaded, and fatigue occurred rapidly.

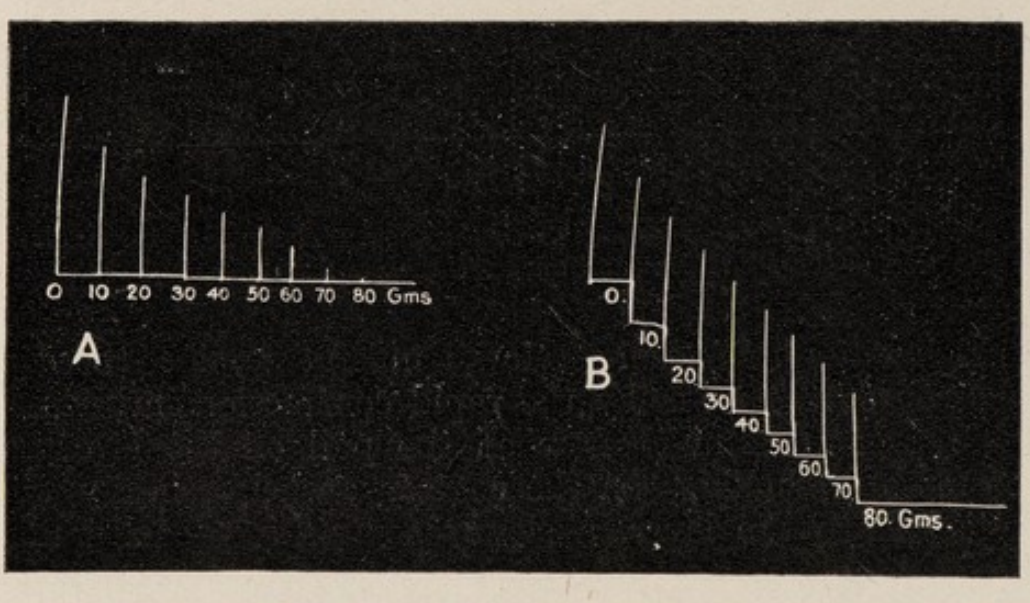
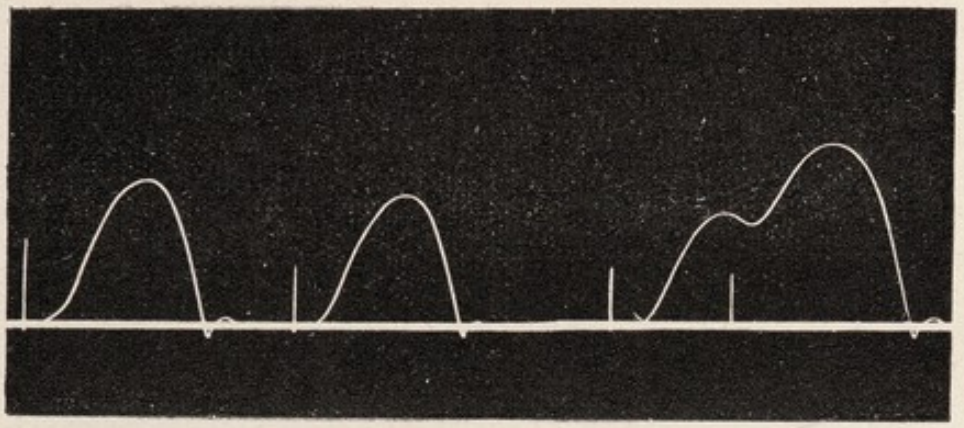


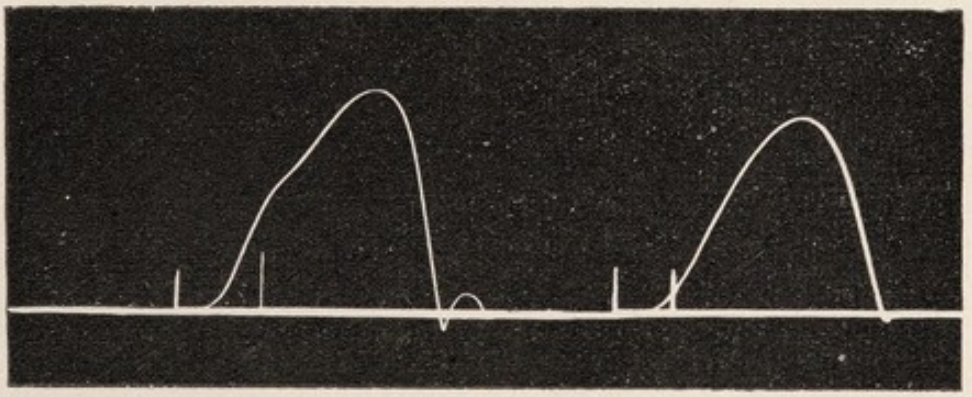
FIG. 6.—Tracing to show the effect of different loads on the extent of contraction of the gastrocnemius of the frog; A, when after-loaded; B, when free-weighted.

effect on the extent of the contraction varies according as the muscle is "free-weighted" or "after-loaded." A muscle is said to be after-loaded when the lever rests on a fixed point, so that the weight does not stretch the resting muscle, though, as soon as it begins to contract, the muscle pulls on the weight. The muscle is free-weighted if the weight is allowed to stretch the muscle even when it is at rest; in these circumstances the

heavier the load the greater will be the length of the resting muscle. Hence the length of a resting muscle, which is called its *initial* length, is constant for an after-loaded muscle, whatever may be the weight on the lever, whereas, if the muscle is free-weighted, its initial length varies with the load.



A B



C D

FIG. 7. — Tracing to show summation of muscular contractions (gastrocnemius of frog). From A to D the interval between two successive stimuli was progressively shortened as shown by the points of stimulation marked on the tracing.

The influence of the initial length of a muscle upon the force with which it contracts is shown in fig. 6. The height through which a weight can be raised by an after-loaded muscle rapidly diminishes as the weight becomes larger. If the muscle is free-weighted, the extent of the contraction decreases very gradually as the weight is increased ; and a free-weighted muscle can lift a weight which, if after-loaded, it would fail to move. It is clear, therefore, that, up to a certain point, the greater the initial length of the muscle the more forcible is its contraction ; and, since the work done by a muscle is measured by the product of

the weight raised and the height through which it is raised, the maximum work of which a muscle is capable is greater when its initial length is increased by stretching it.

Isotonic and Isometric Curves.—When a muscle lifts a weight attached to a lever, the weight follows the movement of the lever, and the pull or tension which it exerts upon the muscle remains unchanged during the contraction; the curve thus obtained is called *isotonic*. The muscle may be made, however, to pull against a strong spring so that its length remains almost unaltered during its contraction, although it exerts a varying tension upon the spring; the minute movements of the spring

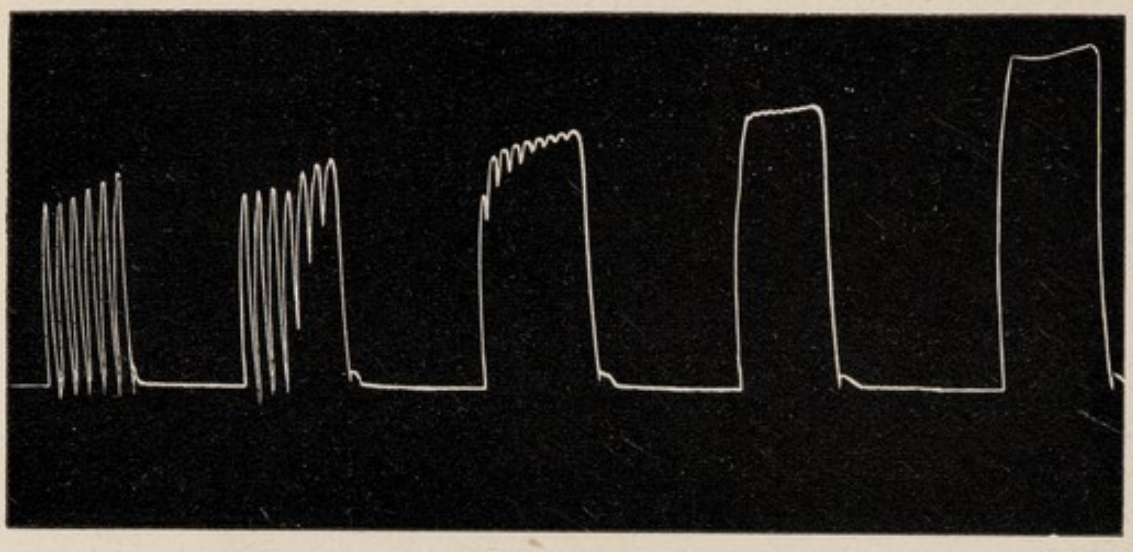


FIG. 8.—Tracing to show the genesis of tetanus. The first group of contractions resulted from the application of ten stimuli per second; in each succeeding group the frequency of the stimuli is increased; the fifth shows complete tetanus Note the marked shortening of the muscle during tetanus.

are magnified and recorded photographically. In this case the contractile stress set up in the muscle varies throughout the contraction, though the length of the muscle undergoes no appreciable change. Curves thus obtained are called *isometric*; they resemble isotonic curves in their general form.

Tetanus.—If a second stimulus is sent into a muscle before the shortening caused by the first stimulus is at an end, the muscle shortens still further, this being called *summation* of effects (fig. 7). When the stimuli are rapidly repeated (fifty or more per second), the muscle contracts very strongly, and remains contracted so long as the stimuli are continued; the prolonged contraction is known as *tetanus* (fig. 8).

Constant Current.—When a constant current is passed through a muscle, it enters at one point called the anode, and, after traversing the muscle, leaves it at the kathode. When the

circuit is completed, *i.e.* at the "make" of the current, the muscle gives a single twitch, and there is another twitch when the current is broken ; during the passage of the current the muscle remains relaxed. The contraction taking place when the current is made starts at the kathode, whereas the contraction occurring at the "break" of the current starts at the anode. This can be observed by clamping a skeletal muscle in the middle and attaching a lever to each end ; one electrode is placed on each half of the muscle. When the current is made, the portion of the muscle connected with the kathode contracts first, and the lever attached to this half of the muscle rises before the other lever. The same phenomenon is still more readily seen, and can be directly observed, in slowly contracting muscles, such as the cardiac muscle of the frog.

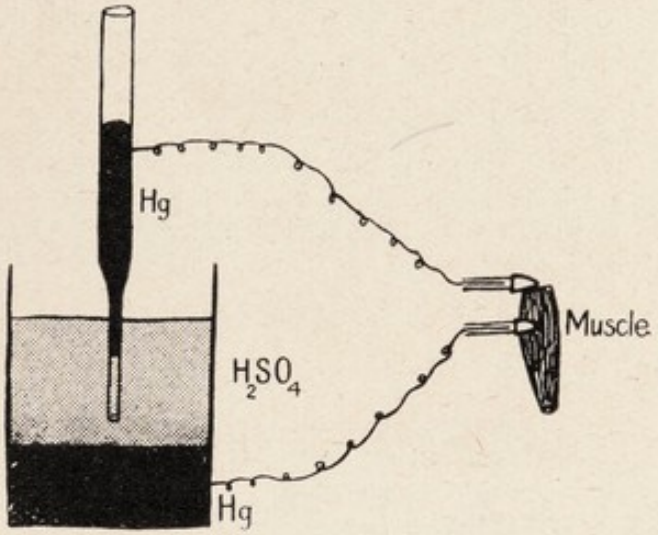


FIG. 9.—Scheme of capillary electrometer.

Electrical Changes in Muscle. — When a constant current is passed into a muscle through metallic electrodes, electrolysis takes place in the muscle ; the electrolytes accumulate near the electrodes and give rise to a current, which passes in the opposite direction to that in which the constant current is passing and tends to neutralise the latter. This phenomenon is known as polarisation and, in recording the electrical currents occurring in muscle, it is necessary to use non-polarisable electrodes.

The electrical currents in muscle may be observed by means of either the capillary electrometer or the string galvanometer. The capillary electrometer consists of a glass tube drawn out at one end to a capillary, and partly filled with mercury ; the capillary tube opens into another tube containing 10 per cent. sulphuric acid. Two platinum wires pass, one into the sulphuric acid, the other into the mercury (fig. 9). A little mercury is placed below the sulphuric acid in order to make a better contact with the platinum than would be the case if the latter dipped directly into the sulphuric acid. When the electrometer is connected with two points of different potential, the mercury moves up or down the capillary tube. If the point connected

with the acid is negative as compared with that connected with the mercury in the capillary tube, the mercury in the latter moves down towards the acid ; if the point connected with the acid is positive, the mercury moves away from the acid. The

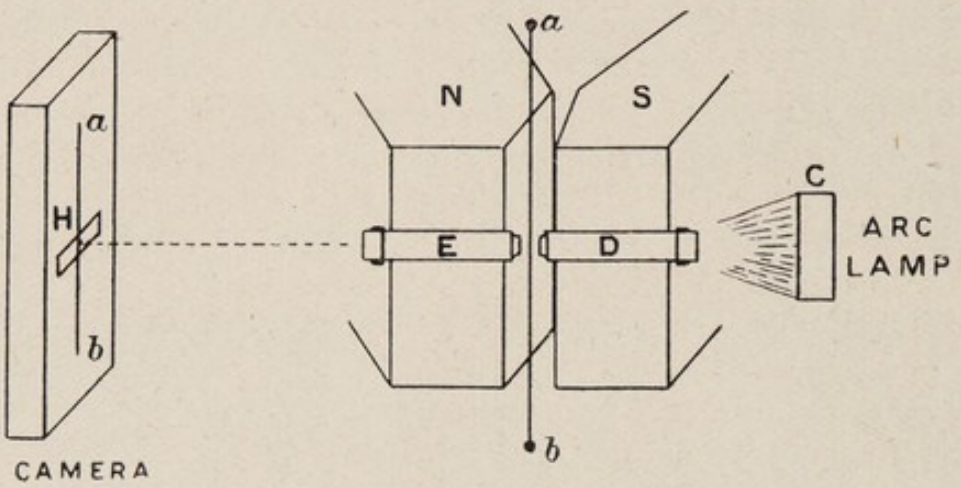


FIG. 10.—Scheme of string galvanometer.

a, *b* is the quartz thread ; N and S are the poles of the electro-magnet ; E is a microscope. The magnified mage of the thread falls on the slit H, and is photographed. (Hume.)

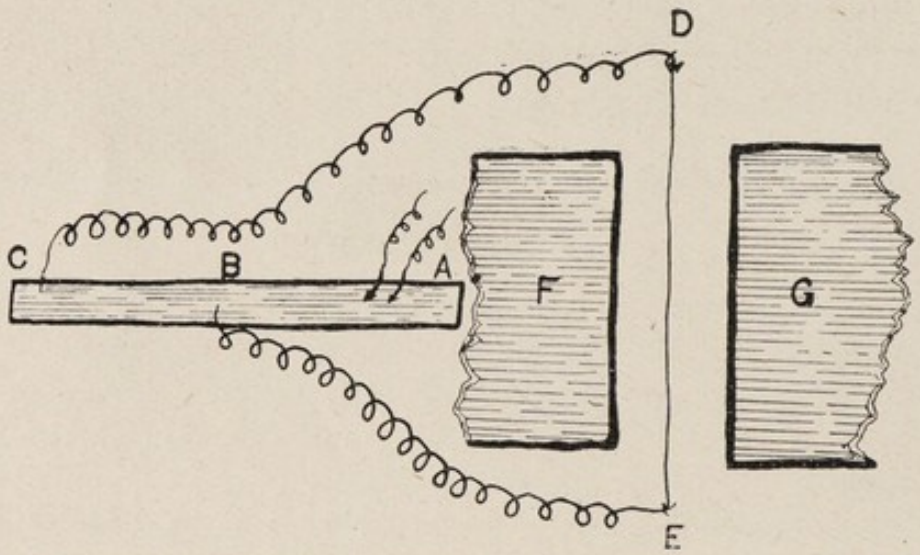


FIG. 11.—Diagram to show the method of investigating electrical changes in muscle.

D E is the thread ; F and G are the poles of the electro-magnet of the string galvanometer.

movements are rapid, and are proportional to the difference of potential between the two points under observation ; they may be directly observed under the microscope, or may be recorded photographically.

The string galvanometer consists of a very delicate quartz thread, silvered over and hanging between the poles of a strong electro-magnet (fig. 10) ; by means of terminals passing from each end of it, the thread can be connected with a muscle or other structure.

When a current passes through the thread, the latter swings in the plane between the poles to one side or the other according to the direction of the current. The thread is illuminated by a strong light, and a magnified image of its movements can be thrown on a screen and observed directly; if the screen is replaced by a moving photographic plate, the movements of the thread can be recorded.

When a perfectly uninjured muscle, *e.g.* the sartorius of a frog, is connected by means of non-polarisable electrodes at B and C (fig. 11) with the string galvanometer, no electrical current can be detected, and the muscle is said to be *isoelectric*. The application of a single induction shock at the point A causes a contraction travelling as a wave from A to C. The wave of contraction is preceded by a chemical change, which travels at the same rate as the contraction. The chemical change involves an alteration in the distribution of the electrolytes within the muscle, and is of such a kind that the excited part of the muscle becomes negative to the resting part. The electrical changes takeplace chiefly during the latent period, and are completed long before the contraction is over.

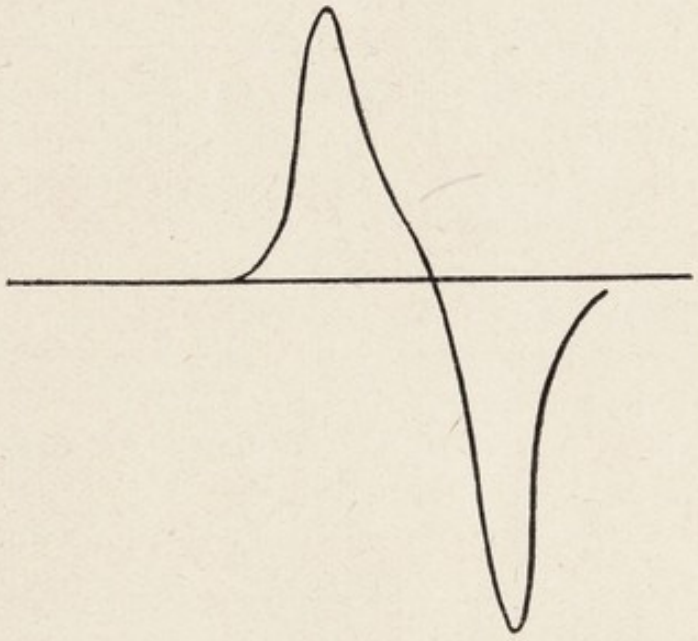


FIG. 12.—Diphasic electrical change in musc e (diagrammatic).

The horizontal line represents the position of the thread when at rest.

Since excited muscle is negative to resting muscle, the electrical change is diphasic, as is shown diagrammatically in fig. 12. The first movement of the thread (represented by the ascending part of the curve in the figure) occurs when the muscle is excited at B, and becomes negative to the resting muscle at C; the current flows through the galvanometer from C to B. When the excitatory process reaches C, and is still present at B, there is no electrical current and the thread swings back to its original position. This period is extremely short, and almost immediately the excitatory process passes off at B, though it is still present at C; the point C is now negative to B and the thread swings once more, this time in the opposite direction.

Finally the whole muscle ceases to be excited, and the thread returns to its resting position. The diphasic current is known as the *current of action.*

If the muscle is injured at the point C, a current flows through the galvanometer from B to C even when the muscle is resting, and is called the *current of rest or injury.* If the muscle is thrown into contraction, the point B becomes electrically negative as compared with its resting state, and then returns to its former condition; the injured muscle at C does not contract, and its electrical condition remains unchanged. The record of the galvanometer, therefore, shows a single (monophasic) deflection. Since the current of action in this case flows in the opposite direction to that of the injury current, it is often spoken of as the *negative variation* of the injury current.

Thus it is evident that both injured and contracting muscle are negative to normal resting muscle. These changes are abolished by the death of the muscle, and are bound up with the chemical changes taking place in a contracting or injured muscle. They are independent, however, of the mechanical shortening, and still occur in an excited muscle even when its power to contract is abolished by steeping it for a short time in distilled water.

Although it is customary to speak of excited muscle as "negative" to resting muscle, it must be remembered that it is really electro-positive to the resting muscle; in the same way, zinc is the electro-positive element in a battery. The term "negative" simply means that the current passes through the galvanometer towards the excited tissue, and has no reference to the actual electrical condition of this tissue.

The electrical changes in muscle can also be demonstrated without the aid of a galvanometer. Two muscle-nerve preparations are made, and the nerve of one preparation A is brought into contact at two points with the muscle of the other preparation B. When the muscle of B contracts, the current of action set up in it acts as a stimulus to the nerve of A; this stimulus is conducted to the muscle of A, which is thrown into contraction.

Chemical Changes during Contraction.—Living muscle is constantly taking up oxygen from the blood and giving off carbonic acid. When it contracts, it takes up more oxygen and gives off more carbonic acid, and at the same time heat is evolved and lactic acid is formed. The production of acid during muscular contraction can be readily demonstrated in a frog's muscle-nerve preparation; if the muscle is made to contract vigorously for a few minutes it becomes acid to litmus paper. Another method of illustrating the same fact consists in injecting

into the dorsal lymph sac of a frog a solution of acid fuchsin, which is almost colourless in neutral, and red in acid, solution. An hour or two after the injection one gastrocnemius muscle is excised and made to contract; the contracting muscle becomes red, whereas the resting muscles are not coloured.

It can be shown that the acid formed is lactic acid by means of Hopkins' test.

A few drops of an alcoholic extract of muscle, two or three drops of a saturated solution of copper sulphate, and 5 c.c. of strong sulphuric acid are mixed in a test tube and placed in boiling water for a minute or two. The fluid is cooled and a few drops of alcoholic thiophene solution are added; on again warming the solution, a cherry-red colour develops if lactic acid is present.

When a muscle contracts, the first chemical change taking place is the formation of lactic acid from a precursor which is probably either glucose or a compound of glucose with some other substance; this is not an oxidative process, and it can take place when a muscle is made to contract in the absence of oxygen. In the presence of an adequate supply of oxygen, the lactic acid is subsequently oxidised to carbonic acid and water according to the following equation:—

$$C_3H_6O_3 + 3O_2 = 3CO_2 + 3H_2O.$$

Lactic acid.

This is shown by the observation that an isolated frog's muscle, when made to contract in an atmosphere free from oxygen, gives off less carbonic acid and contains more lactic acid than when it contracts in an atmosphere containing oxygen. Further, if a muscle which contains lactic acid is exposed for some hours in pure oxygen, the amount of lactic acid in it decreases. Evidently the muscles possess the power of destroying lactic acid; and, if the supply of oxygen is ample, little or no lactic acid accumulates in a muscle even when it is thrown into repeated contractions, because the production of lactic acid and the oxidation of pre-formed lactic acid are proceeding simultaneously.

This process also takes place in the living animal, but, under certain conditions, the production of lactic acid outstrips its oxidation; as a result, lactic acid accumulates in the muscles and some of it escapes into the blood and is excreted in the urine. This may occur either because the supply of oxygen to the muscles is deficient, as is the case during asphyxia, or because, as happens during muscular exercise, the muscles are forming lactic acid so rapidly and in such large amount that they have not time to oxidise the whole of it. In man the excretion of lactic acid in the urine is 3 to 4 mgr. per hour during rest, and this may be raised

by severe exercise to 400 mgr. or more hourly. Hence the appearance of lactic acid in increased amount in the blood and urine may be due either to defective oxidation or to excessive production of lactic acid.

It is possible that part of the lactic acid is not oxidised, but is synthesised again by the muscles into the carbohydrate compound by the decomposition of which it was originally formed.

The chemical changes taking place in contracting muscle are not confined to the process just described, and the oxidation of fat is also increased during muscular activity.

Heat-Production in Muscle.—During muscular contraction heat is produced, and the contraction of a large number of muscles, such as occurs during muscular exercise, may be sufficient to raise the temperature of the whole body 1° or 2° C. The heat produced in a small isolated muscle during a single contraction cannot be measured by a thermometer, but is usually determined by means of a *thermopile*, which consists of a junction between two metals, the metals being connected with a galvanometer. When the junction is heated, an electrical current is set up and passes through the galvanometer. In the more recent forms of thermopile the metals used are copper and an alloy called constantan, and the thermopile may consist of a large number of such junctions, which are connected with a string galvanometer. A muscle, such as the frog's sartorius, is placed in contact with these junctions, and can be made to contract by sending a current through electrodes placed one at each end of the muscle. The muscle is fixed at one end, and attached at the other either to a recording lever or to a spring whereby the tension on the muscle can be varied or the changes in contractile stress occurring during its isometric contraction can be studied. Any production of heat in the muscle gives rise to a current through the thermopile and to deflection of the thread of the galvanometer; the amount of deflection produced by a unit of heat is previously determined. Experiments made with this apparatus show that the production of heat in muscle occurs both during, and for some time after, its contraction.

The Nature of Muscular Contraction.—The mechanical, electrical, chemical, and thermal changes just described constitute different aspects of the complex process of muscular contraction. A normal, resting muscle contains a store of potential energy; and, when it is stimulated, either directly or through its nerve, a fraction of this energy is suddenly transformed into kinetic energy, and lactic acid is produced within the muscle-fibres. It is believed that the appearance of lactic acid in some way brings about this liberation of energy. The energy thus set free can be used in

the performance of work, or can be evolved as heat, or may be manifested partly as work and partly as heat.

The amount of the energy set free and available for this purpose depends upon the initial length of the muscle-fibre. If the muscle is stretched by a spring or weight, the energy set free and the contractile stress, that is, the force with which the fibres tend to contract, are greater than when it is not stretched. The proportion of the energy set free which appears as work or as heat respectively depends upon the mechanical conditions under which the muscle is placed. If the muscle is allowed to lift a weight, it does work which is measured by the product of the weight raised and the height through which it is lifted ; and, if the mechanical conditions are very favourable, the greater part of the energy set free during the contraction may appear as work. If the muscle is not allowed to contract and to do work, the whole of the energy set free during the period of contractile stress appears as heat.

After the contraction is over, the lactic acid is oxidised, the energy provided by this oxidation being for the most part utilised in restoring the potential energy of the muscle, although some of it appears as heat.

The appearance of lactic acid and the conversion of potential into kinetic energy can take place in the absence of oxygen, whereas, for the subsequent removal of lactic acid and the restoration of potential energy, oxygen is necessary. If the supply of oxygen is adequate, a muscle may be made to contract repeatedly for a long time, since its store of potential energy is renewed by the oxidation of lactic acid almost as rapidly as this is formed. But when the muscle contracts in the absence of oxygen, its potential energy is not restored, and lactic acid accumulates within it ; in these circumstances, the muscle soon becomes fatigued, and contracts feebly or not at all.

Fatigue then is due, either to exhaustion of the muscle's store of energy, or to the accumulation of lactic acid. That the presence of an excess of lactic acid in muscle can cause fatigue is shown by the fact that the contraction characteristic of fatigue can be induced in a perfectly fresh muscle if the latter has been perfused with blood containing lactic acid.

The *efficiency* of muscular contraction is the proportion of the total energy set free during and just after the contraction, which appears as work. The mechanical conditions under which muscular contraction takes place in the body are usually such that the efficiency is comparatively constant ; in man, from 20 to 30 per cent. of the total energy set free during muscular contraction appears as external work.

Rigor Mortis.—When a muscle passes into rigor mortis it shortens slightly, becomes rigid and opaque, and loses its elasticity and extensibility. During its passage into rigor the muscle becomes acid, the acid formed being lactic acid, and heat and carbonic acid are evolved.

These changes are all due to the breaking down of the carbohydrate precursor of lactic acid. In this process heat is evolved, and the lactic acid, as it is formed, reacts with the sodium bicarbonate in muscle, setting free carbonic acid, which is given off. When the amount of lactic acid formed in the muscle attains a certain level, the proteins are coagulated, and the physical characters of the muscle are altered. It is for this reason that the muscles of fatigued animals pass into rigor mortis more rapidly after death than the muscles of resting animals, since, at the time of death, they already contain some lactic acid. Fatigue is thus brought about in part by the same cause as that which ultimately leads to rigor mortis ; but the larger amount of acid produced in the latter brings about an irreversible change in the proteins, causing the death of the muscle, whereas the acid is gradually removed from a fatigued muscle, which is thereby restored to its normal condition.

VOLUNTARY CONTRACTION

The contraction of a muscle under the influence of the will is much longer than a single twitch and represents a short tetanus, since even the quickest movement which an individual can carry out voluntarily lasts at least one-tenth of a second, and usually longer. The nature of voluntary movement has recently been demonstrated by recording the electrical changes occurring during a voluntary contraction. Using the string galvanometer, about 50 electrical variations per second can be observed in the contracting muscle ; and, if the electrical variations of a motor nerve during a voluntary or reflex contraction of the muscle which it supplies are similarly recorded, it is found that about 50 impulses per second are passing along the nerve. When a skeletal muscle is stimulated 50 times a second it passes into tetanus ; and it may be concluded that voluntary muscular contractions are almost always tetanic in character, and are brought about by the discharge of rapidly repeated impulses from the central nervous system.

INVOLUNTARY MUSCLE

The muscle-fibres which occur in the walls of the digestive tract, blood-vessels, and other organs show no transverse striation,

and are called plain, unstriped, or involuntary muscle-fibres. Each fibre is spindle-shaped and has an oval nucleus ; its cell substance frequently shows a delicate longitudinal striation. The fibres are arranged in sheets, and are united to one another by a cement-substance which can be stained with silver nitrate.

The changes taking place in smooth muscle, when it contracts, differ in many respects from those occurring in skeletal muscle. In the first place, the duration of the contraction is very prolonged ; the latent period may be from 0·2 to 0·5 second, and the contraction may last for two or three minutes.

In the second place, the muscle is much more easily excited by the making or breaking of a constant current than by induction shocks, and frequently fails to give any response to a single induction shock. Owing to the slowness of the process, the origin of the contraction at the kathode when a constant current is made, and at the anode when the current is broken, can be observed with great ease.

In the third place, smooth muscle shows a great tendency to contract rhythmically, the rhythm being most easily evoked when the muscle is stretched. The effect of tension is often well seen in the hollow organs whose walls are partly composed of smooth muscle. If such an organ is rapidly distended by the injection of fluid, the sudden tension placed on the muscle-fibres in its wall causes them to contract forcibly, the contraction being sometimes continued in a rhythmic manner for a short time.

One of the most characteristic features of smooth muscle is its power to remain in a state of partial contraction or *tone*, even after it is cut off from any connection with the central nervous system. Stimulation of the nerves to the muscle may bring about either an increase or a decrease of this tone ; and most unstriated muscles have a double nerve-supply, one set of nerves when stimulated causing contraction, and the other set causing relaxation, of the muscle.

CILIARY MOVEMENT

Cilia are delicate filaments projecting from the border of columnar epithelial cells, and are found in the greater part of the respiratory passages, in the generative organs, and elsewhere.

Their movement consists in a rapid bending of each cilium, followed by a slow return to the erect position. All the cilia on a ciliated surface bend in the same direction, the movement travelling as a wave over the surface. The movements are repeated ten to twelve times a second, and serve to carry forward solid particles of dust or mucus in the respiratory passages ; in

the Fallopian tubes they assist the passage of the ovum. If a section of a ciliated membrane is cut out, and replaced in the reverse direction, the movement of the cilia of the transplanted portion retains its original direction, that is, it is now in opposition to that of the remainder of the membrane.

Ciliary movement is entirely independent of the central nervous system, and its mode of production is unknown.

CHAPTER IV

THE NERVOUS SYSTEM

SECTION I

The nervous system consists of (1) the brain and spinal cord (spinal medulla), together forming the central nervous system, (2) the nerves, which form the paths of communication between these central organs and the muscles, glands, and peripheral sense-organs, and (3) nerve-ganglia, which are small masses of nerve-cells found on the course of many of the nerves.

The essential characteristic of life is the power of reaction to a stimulus, and in the higher animals this reaction is effected through the intermediation of the nervous system, and constitutes reflex action. The life of the individual is, to a large extent, made up of a long series of reflex acts, varying in complexity and carried out in response to stimuli arising either in the outer world or within his own body. In response to external stimuli, the animal acts as a whole and carries out movements directed to attack or defence, to the procuring of food, and the like; in response to internal stimuli, the activities of the different organs of the body are co-ordinated in such a way that the individual behaves as such and not as a group of independent organs. Instances of this nervous control will be referred to in connection with the work of the heart, the function of respiration, the production of the digestive juices, and the other functions which are concerned with animal life.

The activities of the nervous system are not limited, however, to the management of these vital functions. In addition, the brain is the seat of those processes which are concerned with conscious existence. Impressions are conveyed to the brain from the outer world, and give rise to sensations of smell, taste, hearing, sight, and touch, and these in their turn call forth emotions, such as pleasure or pain. The activities of the central nervous system find expression in muscular movement, resulting in locomotion, speech, writing, or gesture. In the study of the various functions of the central nervous system, the science of

Physiology has to deal with the mechanism by means of which afferent impressions are received and conducted to the nerve-centres, with that by which they are associated in these centres, and with the further mechanism by means of which efferent impulses are transmitted to the active tissues of the body. The consideration of the mental processes and the emotions is the province of the sister science of Psychology.

Microscopic examination of the brain and spinal cord shows that they are built up of nerve-cells and nerve-fibres, supported by a special form of connective tissue called neuroglia. The nerves contain nerve-fibres only, held together by ordinary connective tissue. Every nerve-fibre, however, is a process of a nerve-cell; and, if a nerve-fibre is divided, the part which is no longer in connection with the nerve-cell undergoes degeneration. The histological unit of the nervous system is therefore the nerve-cell with its processes, and this unit is known as a neuron.

The Neuron.—Every neuron consists of a nerve-cell, known as a cyton, and its processes. In the simplest form the cyton is bipolar, with one process arising from each pole. Examples of this type are found in the spinal ganglia of fishes and in the ganglion on the auditory nerve in man. A modification of this form occurs in the human spinal ganglia, the two processes becoming fused together for a short distance in the course of development, so that the cell is histologically unipolar, though physiologically it is still a bipolar cell. A third form is multipolar, there being more than two processes connected with each cell. One of these processes is unbranched, and is known as the axon; the others are branched, and are called dendrons. The neurons which enter into the structure of the brain and spinal cord belong to the multipolar type, varying however in the shape of the cyton, the number and character of the dendrons, and the length of the axon in different regions (fig. 13).

The *cyton*, although differing in shape and size in different regions, is always distinguished by certain definite characteristics. It is usually large as compared with other cells, varying in diameter from 20 to 100 μ. It possesses a large, spherical nucleus which contains little chromatin, and, within the nucleus, a well-marked nucleolus. The cell-substance, in fixed and hardened preparations, is characterised by the presence of certain bodies known as Nissl-spindles (fig. 14, *a*), and also by having delicate fibrils running through it. The Nissl-spindles are fusiform aggregations of granules, arranged more or less concentrically in relation to the nucleus, and stain well with methylene blue or toluidin blue. They appear to consist mainly of nucleoprotein, and also contain some iron. They are found in all parts of the

cyton and in the basal parts of the dendrons, but not in the axon-hillock, which is that part of the cell from which the axon takes origin. The fibrils run through the cell from dendrons to axon, and, with some interfibrillar material, form the substance of the latter structure. Many nerve-cells have a well-marked capsule surrounding them, separated from the cell by a space containing lymph.

Fibrils cannot be detected in nerve-cells freshly removed from the body when examined by the dark ground method, and some authorities believe they are artefacts in the hardened specimen.

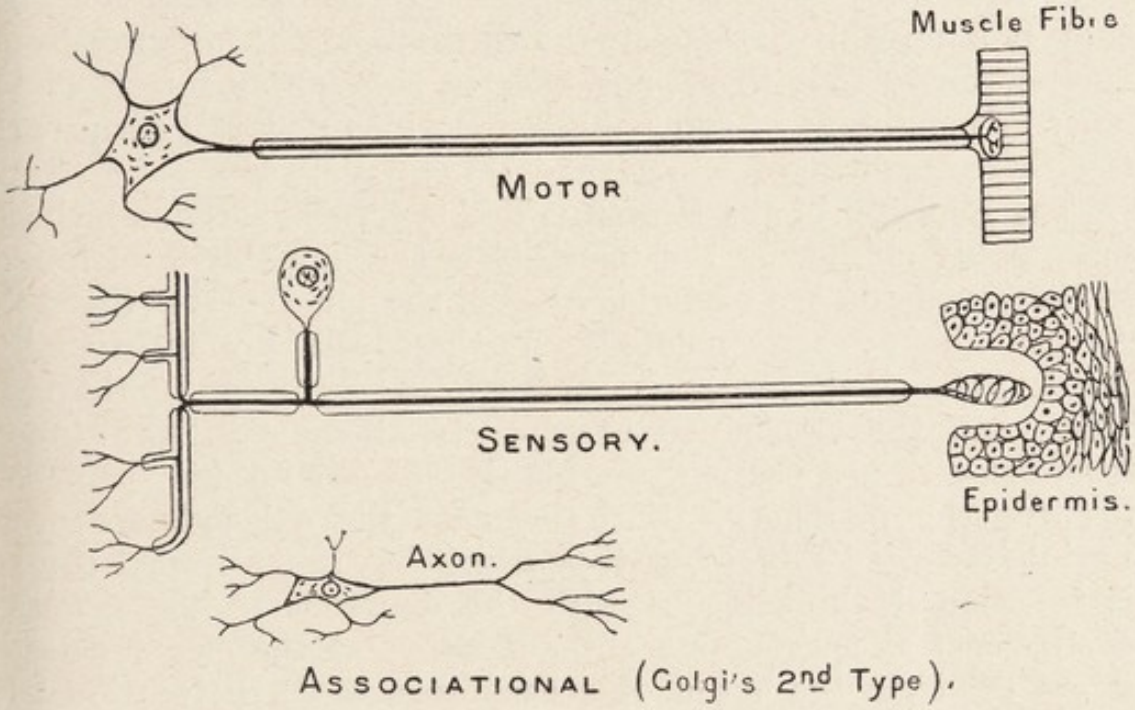


Fig. 13.—Diagram showing different types of neuron.

The *axon* usually becomes the axis-cylinder of a nerve-fibre, acquiring a sheath soon after leaving the cyton. Axons are of variable length, the longest being those which extend from the lumbar region of the spinal cord to the foot. They do not branch as the dendrons do, but those which run a course in the central nervous system give off delicate twigs, known as *collaterals*, at right angles to their course. Each axon ends by a terminal arborisation, either in relation with the cyton or dendrons of another neuron or in relation with muscle-fibres or gland-cells. In the case of a motor nerve the terminal arborisation of each fibre occurs in a special end-plate situated in the substance of a muscle-fibre. The axons of certain cells in the central nervous system, belonging to what is known as Golgi's second type, are very short, do not acquire a myelin sheath, and form their terminal

arborisation in relation with the cell-body or dendrons of a neighbouring neuron (fig. 13).

Dendrons are found in their most typical form in the neurons of the brain and spinal cord. They branch in a tree-like manner, and the branches frequently exhibit minute enlargements or projections. The dendrons are short as compared with the axon, and rarely extend any distance from the cyton.

The processes of nerve-cells do not anastomose, but come into relationship by the more or less intimate application of the terminal arborisation of the axon of one neuron to the dendrons or cyton of another neuron. Such a communication, in which there is contact without continuity, is called a *synapse*. The contact is possibly not direct, the transmission of impulses from one neuron to the other being effected through an intermediate layer or membrane of some substance which does not form part of either neuron.

The Function of the Neuron.—The type of neuron which is most easily studied in the mammal is the unipolar form found in the ganglia on the posterior roots of the spinal nerves (fig. 13). As has already been pointed out, these cells are functionally bipolar, the single process resulting from the fusion of the two poles, and the two processes separate at some little distance from the cell, one passing towards the spinal cord and the other towards the periphery. Each becomes the axis-cylinder of a medullated nerve-fibre, but that which has a centrifugal course is functionally homologous with the dendrons of the neurons of the central nervous system. If either of the two processes is cut off from the cyton, it degenerates, while the portion left in connection with the cell-body undergoes no obvious change. It may therefore be assumed that the cyton governs the nutrition of all parts of the neuron. Moreover, when one of its processes has been divided in this way, so that the normal function of the neuron is interfered with, changes occur in the substance of the cyton itself. The Nissl-spindles undergo disintegration, so that the cell stains diffusely with methylene blue. This change is known as *chromatolysis*, and it indicates that the Nissl-bodies are concerned in some way with the functional activity of the neuron. Further evidence in support of this conclusion is afforded by the fact that the Nissl-bodies of the cells of the central nervous system diminish in number after an animal has been in active exercise (fig. 14, *b*). Chromatolysis also occurs as a result of the action of certain poisons, in fevers, and in asphyxia.

Conduction of an impulse in a neuron takes place in one direction only. In the case of the fibres of the posterior (dorsal)

spinal nerve-roots, the conduction is from the periphery to the central nervous system. The fibres of the anterior (ventral) roots, on the contrary, conduct from centre to periphery. They are the axons of multipolar nerve-cells which lie in the grey matter of the spinal cord. If the posterior root be divided between the spinal cord and the ganglion, stimulation of the peripheral portion will give rise neither to sensation nor to muscular contraction. Stimulation of the central portion is, however, followed by sensation, and may result in reflex muscular movements. If the anterior root be divided, stimulation of the peripheral portion is followed by muscular movements, while stimulation of the central end gives rise neither to sensation nor to reflex action. In the production of a simple reflex, by stimulation of the central end of the divided posterior root, the impulse passes from the terminal arborisation of the fibre, or of its collaterals, in the grey matter of the spinal cord across a synapse to the dendrons of a second neuron, the axon of that neuron passes it on to the dendrons of one or more of the multipolar cells, the axons of which constitute the anterior nerve-roots, and the impulse, altered in character, is thus transmitted to the responding muscles. There is thus a law of conduction, called the "*law of forward direction*," according to which an impulse will pass across a synapse from the axon of one neuron to the dendrons or cyton of another, but not in the reverse direction.

FIG. 14.—Two motor nerve-cells from the dog. (Photographed from preparations by Dr. Gustav Mann.) From Sharpey Schafer's *Essentials of Histology*.

a, normal (note the Nissl-spindles); *b*, after a period of prolonged activity.

The Function of the Cell.—In a reflex action the afferent impulse is usually greatly modified in its passage through the central nervous system. For example, the comparatively slight stimulus of a crumb in the larynx may be followed by violent coughing, accompanied by contraction of other muscles in addition to those concerned with expiration. Again, when a reflex movement is excited by stimulation of an afferent nerve, the impulses travelling along the efferent nerve have a rhythm which is independent of that of the exciting stimulus. It was

formerly thought that these and other modifications of the impulses in the nervous system were brought about by the nerve-cell. It has been shown in certain invertebrates, however, that reflex action can still take place for a short time when the cells associated with the fibres forming the reflex arc have been destroyed. This and other observations indicate that the characteristic features of reflex action must be attributed not to the nerve-cell but to the synapse, though impulses are normally conducted through the body of the cell from dendrons to axon. The function of the nerve-cell is purely nutritive.

The Function of the Axon.—The function of the axon is most conveniently studied in the spinal nerve-trunks. These contain true axons, which arise from the multipolar cells in the grey matter of the spinal cord, as well as afferent fibres in connection with the cells of the ganglia of the posterior roots of the spinal nerves, the latter not being axons in the restricted sense of the term, but showing no difference in function from the axons proper except as regards the direction in which they normally conduct impulses.

SECTION II

THE NERVES

A nerve to a limb, for example the sciatic, is composed of a number of cylindrical cords or funiculi, held together by connective tissue. Each funiculus is a bundle of nerve-fibres, and has a sheath of dense connective tissue, known as the *perineurium*. The nerve-fibres in the funiculus are supported by delicate processes of connective tissue, called the *endoneurium*. The loose tissue which binds the funiculi together and surrounds the whole nerve is known as the *epineurium*.

There are two kinds of nerve-fibres, medullated and non-medullated. The medullated variety consists of an *axis-cylinder*, the axon of a nerve-cell, enclosed in two sheaths: (1) a fatty-substance called *myelin*, immediately surrounding the axis-cylinder, and (2) an outer sheath, consisting of a transparent structureless membrane, called the *neurolemma*. The myelin sheath is interrupted at considerable intervals, the positions where it is wanting being known as *nodes of Ranvier*. About the middle of each internodal segment a nucleus is found, lying under the neurolemma and surrounded by a little protoplasm. The fixed and hardened axis-cylinder consists of parallel fibrils, embedded in an interfibrillar material. There is some reason to believe, however, that in the living condition the axis-cylinder may be in a semi-fluid state.

A non-medullated nerve-fibre has no myelin sheath, and consists only of an axis-cylinder ensheathed in a neurolemma, under which nuclei are found at irregular intervals.

Most nerves contain both medullated and non-medullated fibres, but in the nerves to the head, limbs, and body-walls medullated fibres predominate.

The chief chemical constituents of nerve-fibres are water, protein, nucleo-protein, lecithin, and cholesterol. The myelin sheath of medullated fibres is mainly formed of lecithin.

Physiological Properties of Nerve-Fibres.—Nerve-fibres have two properties, excitability and conductivity. If the nerve to a muscle be pinched with forceps, the muscle contracts. This experiment shows that, as a result of the mechanical stimulation, an impulse has been conducted from the stimulated spot to the muscle, and has caused the latter to contract. The nerve may be excited by other than mechanical stimuli. Drying or heating it, or the application to it of certain chemical substances, such as a strong solution of common salt, or the sudden variation in strength of an electric current passing through the nerve, will in like manner originate an impulse, causing the muscle to contract. As in the case of muscle, the most convenient stimulus for experimental purposes is the electric current.

There is reason to believe that, when a nerve is stimulated, the impulse projected along its fibres differs in kind from the condition at the stimulated point, just as, to use a crude illustration, the passage of a bullet along the barrel of a rifle differs from the explosion which causes it. An electrical stimulus may be applied to a nerve, and no impulse may be initiated, because the stimulus is too weak. Repetition of the stimulus may, however, be followed by the passage of an impulse. Obviously in such a case the original stimulus produced a change in the nerve, making it more sensitive to the succeeding stimulus. There may thus be an excitatory state without a resulting propagated impulse.

A second fact which may be cited in this connection is the effect of the passage of a constant current along a nerve. While the current is passing, the region of the nerve on either side of the negative pole has its excitability increased, that is, the excitatory state is more easily produced in that region. The conductivity in the same part of the nerve is, however, with a medium strength of current, diminished.

In view of these facts, the application of a stimulus to a nerve must be regarded as setting up a localised condition of excitement, which in its turn determines the projection of an impulse along the fibres of the nerve.

The Excitatory State.—The ease with which the excitatory

state may be set up, or, in other words, the excitability of the nerve to artificial stimuli, is found to vary with the conditions under which the nerve is placed.

1. The passage of an impulse along a nerve is followed by a brief period, ·0025 sec., during which the nerve is *refractory*, that is, it is not capable of being excited by a second stimulus. The period during which the nerve is absolutely inexcitable is followed by another, also very brief, in which it is relatively refractory, but the excitability is gradually returning. The refractory period is the result of the passage of the propagated impulse, and not of the excitatory state itself. This is proved by sending the second stimulus into the nerve at a different point from the first, in which case the refractory condition is found to be the same as when the second stimulus is applied at the same spot as the first.

2. The excitability of the nerve is increased by a moderate reduction of *temperature*, but, in order to demonstrate the rise in irritability, the make or break of a constant current must be used, the duration of induction shocks being too brief to be efficient with the cooled nerve.

3. The excitability is also varied by the passage of a *constant current* through the nerve, as has already been mentioned. When the current is made, an excitatory process is set up at the kathode, and, if the nerve is connected with a muscle, the muscle contracts. When the current is broken, an excitatory process is set up at the anode. This can be proved by tying a ligature tightly round the nerve of a muscle-nerve preparation between the electrodes. The ligature prevents the passage of the nervous impulse, but allows the passage of the electric current. If the electrode next the muscle is the kathode, the muscle contracts when the circuit is made, but not when it is broken. If, however, the direction of the current is altered by means of a commutator in the circuit, so that the anode is next the muscle, contraction of the latter occurs when the current is broken, but not when it is made.

When a constant current is passing along the uninjured nerve of a muscle-nerve preparation, the muscle is quiescent, but it can be shown by means of the experiment illustrated in fig. 15 that the excitability of the nerve is profoundly modified. A constant current is passed through the nerve of a muscle-nerve preparation, a commutator being introduced into the circuit, by which the direction of the current can be altered at will. Non-polarisable electrodes (B, C) are used to obviate fallacies arising from the setting up of polarisation currents. Electrodes from an induction coil (A) are applied to the nerve between the non-polarisable electrodes and the muscle. If, while the constant current is passing, stimuli are sent into the nerve from the induction coil, it

is found that shocks of medium strength vary in their effect according to whether the constant current has an ascending, or a descending, direction. If the current is descending, that is, if the kathode is next the stimulating electrodes, each induction shock excites a contraction of the muscle. If the constant current

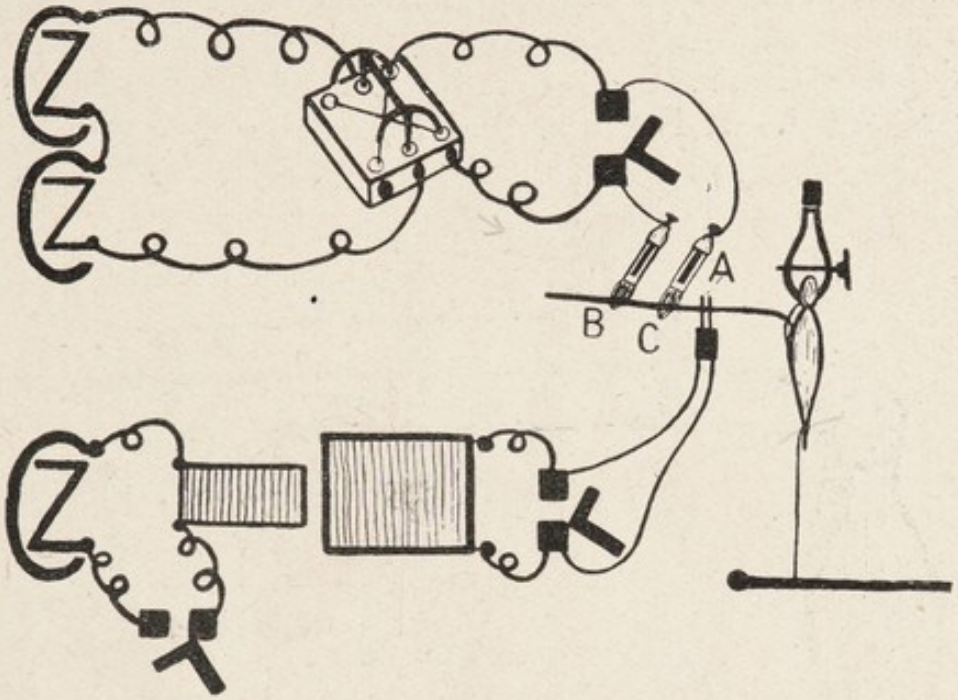


FIG. 15.—Diagram of apparatus used to demonstrate electrotonic changes of excitability in a nerve. A, stimulating electrodes; B and C, non-polarisable electrodes of constant current circuit.

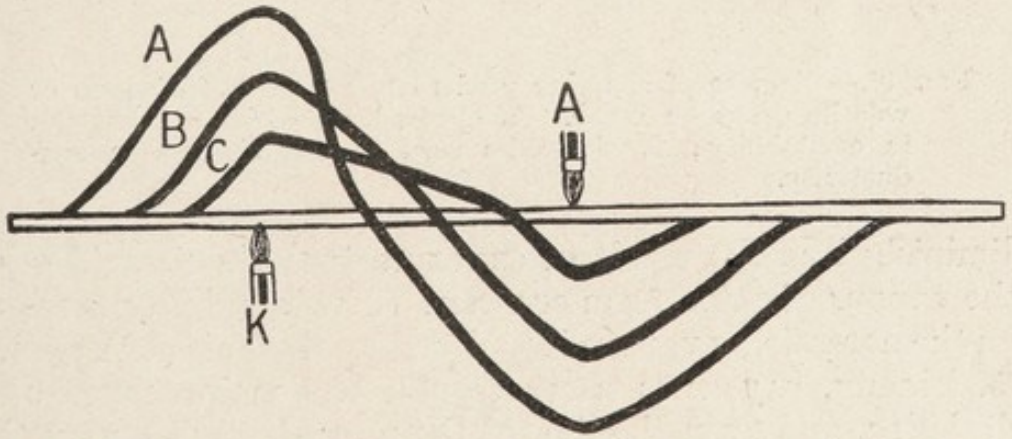


FIG. 16.—Diagram to show electrotonic changes of excitability in a nerve, A, with strong; B, with medium; C, with weak current. K, kathode; A, anode.

is reversed, so that the anode lies next the stimulating electrodes, the same strength of induction shock fails to produce a muscular contraction. A certain length of the nerve on either side of the kathode has its excitability increased, and is said to be in a condition of *kathelectrotonus*, while the part on either side of the anode has its excitability diminished, and is in a condition of *anelectrotonus* (fig. 16).

4. Various *chemical agents* modify the excitability of nerve. This can be demonstrated in the case of gaseous substances by placing the nerve of a muscle-nerve preparation in a tube with an inlet and outlet by which gases can be made to circulate through it (fig. 17). Electrodes, by which the nerve can be stimulated, are let into the tube between the gas apertures (A). A gas is allowed to circulate through the tube, and the nerve is stimulated at intervals, the contraction of the muscle, if any, being recorded. It is found that the excitability of the nerve

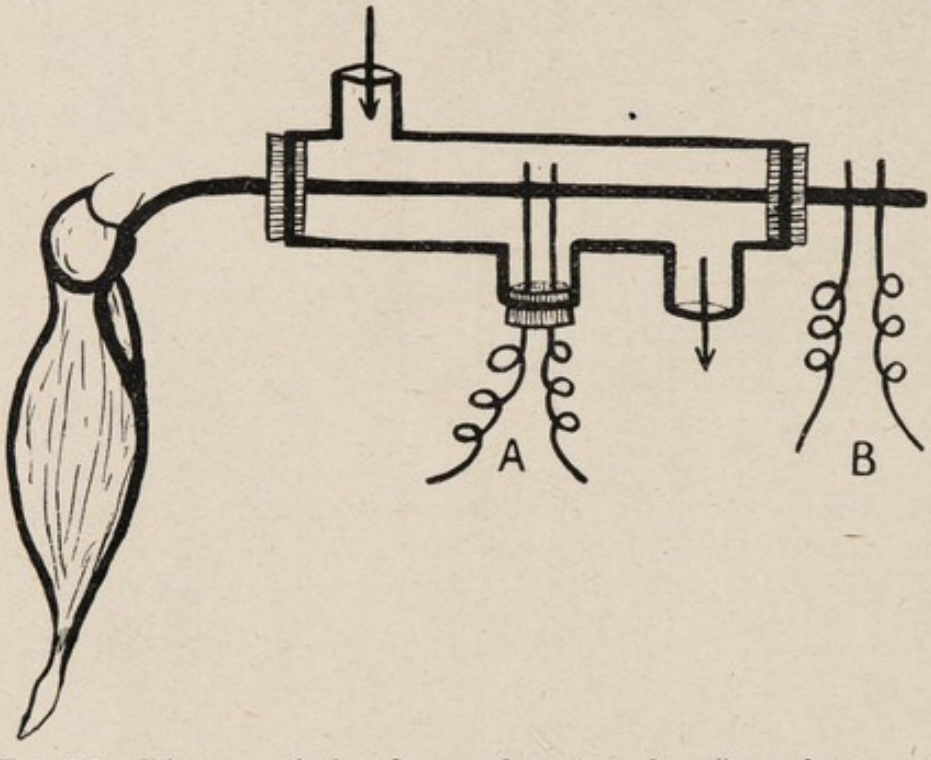


FIG. 17.—Diagram of chamber used to test the effect of gases or volatile drugs on nerve. A, electrodes used to test changes in excitability; B, electrodes used to test changes in conductivity.

is diminished as the result of exposure to carbonic acid gas, or to the vapour of chloroform or ether. The irritability is restored when the narcotising vapour is replaced by fresh air or oxygen.

5. Finally, *oxygen* is necessary for the maintenance of the excitability, and even the life, of the nerve-fibre. A nerve kept for a short time in an atmosphere consisting of an inert gas, such as hydrogen or nitrogen, no longer responds to a stimulus, though it is still capable of conducting an impulse. The loss of irritability takes place more rapidly if the nerve is stimulated.

The Propagated Impulse.—The impulse travels along a nerve-fibre at a definite rate, about 28 metres per second in frog's nerve. In human nerve the rate is estimated at about 120 metres per second. The rate of conduction is ascertained by means of the apparatus shown in fig. 18. The muscle of the muscle-nerve

preparation is attached to a lever, by which it records its contraction on a rapidly revolving drum. The drum has a contact key by means of which the primary circuit of an induction apparatus is made and broken during each revolution. The secondary coil is adjusted so that only the break shock excites a muscular contraction. Two pairs of electrodes are connected with the secondary coil by means of a commutator without cross wires. One pair is applied to the nerve close to the muscle (fig. 18, B), the other pair as far from the muscle as possible (fig. 18, A). Two tracings of the contraction of the muscle are

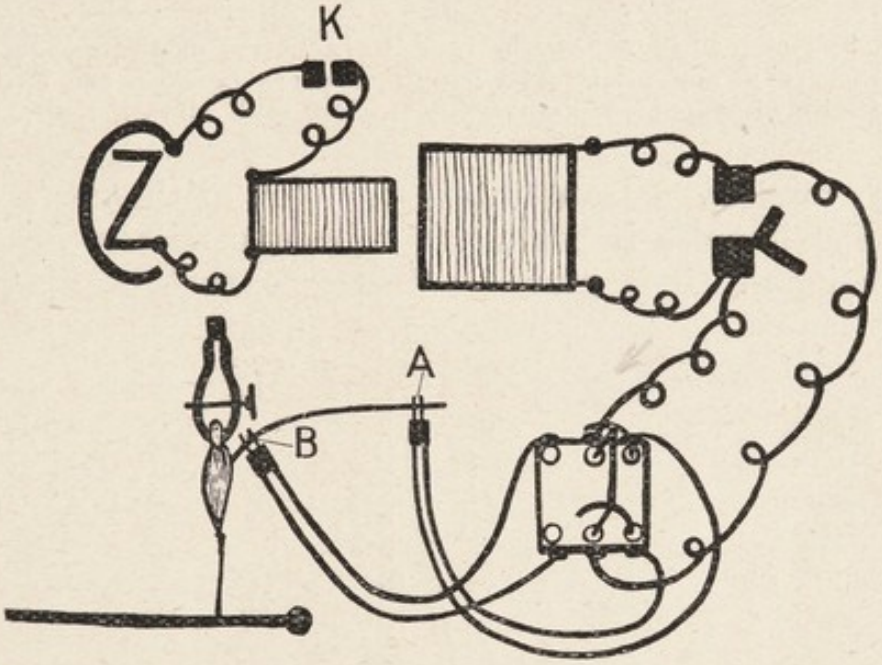


FIG. 18.—Diagram of apparatus used to ascertain the rate of conduction of the propagated impulse in a nerve. K, key; A and B, the two pairs of electrodes, which are used alternately.

recorded, one when the stimulus is applied close to the muscle, the other when the shock reaches the nerve through the farther electrodes. Finally, a time-tracing is taken by means of a recording tuning-fork. By measuring the length of nerve between the two pairs of electrodes, and the time interval between the two twitches, the rate of transmission of the impulse can be calculated. For example, in the accompanying tracing (fig. 19), the length of nerve between the two pairs of electrodes was 45 mm., and the tuning-fork recorded 100 vibrations per second. The difference in the duration of the latent period of the two twitches is measured, and represents the time required for the impulse to traverse 45 mm. of nerve.

The passage of the impulse is not accompanied by any measurable production of heat, nor is there any increase in the consumption of oxygen or the output of carbonic acid. The only

indication that an impulse is being transmitted is the simultaneous appearance of an electric wave, which can be detected by the

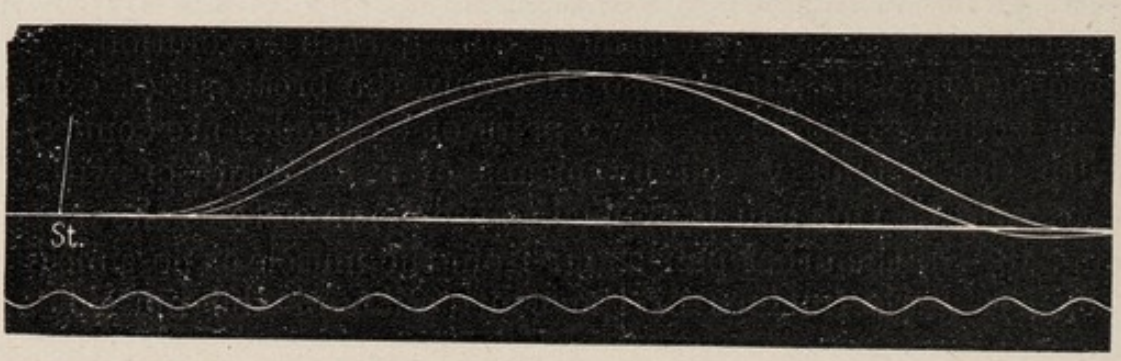


FIG. 19.—Tracing to show how the rate of conduction of a propagated impulse in a nerve is measured. The length of nerve between the two pairs of electrodes measured 45 mm. Time tracing, each vibration = $\frac{1}{100}$ second.

capillary or string galvanometer; the part of the nerve through which the impulse is passing is galvanometrically negative to the remainder. It is probable, therefore, that the propagation

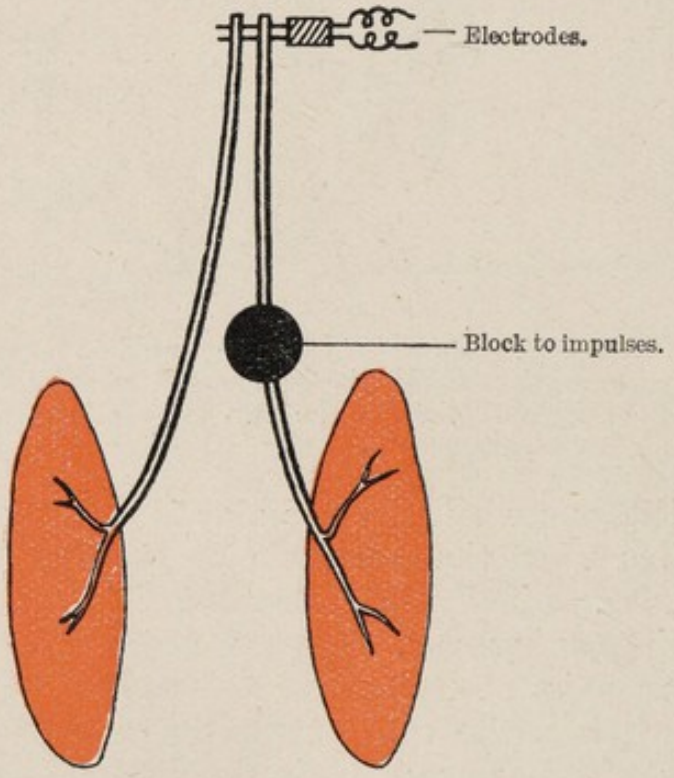


FIG. 20.—Diagram showing method of demonstrating non-fatiguability of nerve-fibres.

of the impulse is to be explained on physical rather than on chemical grounds.

The facility with which impulses may be conducted along a nerve is, like the excitability, subject to variations, according to the conditions under which the nerve is placed.

1. The conductivity is diminished by cold, and is abolished altogether by freezing. On the contrary, up to a certain point, it is increased by a rise of temperature.

2. It is diminished by the electrotonic state, that is, by the passage of a constant current through the nerve, the diminution being most marked in the region of the kathode.

3. The conductivity is also lowered by placing the nerve in an atmosphere of carbonic acid, or in the vapour of alcohol, chloroform, or ether. This can be shown by placing the nerve in the gas tube already described (p. 48), the stimulating electrodes in this case being placed outside the tube at the opposite end to the muscle (fig. 17, B).

A living nerve can transmit impulses for an indefinite period ; in other words, it cannot be fatigued so long as the oxygen-supply is adequate. If the nerves of two muscle-nerve preparations from the same frog are stimulated by a tetanising current through one pair of electrodes, the stimuli being prevented from reaching one muscle either by freezing a small section of the nerve between the stimulating electrodes and the muscle (fig. 20) or by the passage of a constant current through the same section, and if the experiment be continued till the unprotected muscle no longer responds to the stimulation, it will be found, on thawing the frozen section (or breaking the constant current), that the protected muscle immediately becomes strongly tetanised. Since both nerve-trunks have been equally stimulated, the failure of the unprotected muscle to contract is clearly not caused by fatigue of its nerve. It must therefore be due to fatigue either of the muscle itself or of the nerve-endings (end-plates) in the muscle ; and since, in the above experiment, the unprotected fatigued muscle will still contract when directly stimulated, the fatigue must have its seat in the nerve-endings.

Double Conduction in Nerve.—Generally speaking, normal conduction in any nerve-fibre takes place in one direction only, though it is believed that every nerve-fibre is capable of conducting an impulse in either direction. This belief rests on experimental evidence. (1) Electrical stimulation of the middle of a nerve-trunk is followed by a wave of negativity, starting from the excited area, and travelling to each end of the nerve. It has been shown that this result holds good, not only for mixed nerves, but also for the optic nerve, and for the dorsal roots of the frog's spinal nerves. (2) The gracilis muscle of the frog is divided by a tendinous intersection, in the neighbourhood of which each nerve-fibre to the muscle divides into two, one branch going to the muscle above the septum, and the other to the part below. If a nerve-containing part of the muscle below the

intersection is stimulated, both sections of the muscle contract, and it is supposed that the impulse passes up the efferent nerve-fibres to their point of division, and then down the branches to the upper portion of the muscle.

Function of Nerve-Fibres.—The only function of a nerve-fibre is to conduct impulses. These may, in normal circumstances, result from excitation of the peripheral termination of the fibre, in which case they travel towards the nerve-centre, and are described as *afferent*; or the excitation may be central and the direction of the impulse centrifugal, the impulse being described as *efferent*. In any one nerve-fibre, with the possible exception of the fibres of the dorsal spinal nerve-roots, the normal direction of the impulse is always the same, that is, it is either afferent or efferent.

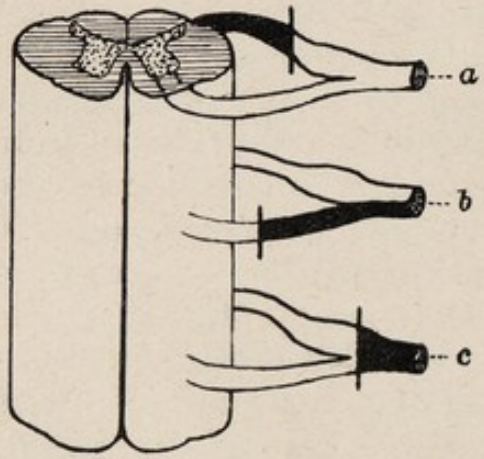


FIG. 21.—Diagram showing effects of section of spinal nerve-roots.

Degenerated portions black. *a*, section of posterior root central to ganglion; *b*, section of anterior root; *c*, section of both roots peripherally to ganglion.

Degeneration and Regeneration of Nerves.—It has already been pointed out that when an axon is cut off from the cyton to which it belongs, the severed part undergoes degeneration. When a nerve is cut, all the nerve-fibres in the peripheral portion are separated from their parent cells, and the severed nerve exhibits the physiological and histological changes which constitute degeneration (fig. 21). The excitability is increased for a brief period, then gradually dies away, and after two to five days the nerve is no longer excitable, nor will it conduct impulses.

The *degenerative changes* take place simultaneously along the entire length of the part of the nerve cut off from the cell, and may be visible within twenty-four hours in a warm-blooded animal. The histological changes in a medullated nerve-fibre consist first in a thickening of the neurolemma, with enlargement of the nuclei and increase of their surrounding protoplasm, while the myelin sheath becomes broken into fragments. A few days later the nuclei are seen to have divided and become more numerous; the myelin is in scattered droplets, and the axis-cylinder is broken up into short lengths. The myelin and axis-cylinder are gradually absorbed by the action of phagocytes, and after three or four weeks nothing is left but the neurolemma, containing protoplasmic material in which are imbedded many nuclei (fig. 22).

The chemical changes are equally marked. The complex lipoids which compose the myelin are broken down with the formation of simpler substances. Lecithin is split up into (1) a nitrogenous base, choline, (2) a fatty acid, which is usually oleic

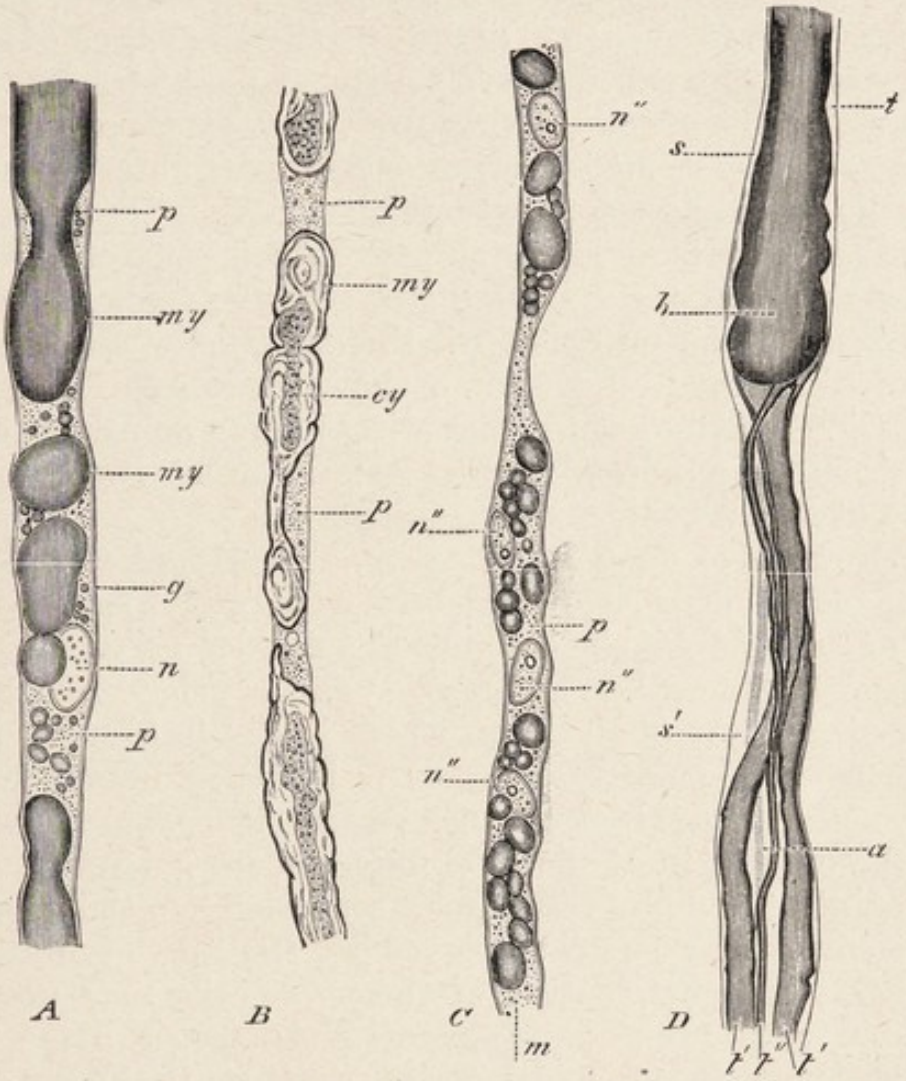


FIG. 22.—Degeneration and regeneration of nerve-fibres in the rabbit. (Ranvier.) From Sharpey Schafer's *Essentials of Histology*.

A, part of a nerve-fibre in which degeneration has commenced in consequence of the section, fifty hours previously, of the trunk of the nerve higher up; *my*, medullary sheath becoming broken up into drops of myelin; *p*, granular protoplasmic substance which is replacing the myelin; *n*, nucleus; *g*, neurolemma. *B*, another fibre in which degeneration is proceeding, the nerve having been cut four days previously; *cy*, axis cylinder partly broken up. *C*, more advanced stage of degeneration. *D*, commencing regeneration of a nerve-fibre. Several small fibres, *t'*, *t''*, have sprouted from the somewhat bulbous cut end, *b*, of the original fibre, *t*; *a*, an axis-cylinder which has not yet acquired its medullary sheath; *s*, *s'*, neurolemma of the original fibre.

acid, (3) phosphoric acid, and (4) glycerol. In consequence of these chemical changes it is possible at this stage to distinguish degenerating from normal fibres by means of Marchi's fluid, which is a mixture of osmic acid with potassium bichromate. This fluid stains degenerating myelin black, but leaves normal nerve-fibres unaffected. When all the myelin has been absorbed, the

completely degenerated fibre no longer stains with Marchi's fluid ; hence this method of identifying degenerating nerve-fibres is only available during the first three or four weeks after the fibres have been cut off from the nerve-cells.

When the nerve-fibres are completely degenerated, they can be distinguished from normal fibres by a special method of staining with hæmatoxylin called the Weigert-Pal method. The hæmatoxylin stains the myelin bluish-black, and consequently normal fibres are deeply stained whereas degenerated fibres from which the myelin has disappeared are left unstained.

When a nerve is divided, the portion still connected with the cell does not degenerate, though changes take place in the cyton itself. Within one or two days the cell swells and the Nissl-granules disappear ; and after a time the cell shrinks. Later, regeneration usually occurs, and within three months the cyton may return to a normal condition ; in other cases complete atrophy of the cell takes place.

Regeneration of nerve.—After a time regeneration takes place and the nerve may be restored to a normal condition ; this occurs more rapidly if the cut ends of a divided nerve are sutured together. Regeneration is brought about solely by the outgrowth of the part of the axon which is still in connection with the nerve-cell, though the process is hastened by the presence of the neurolemma of the degenerated fibre, which seems to assist the outgrowth of the new fibre, and to guide it along the right path to the muscle or gland with which it ultimately forms a new connection. The part played by the nerve-cell is shown by the fact that extirpation of the nerve-cells in a portion of the spinal cord prevents regeneration in motor fibres arising from that part of the spinal cord. Further, if the cut end of the peripheral portion of a divided nerve is covered by a rubber cap so as to prevent the growth of new fibres into it, no regeneration takes place.

Histological observations show that in the course of regeneration small fibrils with bulbous ends extend from the axis-cylinders of the central portion of the divided nerve, and pass along and between the neurolemmal sheaths of the degenerated distal portion. The mode of growth seems to be similar to that which has been observed to occur in the embryonic nerve-tissue of the frog. If fragments of the primitive nerve-tube of an embryo frog are kept in lymph, the fibres can be seen under the microscope to grow out from the nerve-cell.

The new fibres remain non-medullated for a time, a myelin sheath is developed later, and finally the neurolemma is formed.

The time taken for a nerve to regenerate, and to become

functionally connected with the motor or sensory structures to which it was formerly attached, varies with the distance to be traversed by the outgrowing fibres, and may be several months.

Regeneration still takes place if two nerves are divided and the central end of one is connected with the peripheral end of the other, provided that both nerves are either afferent or efferent. Thus, if the vagus nerve and the cervical sympathetic nerve are divided, and the central portion of the vagus is sutured to the headward (peripheral) portion of the cervical sympathetic, regeneration will occur, and stimulation of the vagal portion of the united nerve will produce the effects formerly resulting from stimulation of the sympathetic nerve. This experiment shows that the specific effects brought about by stimulation of a nerve are really due to changes in the nerve-ending, and not to any specific change in the nerve itself.

When nerve-fibres are divided in their course in the brain or spinal cord they undergo degeneration, but regeneration never occurs.

SECTION III

THE SPINAL CORD (SPINAL MEDULLA)

The spinal cord is a cylindrical structure, and consists of two symmetrical halves, right and left, separated on the ventral side by the anterior median fissure, and on the dorsal side by a septum of pia mater, the posterior median fissure (septum). Between the two fissures is a bridge of nervous substance connecting the two halves of the cord.

Examination of a transverse section of the spinal cord shows that it is composed of white matter (substance) and grey matter (substance), the former lying superficially, the latter deeply. The grey matter forms a crescent in each half, the convexity of each crescent being towards the middle line and being connected with the convexity of the crescent in the other half of the spinal cord by a commissure of grey matter. The central canal, containing cerebro-spinal fluid and lined by ciliated epithelium, lies in this commissure. In front of the grey commissure, and uniting the white matter of the two halves of the spinal cord, is the white commissure.

The white matter is subdivided by the posterior horn of grey matter into an antero-lateral, and a posterior, column (funiculus). The former is again roughly subdivided by the lateral bundles of the anterior nerve-roots into an anterior and a lateral column.

The grey matter contains numerous nerve-cells, arranged in

groups, each group representing a section of a column of cells running in the length of the cord. The columns are not uniform, but the cells are collected in masses corresponding with the primitive segments of the body. In a transverse section the cells are seen to lie for the most part in the respective horns, anterior and posterior, of the crescents of grey matter.

The white matter is composed of medullated nerve-fibres, running in a longitudinal direction, and having no neurolemma. These give off at right angles finer medullated branches, called collaterals, which run into the grey matter and terminate by forming arborisations in relation with the nerve-cells.

A pair of spinal nerves, right and left, arises from each segment of the spinal cord. Each nerve has two roots, an anterior, formed of the axons of the nerve-cells lying in the anterior horn of grey matter, and a posterior, consisting of fibres which are processes of nerve-cells contained in a ganglion placed on the root itself.

THE REGIONS OF THE SPINAL CORD

Three regions are distinguished in the spinal cord, the cervical, thoracic, and lumbar, and each of these possesses definite structural characteristics. The cervical and lumbar regions exhibit enlargements corresponding with the outflow of nerves to the arm and leg respectively. The differences in structure between the three regions are best seen by a comparison of transverse sections. The *cervical* region is oval in section, the long axis of the oval lying transversely; its anterior median fissure is relatively shallow, and the central canal is ventral to the true centre of the cord. The white matter is large in amount, the anterior horn (column) of grey matter is broad, and there is a well-marked septum subdividing the posterior column (funiculus) of white matter into medial and lateral portions. The *thoracic* region is cylindrical, its anterior median fissure is deeper, and the central canal is centrally placed. The anterior and posterior horns of grey matter are both narrow, and each grey crescent shows a projection in its concavity, known as the lateral horn. At the base of each posterior horn of grey matter, towards its medial aspect, is a special column of nerve-cells, called Clarke's column (the dorsal nucleus). The *lumbar* region resembles the thoracic region in shape, depth of anterior median fissure, and position of central canal, but its white matter is absolutely and relatively smaller in amount, and both anterior and posterior horns of grey matter are broad in section. Generally speaking, the white matter diminishes progressively in amount from above downwards, and the grey matter is most abundant in the

regions from which the outflow of the nerves to the limbs takes place.

THE NERVE-CELLS OF THE SPINAL CORD

The nerve-cells in the grey matter are multipolar and are for the most part irregular in shape, but those in Clarke's column are somewhat fusiform, with their long axes in the long axis of the spinal cord. The cells in the anterior horn are larger in size than those in the posterior horn. The axons of the anterior horn emerge from the anterior surface of each segment of the spinal cord in several groups, which unite to form the anterior root of a spinal nerve. The cells of the posterior horn are of two kinds: (1) those with axons which run a short course in the grey matter (cells of Golgi's second type), (fig. 13), and form terminal arborisations in relation with other nerve-cells in the grey matter, and (2) those the axons of which acquire a myelin sheath, run into the white matter, and divide into short descending and longer ascending branches.

In a transverse section of the spinal cord, especially if it be taken through the region from which the outflow of nerves to the anterior or posterior limbs takes place, the nerve-cells are seen to be arranged in well-marked groups. There are two groups in the ventral horn, a medial and a lateral; a third group, the intermedio-lateral column, lies in the lateral horn; and a fourth forms Clarke's column, already described. The cells in the dorsal horn are scattered irregularly.

The Nerve-Roots.—The anterior and posterior roots meet a short distance from the lateral aspect of the spinal cord, and unite to form a spinal nerve. Just before it joins the anterior root the posterior root exhibits a swelling, the spinal ganglion; the cells of the ganglion are unipolar, but the single process of each cell divides in a T-shaped manner into two fibres, one of which runs into, and the other away from, the spinal cord (fig. 13, Sensory).

The exit of the anterior root has already been described. The fibres of the posterior root, consisting of the central divisions of the processes of the ganglion-cells, enter the spinal cord in the neighbourhood of the posterior horn of grey matter. Each divides into a short descending and a longer ascending branch. The longest ascending divisions run upwards in the posterior column (funiculus) to reach the medulla oblongata. Others have a shorter course, and turn into the grey matter at varying distances above their point of entry to terminate by arborisations around nerve-cells; the descending fibres end in the same manner. Both ascending and descending fibres give off fine medullated

collateral branches at intervals, these also entering the grey matter to form terminal arborisations in relation with nerve-cells.

The Collateral Fibres.—Four main groups of collaterals arise from the ascending and descending divisions of the posterior root-fibres, and run into the grey matter. These are (1) fibres to the anterior horn of the grey matter of the same side, (2) fibres to the posterior horn, (3) fibres to Clarke's column, and (4) fibres to the grey matter of the opposite half of the spinal cord, running

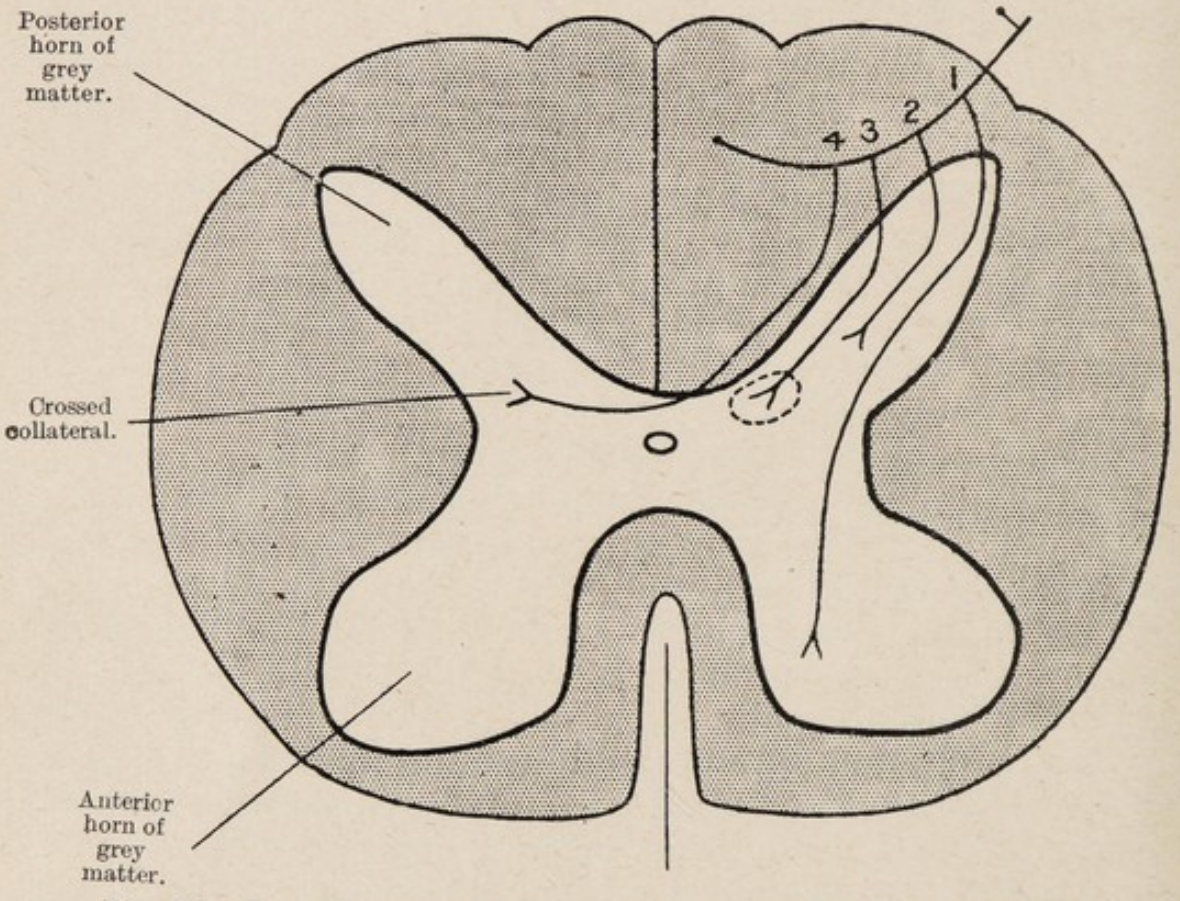


FIG. 23.—Diagram to show distribution of collateral fibres in spinal cord.

1, to anterior horn of grey matter; 2, to posterior horn; 3, to Clarke's column; 4, to grey matter of opposite side.

across in the grey commissure (fig. 23). These groups include the terminations of the descending divisions of the posterior root-fibres, as well as those of such of the ascending divisions as end in the cord itself. Both collaterals and terminal fibres end by forming arborisations in relation with nerve-cells, and are concerned, for the most part, with the formation of reflex arcs in the spinal cord.

Collaterals also enter the grey matter from white fibres in all parts of the anterior, lateral, and posterior columns (funiculi). Those from the long tracts of the white matter may be looked upon as associational in character, serving either (1) to distribute the impulses conveyed by the main fibres and so promote co-

ordination, or (2) to form part of a system of relays by which impulses are conveyed from segment to segment of the spinal cord.

THE FUNCTIONS OF THE SPINAL CORD

The functions of the spinal cord are two: (1) it is a centre or series of centres for reflex actions, and (2) it conducts impulses between the higher centres in the brain and the spinal nerves which transmit these impulses to, or from, the active or receptive tissues of the body.

SECTION IV

CONDUCTION IN THE SPINAL CORD

The spinal cord forms a pathway for impulses from the brain, these being distributed to all parts of the body through the anterior spinal nerve-roots and the spinal nerves. It also conducts impulses which are set up by stimulation of afferent nerve-endings, chiefly in the skin and muscles, and which reach it by the spinal nerves and posterior spinal nerve-roots to pass in an upward direction to the brain.

Impulses may be conducted: (1) by long tracts (*i.e.* collections) of nerve fibres situated in the white matter, and (2) by short association tracts or relays. Most of the long tracts are found in the peripheral part of the white matter. The short tracts lie more deeply, their fibres running a little way in the white matter, then turning into the grey matter to terminate by arborisations in relation with nerve-cells, the axons of which in their turn form other short tracts in the white matter; thus the impulses are conducted by a series of relays.

The tracts have been mapped out by two methods: (1) by observing the time during development at which the fibres in the various areas of the white matter of the spinal cord acquire a myelin sheath, and (2) by studying the degeneration which follows various lesions, either pathological or produced experimentally.

The Myelination Method.—This method depends upon the fact that in the course of development the various conducting tracts acquire their myelin sheaths at different periods, so that by examining embryos at different stages of development it is possible to determine the limits of each particular tract. Generally speaking, the longer fibres in the spinal cord become myelinated later than those fibres which run a shorter course; thus the pyramidal tracts do not acquire their myelin till after

birth (fig. 24). The beginning of functional conduction coincides with the period of acquisition of myelin. Fibres devoid of a medullary sheath are not stained by Weigert's method.

The Degeneration Method.—The degeneration method is based upon the fact that, when a medullated nerve-fibre is divided, the portion which is cut off from the nerve-cell of which it is a process undergoes degeneration. If the spinal cord is cut across in an animal, certain tracts degenerate in the part of the cord above the section, and other tracts degenerate in the part below the section. The former are said to have undergone ascending degeneration, and their fibres are axons of cells which lie below the point of section. The latter are said to have undergone descending degeneration, and their fibres are axons of cells which lie above the point of section. The extent of the degeneration varies in different parts of the white substance. In the case of the short tracts it extends for a limited distance from the section; in the case of the long tracts it may extend from the section to the upper or lower extremity of the spinal cord. From what has been said of the function of the neuron it will be evident that the tracts which show descending degeneration are those which convey descending impulses, while those which show ascending degeneration are those which carry ascending impulses.

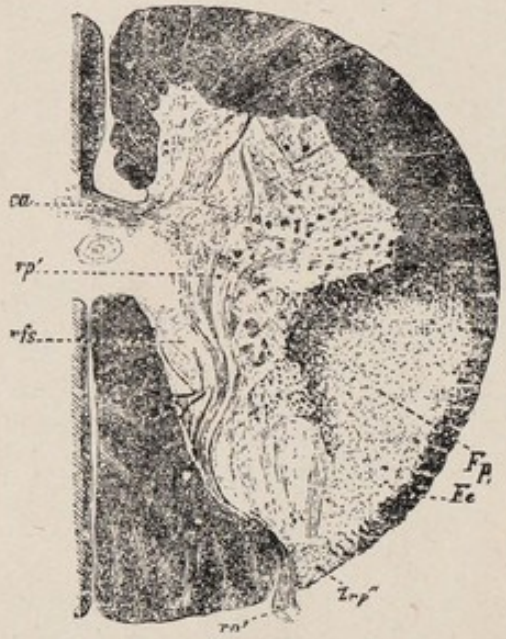


FIG. 24.—Section through the cervical spinal cord of a newborn child, stained by Weigert's method to show absence of medullation in pyramidal tract. (Bechterew.) From Starling's *Principles of Physiology.*

ca, anterior commissure; *Fp*, crossed pyramidal tract; *Fe*, direct cerebellar tract; *rp'*, posterior root-fibres.

The chief conducting tracts of the spinal cord are shown in fig. 25.

THE DESCENDING TRACTS (OR FASCICULI)

The principal long, descending tracts are the direct and crossed pyramidal tracts (the anterior and lateral cerebro-spinal fasciculi), both of which take origin in the cerebral hemisphere. The precentral convolution of each hemisphere contains certain large pyramidal cells, known as Betz cells, the axons of which are collected into a tract which runs through the mid-brain and pons

to the medulla oblongata. In the latter structure the majority of the fibres in each tract cross to the opposite side to become the *crossed pyramidal tract* (lateral cerebro-spinal fasciculus) of the spinal cord, while the remaining fibres run down without crossing to become the *direct pyramidal tract* (anterior cerebro-spinal fasciculus) of the same side.

The fibres of the crossed pyramidal tract terminate by running

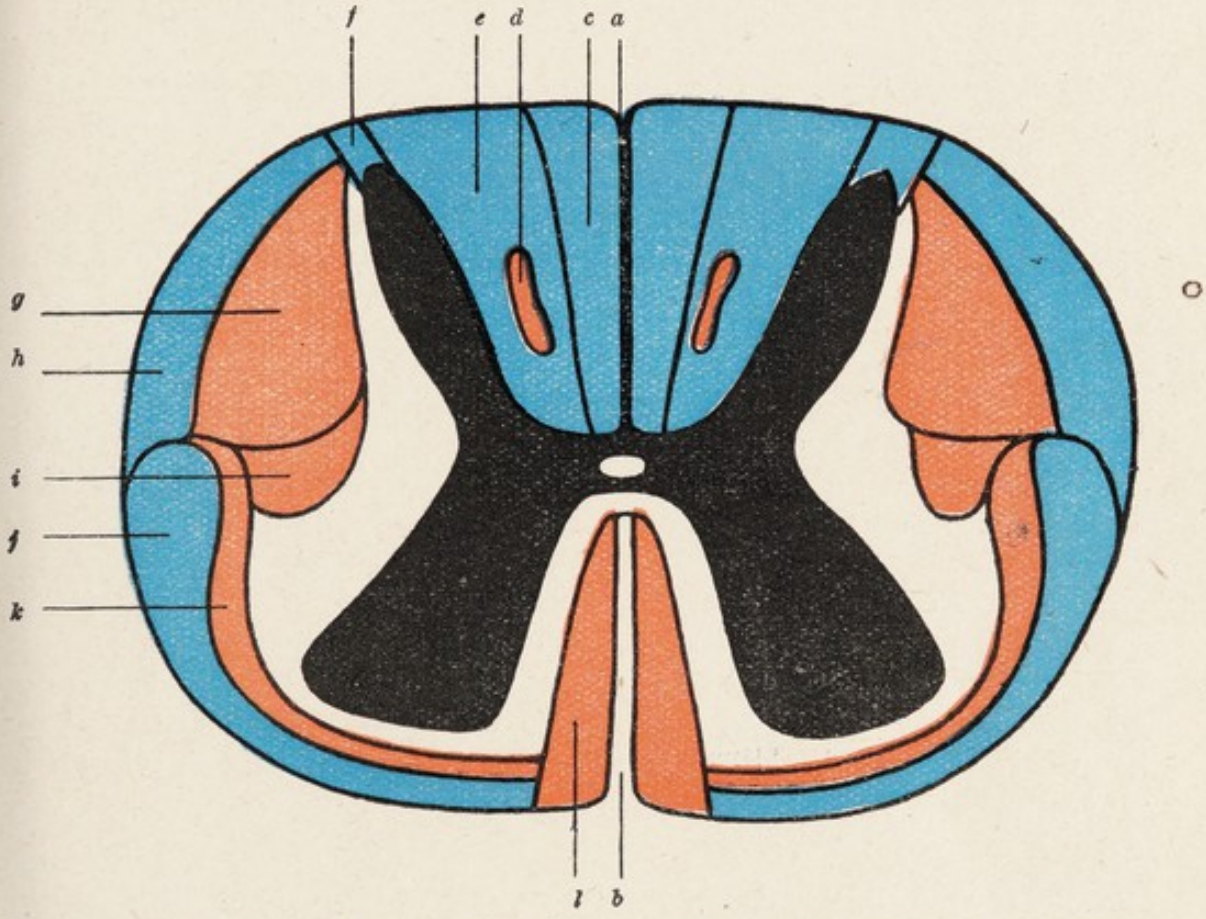


FIG. 25.—Diagram of the principal conducting tracts in the spinal cord. Descending tracts are coloured red; ascending tracts are blue.

a, Posterior median sulcus; *b*, anterior median fissure; *c*, fasciculus gracilis; *d*, comma tract; *e*, fasciculus cuneatus; *f*, Lissauer's tract; *g*, crossed pyramidal tract; *h*, direct cerebellar tract; *i*, rubro-spinal tract; *j*, ascending antero-lateral tract; *k*, descending antero-lateral tract; *l*, direct pyramidal tract.

into the grey matter at the base of the posterior horn of grey matter, where they form arborisations. By means of intermediate neurons the pyramidal fibres are brought into relationship with the cells of the anterior horn of grey matter, the axons of the latter forming the nerve-fibres of the anterior nerve-roots.

The fibres of the direct pyramidal tract cross in the spinal cord itself in the anterior white commissure to terminate in relation with the nerve-cells of the anterior horn of the opposite side.

Each pyramidal tract conveys motor impulses from one cerebral hemisphere to the opposite side of the body, a number of fibres terminating in each segment of the spinal cord, so that

the tracts become progressively smaller as they descend. The fibres of the direct pyramidal tract all cross in the cervical and thoracic regions.

Less is known of the function of the other tracts and fibres which undergo descending degeneration. The best marked of these is the *rubro-spinal tract,* which lies in the lateral column, immediately in front of the crossed pyramidal tract, and consists of the axons of cells forming the red nucleus of the mid-brain. These fibres cross in the mid-brain close to their place of origin.

The comma tract, lying in the posterior column, consists of the short descending branches of fibres which enter the spinal cord from the posterior nerve-roots.

The *olivo-spinal tract* lies close to the surface opposite the anterior horn of the grey matter. As its name indicates, it is made up chiefly of fibres which are the axons of cells in the olivary nucleus of the medulla oblongata.

Vestibulo-spinal fibres, probably derived from the cells of Deiters' nucleus, are found in the antero-lateral column.

The *cerebello-spinal tract of Löwenthal,* also lying in the antero-lateral column, consists of scattered fibres derived from cells in the cerebellum.

THE ASCENDING TRACTS

The ascending tracts may be classified as exogenous or endogenous, according as they originate from cells in the ganglia of the posterior roots of the spinal nerves, or from cells in the grey matter of the spinal cord itself.

The exogenous tracts are the funiculus (fasciculus) gracilis (Goll's column), the funiculus (fasciculus) cuneatus (Burdach's column), and the bundle of Lissauer. The first and second of these together form the greater part of the posterior column, while the third lies close to the tip of the posterior horn of grey matter.

The *funiculus gracilis* occupies the medial portion of the posterior column. It consists of long ascending fibres derived from the posterior nerve-roots: these terminate in the medulla oblongata by arborisation round the cells of the nucleus gracilis. The fibres of this tract are situated first in the funiculus cuneatus; as they ascend in the spinal cord they come to lie nearer the middle line and more posteriorly, so that in the cervical region those associated with the lower limb occupy a position medial and dorsal to those which have entered the spinal cord at higher levels.

The fibres of the *funiculus cuneatus* are also ascending, and are derived from the posterior spinal nerve-roots. Many of them

terminate by arborisation in relation with the cells of the nucleus cuneatus of the medulla oblongata. Some, however, enter the grey matter of the spinal cord itself.

The *bundle of Lissauer* likewise consists of the ascending divisions of posterior root-fibres. These have a short course, and terminate by running into the grey matter of the spinal cord.

The chief endogenous ascending tracts are the direct cerebellar and the antero-lateral ascending tracts, which lie in the peripheral part of the antero-lateral column.

The *direct cerebellar tract* (dorsal spino-cerebellar fasciculus) consists of fibres which are the axons of cells in Clarke's column of the same side, and it is found only in the thoracic and cervical regions. It runs through the medulla oblongata and forms part of the restiform body, terminating finally in the vermis of the cerebellum.

The *antero-lateral ascending tract* (ventral spino-cerebellar fasciculus) is found in the lumbar, as well as in the thoracic and cervical regions. Its fibres are derived from the cells of Clarke's column of the opposite side, and it runs through the medulla oblongata and pons to the mid-brain, where it turns round to form part of the superior cerebellar peduncle. It ends in the vermis of the cerebellum.

Associated with the ventral spino-cerebellar tract are two other groups of fibres: (1) the *spino-thalamic*, which ascends through the medulla oblongata, pons, and mid-brain to terminate in the thalamus, and (2) the *spino-tectal*, which terminates in the corpora quadrigemina. The ventral spino-cerebellar, spino-thalamic, and spino-tectal fasciculi together form what was formerly known as Gowers' tract.

THE PHYSIOLOGICAL PATHS IN THE SPINAL CORD

The experimental methods described above for the determination of the conducting tracts of the spinal cord give little information regarding the nature of the impulse conveyed by each tract. For this purpose it is necessary to observe the effects of division of the tracts in animals, or of injury of the tracts by accident or disease in man.

Complete section of the spinal cord in the *lower thoracic region* is followed by immediate loss of movement and sensation in the hind limbs. There is also loss of vascular tone with passive dilatation of the blood-vessels (passing off in twenty-four hours), and the hind limbs become poikilothermic, that is, their temperature varies with that of the surrounding medium. Further, the reflex visceral centres in the lumbar region are cut off from the

inhibitory impulses from the higher centres, so that micturition and defæcation become simple reflexes. Later, the crossed pyramidal and rubrospinal tract below the point of section, and the funiculus gracilis, funiculus cuneatus, direct cerebellar and other ascending tracts above the section, undergo degeneration. If the direct pyramidal tract has not crossed entirely above the level of the section, it also will degenerate below the lesion.

Complete section of the spinal cord in the *cervical region* is followed by similar motor and sensory paralysis in all parts below the lesion. In addition there is a great fall of arterial blood-pressure, owing to the greater vascular area involved. If the section is above the origin of the phrenic nerves, there is also paralysis of the diaphragm.

A unilateral lesion of the human spinal cord in the lower thoracic region results in motor paralysis of the homolateral hind limb, accompanied by loss of muscular sense and of tactile discrimination (this being the power of distinguishing two separate, and simultaneous, tactile stimuli) on the same side. There is also loss of heat, cold, and pain in the contralateral hind limb, the fibres for these senses having crossed in the spinal cord shortly after their entrance by the posterior roots. Immediately below the lesion, however, this sensory paralysis occurs in a narrow zone on the side of the section, since some fibres have been divided before their crossing. Sensibility to touch and the power of localising a touch are impaired in both limbs, but are not completely lost in either limb; each half of the spinal cord must therefore contain fibres which convey impulses giving rise to sensations of touch from both limbs. The remote effects of a unilateral lesion or section are degeneration of the descending tracts below, and of the ascending tracts above, the lesion or section, on the injured side only.

If the posterior roots conveying afferent fibres from one hind limb be divided in an animal, there is total loss of sensibility in that limb, and there is also loss of muscular tone, owing to the absence of afferent impulses from the muscles themselves. If the section of the roots has been made between the spinal ganglia and the cord, degeneration occurs central to the section, and can be traced into the fasciculus cuneatus; but as the fibres pass to the higher regions of the cord they are seen to shift into the dorso-medial part of the fasciculus gracilis, and to end in a cell-station in the medulla oblongata.

It has been ascertained by experiments and observations such as these that *motor* impulses are conveyed from one side of the brain to the neurons of the anterior nerve-roots of the opposite side by the pyramidal (cerebro-spinal) tracts. Other tracts are

also used in the lower animals, because, whereas in man interruption of the pyramidal tracts is followed by complete and permanent paralysis of the muscles below the lesion, section of the cerebro-spinal tract in the dog or monkey, for example, is followed by paralysis which is not permanent.

There is a certain degree of weakness of muscles on the opposite side of the body after a unilateral lesion of the upper part of the human spinal cord, because of the interference with the direct pyramidal tract, the fibres of which cross immediately before their termination; but this is relatively insignificant, and, as the fibres of the direct pyramidal tract have all crossed in the cervical and thoracic regions, a unilateral lesion in the lower thoracic region will result in motor paralysis of the corresponding hind limb only.

The afferent paths for *tactile discrimination* and for *kinæsthetic* impulses (from muscles, tendons, and joints) are the fasciculus gracilis and the fasciculus cuneatus. These tracts terminate in the medulla oblongata in cell-stations from which the fillet arises. The fillet crosses to the opposite side close above its origin, the decussation being above that of the pyramids, and runs into the thalamus, from which a third set of neurons is distributed to the cortex of the cerebral hemisphere (fig. 26).

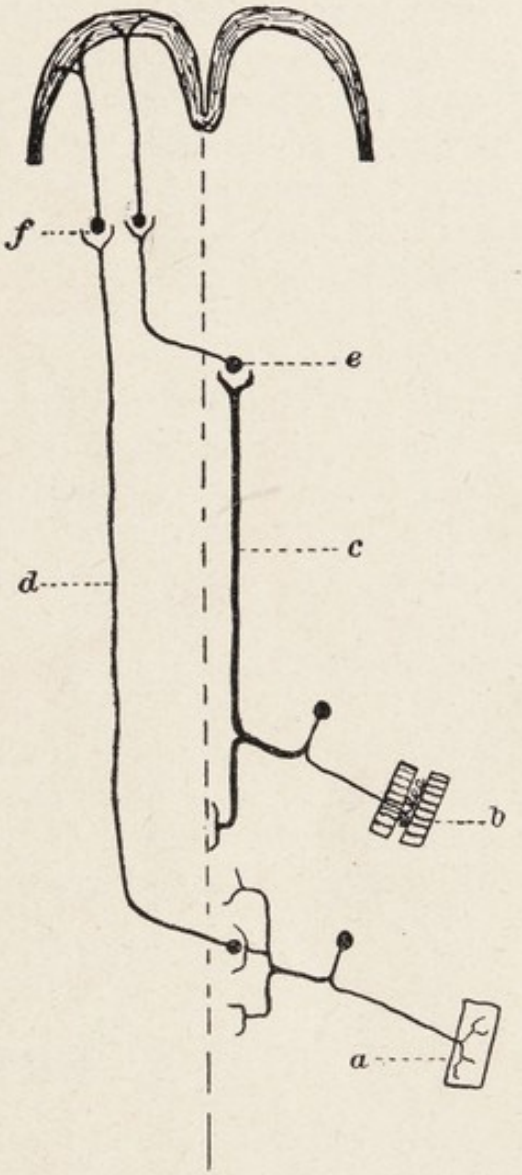


Fig. 26.—Diagram showing paths of sensory impulses.

a, skin; *b*, muscle; *c*, funiculus gracilis; *d*, spino-thalamic tract; *e*, nucleus gracilis thalamus.

The direct cerebellar and the antero-lateral ascending (Gowers') tracts also convey impulses from muscles, tendons, and joints, but these differ from those conveyed to the cerebral hemispheres in that they are not connected with conscious sensation. The fibres of the direct cerebellar tract are derived from the cells of Clarke's column of the same side of the cord, those of the antero-lateral ascending tract from Clarke's column of the opposite side. Both

these tracts are uncrossed in their course to the cerebellum, and in neither is there a cell-station on the path.

The fact that the four long ascending tracts convey impulses of muscular sense is to be associated with the importance of the function of equilibration, a function which requires for its performance delicate muscular adjustments.

Impulses giving rise to sensations of *pain*, *heat*, and *cold* are conveyed into the posterior horn of grey matter by fibres of the posterior roots and their collaterals. They then pass by a second neuron to the spino-thalamic tract of the opposite side, and thus reach a cell-station in the thalamus, from which they are passed on to the cerebral cortex. Impulses producing sensations of *touch* and *tactile localisation* pass up the posterior column of the same side for four or five segments before reaching a cell-station in the grey matter, from which they are conveyed by other neurons to the anterior column of the same and of the opposite side (fig. 27). They too ultimately reach the thalamus, and pass to the cerebral cortex by a fresh relay.

The various sensory impulses which cross in the cord itself appear to be transmitted by independent sets of nerve-fibres. In the disease known as syringomyelia, which is characterised by dilatation of the central canal of the spinal cord with consequent interference with fibres crossing in the grey matter, the sense of pain may be lost, while those of temperature and tactile localisation are unimpaired, or the sense of temperature may be lost while the other senses are intact.

SECTION V

REFLEX ACTION

By reflex action is meant that, in response to an impulse reaching the central nervous system along an afferent nerve, the nervous system sends out an impulse along an efferent nerve to a muscle, or a gland, exciting or inhibiting its activity. The production of a reflex is independent of the will.

In the course of evolution survival has depended, to a large extent, upon the rapidity and efficiency with which reflex movements are carried out. It is important, therefore, (1) that the reflex action should be rapidly effected, and (2) that it should be co-ordinate, that is, that the muscles concerned should contract in such a way as best to attain the end for which the reflex exists. Further, the response to a stimulus must be limited in its extent, and must not involve the whole muscular system. Finally, evolution is made possible by the capacity of the central nervous

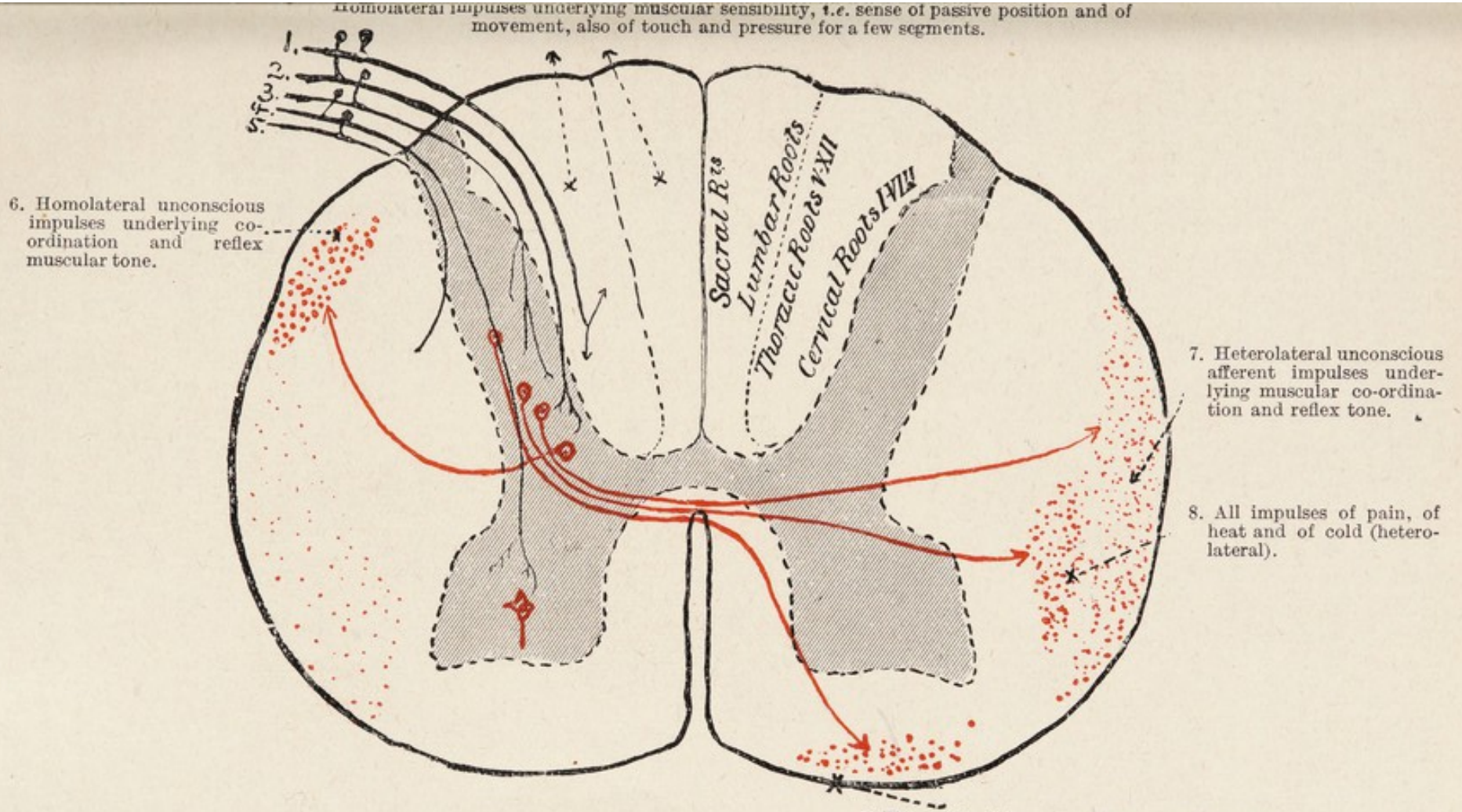


FIG. 27.—Diagram to illustrate the termination of peripheral afferent fibres in the spinal cord, and the origin of the secondary central-paths, with a brief summary of their functions. (W. Page May.) From Starling's *Principles of Physiology.*

1, bundles of fibres passing up in the posterior column, many to spinal cord, the remainder to nuclei in medulla oblongata; 2, fibres terminating round cells in Clarke's column; 3, fibres arborising round cells in posterior horn; 4, fibres arborising round cells of anterior horn; 5, fibres to lateral column; 6, direct cerebellar tracts; 7 and 8, Gowers' tract; 8, spino-thalamic and spino-tectal tracts; 9, ascending tract in anterior column.

system to form new reflexes, and this capacity is the basis of habit and of educability. It is in this respect that the nervous system of man has become so much more highly differentiated and complex than that of the lower animals.

In man the reflex functions of the spinal cord have become to a large extent subordinate to those of the brain ; and the spinal cord, when separated from the brain as a result of injury, displays a very feeble reflex power. In the lower animals the spinal reflexes are more pronounced, and can be readily studied either in the pithed frog or in a " spinal " mammal, that is, an animal which is allowed to recover after transection of the spinal cord, this being usually made in the upper thoracic region.

The Reflex Arc.—The structures concerned in the production of

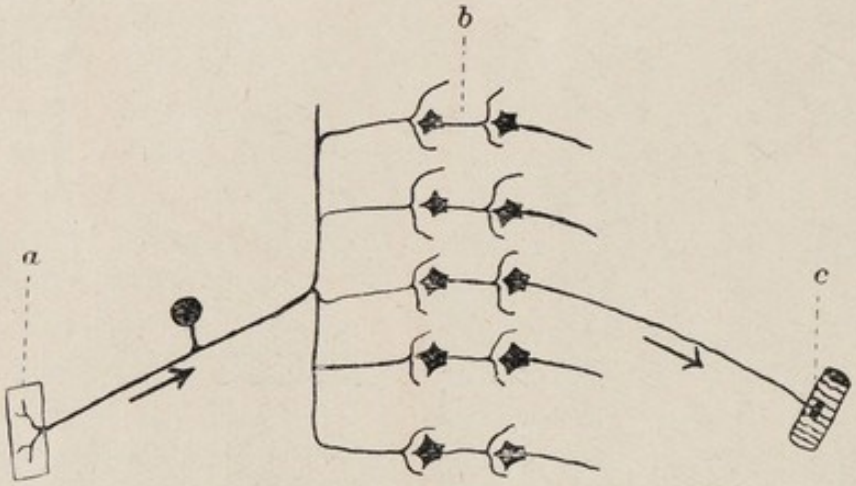


FIG. 28.—Diagram of a reflex arc.
a, receptor; *b*, intermediate neuron; *c*, muscle-fibre.

a reflex constitute what is known as a reflex arc. They consist of (1) a sensory surface or sense-organ, which is called a *receptor*, (2) an afferent nerve, (3) a chain of neurons in the nerve-centre, (4) an efferent nerve, and (5) a muscle or gland, described as the *effector* organ (fig. 28).

A stimulus applied to a receptor sets up an impulse which travels along the afferent nerve, through the neurons, and then along the efferent nerve to the effector organ, arousing or lessening its activity. Impulses which check or abolish the activity of a muscle or gland are called inhibitory impulses. Interruption of the arc at any point abolishes the reflex action.

The time occupied by an impulse in travelling from the receptor through the central nervous system to the effector organ is called the *total reflex time*. A part of this time is occupied in the transmission of the impulse along the afferent and efferent nerves, and by the latent period of the effector organ. When this is deducted from the total reflex time, a period remains, known as

the *reduced reflex time*, which is occupied by the passage of the impulse through the neurons in the central nervous system. Its duration varies with the complexity of the reflex action, and is taken up mainly in the transmission of the impulse across the synapse between the axon of one neuron and the dendrites of the next neuron, the synapse offering a certain resistance to this passage.

It has been found in the frog, for example, that, when one leg moves in response to a stimulus applied to the skin of that leg, the reduced reflex time is rather less than one-hundredth of a second. The reduced reflex time for reflex winking of the eye in man has been estimated at about one-twentieth of a second.

The time required for the production of a reflex becomes less with increasing strength of the stimulus, and becomes longer when the spinal cord is fatigued or is under the influence of drugs, such as chloroform. If the strength of stimulus necessary to elicit a particular reflex is determined, and the experiment is repeated with a stronger stimulus, (1) there may be an increase in the strength of the original response, and (2) additional muscles may also be thrown into contraction. In other words, with a stronger stimulus there is a spread of the excitation in the grey matter of the spinal cord, whereby additional reflex arcs become involved ; this spreading of the excitation is known as *irradiation*.

When, for example, a harmful (nocuous) stimulus, such as a sharp prick, is applied to the sole of the foot in the spinal dog, the leg is flexed and withdrawn from the stimulus. When the strength of the stimulus is increased, the muscular response may extend to the opposite leg and to other parts of the body. This experiment shows that an impulse reaching the spinal cord finds its way most easily along a certain path, and that its spread up or down the cord is normally prevented by the resistance offered by neighbouring synapses.

After the injection of strychnine this resistance disappears, and an impulse reaching the cord at any level evokes generalised muscular movements which are inco-ordinate. The normal limitation of the reflex response is thus an important part of the means by which the object of the reflex is attained.

Inhibition.—Reflexes may be restrained or completely inhibited by impulses, voluntary or involuntary, from the higher nerve-centres. If a reflex is elicited in a frog from which the cerebral hemispheres have been removed, and then a crystal of common salt is applied to the optic lobes and the stimulus is repeated, the reflex movement may not occur, owing to inhibitory impulses resulting from the stimulation caused by the salt. Again, if the spinal cord is isolated from the brain in a mammal,

a stimulus which would, under normal conditions, elicit a spinal reflex of a definite and orderly kind, often brings about more extensive and less orderly muscular contractions. A reflex act which is in progress may also be checked or inhibited by the advent of another stimulus to the central nervous system. Further, inhibition forms a constituent of many reflex actions, the contraction of certain muscles being accompanied by the simultaneous relaxation, that is, inhibition, of others.

Reciprocal Innervation.—When firm pressure is applied to the sole of the foot in a spinal dog, the animal responds by rapid extension of the leg, due partly to contraction of the extensor muscles of the thigh. It is evident that full extension is only possible if the flexor muscles (hamstrings) are at the same time relaxed; and their relaxation is not a passive, but an active, process, and forms an essential part of the extensor reflex. This can be shown by separating the extensor and flexor muscles of the thigh from their lower attachments, and connecting them with recording levers. It is then found that the application of firm pressure to the foot produces simultaneously contraction of the extensor, and inhibition of the flexor, muscles, the inhibitory effect manifesting itself as diminution of muscular tone; and if it is already under slight tension, the relaxed muscle lengthens. In the same way contraction of a flexor muscle in response to a suitable stimulus is accompanied by inhibition of the antagonistic extensor muscle (fig. 29).

This relationship, which holds for the action of antagonistic muscles in general, is spoken of as *reciprocal innervation*, and its importance for the efficiency of a reflex action is demonstrated by the effects which are observed when it no longer takes place. The scratch-reflex, for example, in the dog consists of rhythmic movements of flexion and extension of the leg, each flexion recurring about four times a second; in the normal animal the movements are directed to the removal of an irritant. The region of the skin affected by the scratching movements is a saddle-shaped area occupying the thoracic region, and is known as the "scratch-area." The same reflex can be evoked in a spinal dog by the application of a weak electrical stimulus to the skin of this region, and, if the movements of the muscles are recorded by levers writing on a smoked surface, it is found that, with each flexion of the leg, the flexor muscles contract and the extensors are inhibited; with each extension of the leg the converse takes place. After the injection of strychnine into the animal, the application of the stimulus produces simultaneous contraction of both flexor and extensor muscles, and, since the extensors are the more powerful, the limb becomes rigidly ex-

tended and the scratch-reflex can no longer be carried out. The process of inhibition is therefore as important as that of contraction in any reflex movement, and the inhibitory impulses arise in the central nervous system. The nature of the process whereby at one time motor, and at another time inhibitory, impulses are sent to the same muscle is not understood.

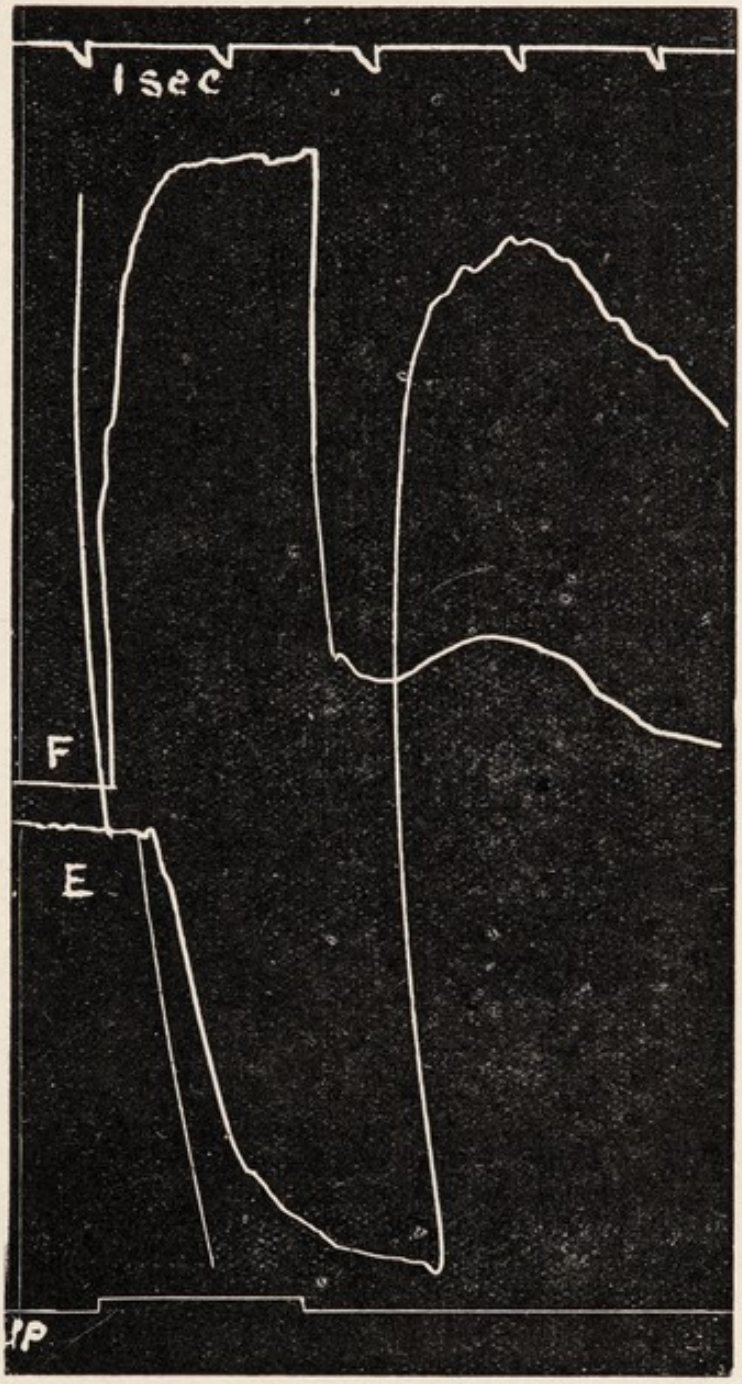


FIG. 29.—Reciprocal reflex of antagonistic muscles of knee (cat). Stimulation of the central end of the (ipsilateral) popliteal nerve (I.P.) causes contraction of a flexor of the knee (F) and relaxation of an extensor of the knee (E). Rise of lever = contraction. (Sherrington.)

Since the muscles in the body are limited in number, whereas the impulses which may reach the spinal cord or brain are almost infinite in variety, it is clear that the same muscle must at times be used in response to different kinds of stimuli in different reflex actions. For example, the flexor muscles of the leg contract during the scratch-reflex, and also in response to a painful stimulus; in each case the impulse travels down the efferent nerve to the muscle. Hence the motor side of the reflex arc is, to some extent, identical for both the scratch-reflex and the response to the painful stimulus; it is therefore spoken of as a *final common path.*

Further, we find, as might be expected, that the final common

path can only be traversed by one set of impulses at the same time. If, for example, the scratch-reflex is evoked in a spinal animal, and, while it is taking place, a strong painful stimulus is applied to the sole of the foot, the scratch-reflex immediately stops, and is replaced by flexion of the leg (fig. 30). Conversely, if the flexion-reflex is in progress, the application of the scratch stimulus, if sufficiently strong, may inhibit the flexion-reflex and produce the scratch-reflex.

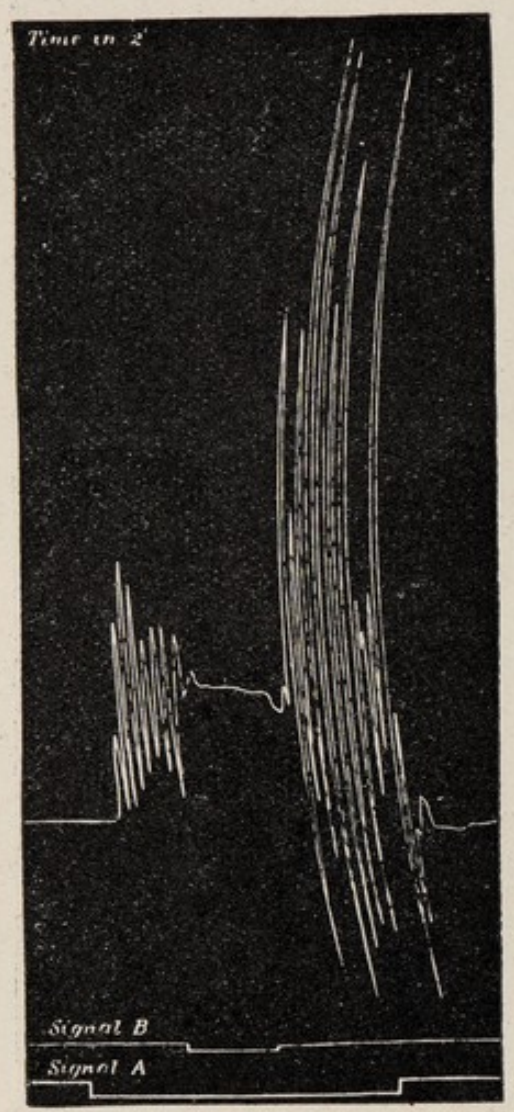


FIG. 30.—Scratch-reflex temporarily inhibited by application of a painful stimulus to foot. (Sherrington.) From Starling's *Principles of Physiology.*

Signal A, stimulation of scratch-area. Signal B, stimulation of paw by strong induction shocks.

The two reflexes cannot coexist; one or the other must prevail, and the one which prevails is called the *prepotent* reflex, and is usually that which is most important for the well-being of the body. The fact that two opposed reflexes, such as those just mentioned, cannot coexist is of great importance, since, if they were taking place simultaneously, neither would be carried out effectively.

Facilitation.—When a stimulus which is too weak to produce a reflex response is repeated at short intervals, the reflex is often ultimately evoked (fig. 31). Evidently the preceding stimuli, though causing no visible response, bring about some change in the neurons concerned with the reflex act, whereby the stimulus finally becomes effective. This process is known as facilitation, and forms the basis of habit. Each time a reflex takes place it becomes easier for it to be brought about on a subsequent occasion. This is well seen in the case of many skilled movements, such, for example, as walking, which, in the first instance, are learnt by voluntary effort; in time, the adjustment of the impulses concerned in the carrying out of these movements becomes so exact that, in response to a suitable stimulus, they take place without voluntary effort and almost independently of consciousness.

By these means reflex actions are so adjusted as to bring about

a definite movement as rapidly as possible in response to a suitable stimulus. For this purpose the coexistence of consciousness is

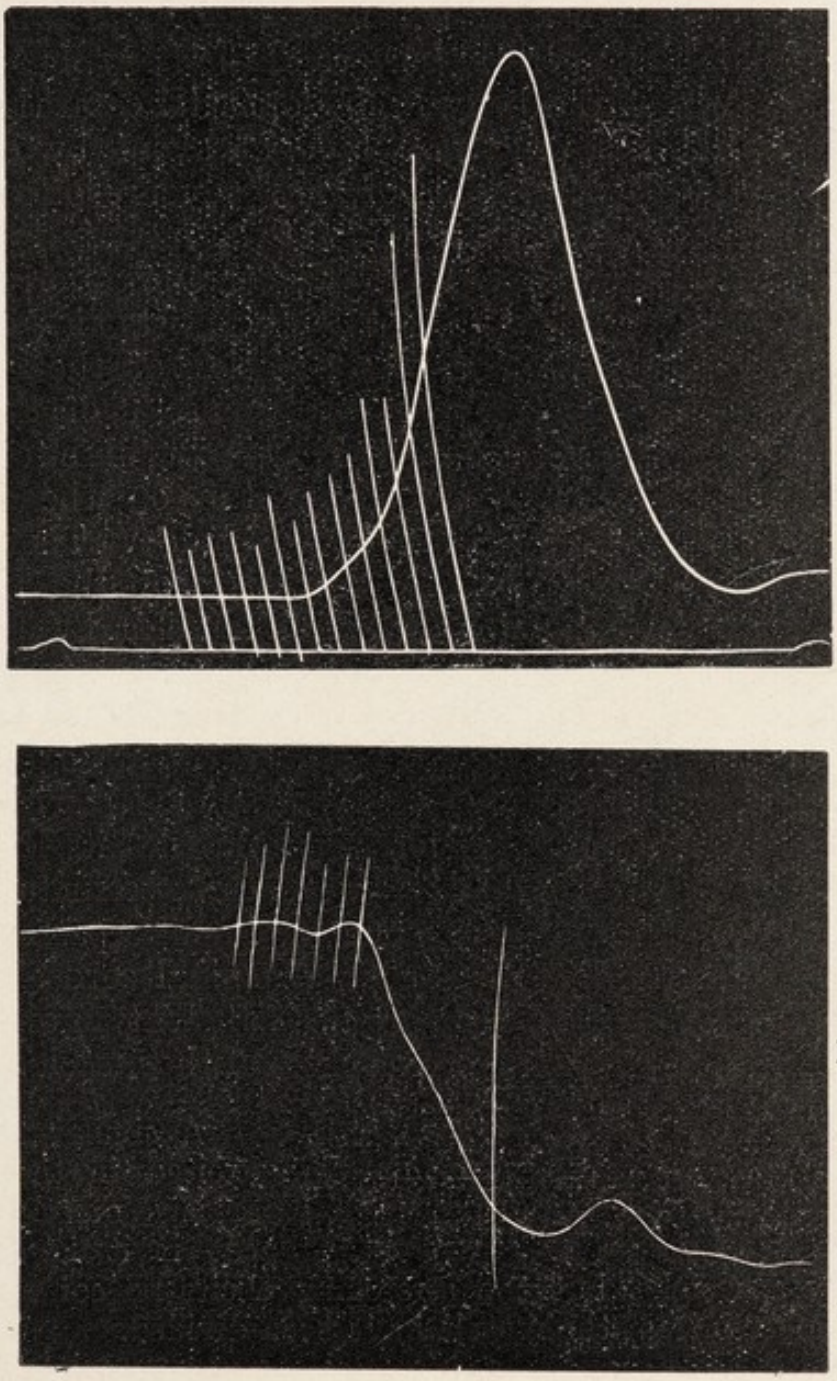


FIG. 31.—Reflex produced by summation of weak stimuli. (Sherrington.) Starling's *Principles of Physiology.*

A, Reflex contraction of flexor muscles of knee. B, Reflex inhibition of extensor muscle. In each case the effect follows the sixth stimulus, the stimuli being applied to the central end of the internal saphenous nerve.

not necessary, indeed it is sometimes a hindrance. Many reflexes, particularly those occurring in connection with the visceral system, take place without affecting consciousness at all. Others, for instance the closing of the eye when an object approaches it suddenly, are associated with consciousness, though the reflex

act precedes, and takes place independently of, consciousness. A third group of reflexes, for example micturition, can to some extent be modified by voluntary impulses.

The Knee-Jerk.—Reflex action may be brought about not only by stimuli falling upon the surface of the body, but also by stimuli arising within the body itself, for instance in the joints and muscles. Reflexes which are brought about by impulses originating in the deeper tissues of the body are often called "deep," or "tendon," reflexes. One of the most important is the knee-jerk, which consists in contraction of the extensor muscles of the thigh in response to a sharp tap on the patellar tendon. The stretching of the extensor muscles by this tap gives rise to a stimulus in sensory structures (muscle-spindles) within the muscle itself; from these structures the impulse passes to the spinal cord along the afferent nerve-fibres of the muscle (fig. 32).

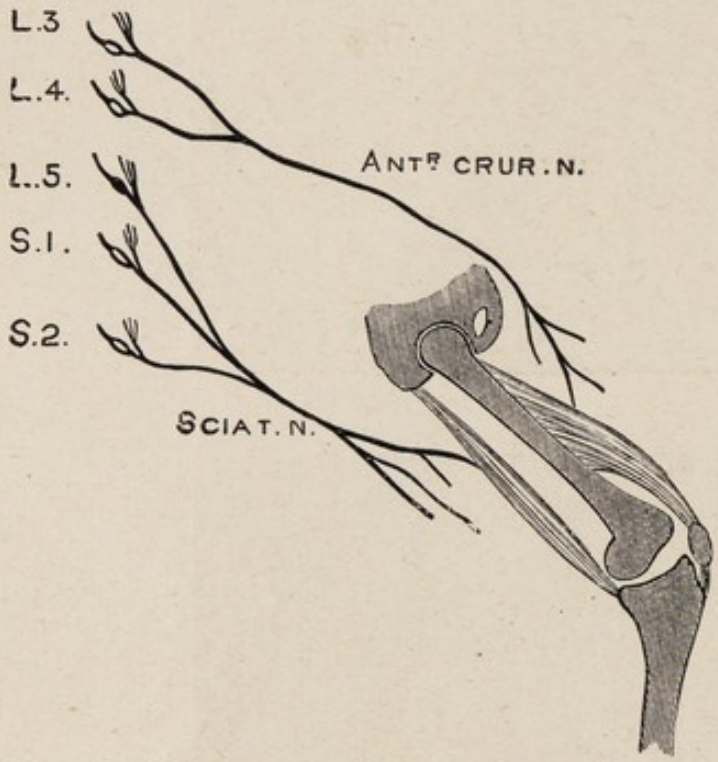


FIG. 32.—Diagram to show muscles and nerves concerned in the knee-jerk. (Starling's *Principles of Physiology.*)

L.3, L.4, L.5: 3rd, 4th, and 5th lumbar nerve-roots. S.1, S.2: 1st and 2nd sacral roots.

A similar twitch is excited in the tibialis anticus muscle of the cat if it is suddenly stretched by a weight, but the stretching elicits no contraction if the afferent nerves from the muscle have been divided.

The reflex character of the knee-jerk has been denied on the ground that it is a single twitch of the muscle, whereas in genuine reflexes there is a rhythmic discharge of impulses to the muscle so that the contraction is a short tetanus. This argument is discounted by the fact that the sudden extension of the leg, which is produced by applying pressure to the foot of a spinal animal, is undoubtedly a reflex action and is also a single twitch.

The knee-jerk takes place very rapidly, the reduced reflex time being only 0·002 second; and, therefore, though it must be regarded as a true reflex, the impulse passes, in all probabiilty,

through only one synapse in the spinal cord. In the case of reflexes in which several synapses are involved, the reduced reflex time is much greater than that required for the knee-jerk. Thus the reduced time for blinking the eyelid when the conjunctiva is stimulated is about 0·05 second.

Additional evidence that the knee-jerk is a reflex action is furnished by the fact that it exhibits reciprocal innervation, the contraction of the extensor muscles being accompanied by simultaneous inhibition of the hamstring muscles. The inhibition can only be explained on the view that the knee-jerk is truly reflex in nature.

In man the part of the spinal cord concerned with the knee-jerk is the third and fourth lumbar segments ; and the knee-jerk is abolished either by destruction of this part of the spinal cord or by division of the afferent or efferent nerves of the extensor muscles of the thigh. The knee-jerk is absent in locomotor ataxia, in which the posterior lumbar nerve-roots are diseased and the afferent path of the reflex arc is interrupted.

The knee-jerk can be increased by impulses from the higher parts of the central nervous system. If, for example, the fists are firmly clenched at the moment at which the knee-jerk is elicited, the jerk is more marked, this being called *reinforcement* of the knee-jerk. Further, it is often exaggerated in disease of the cerebral cortex or of the pyramidal tracts, probably owing to the cutting off of restraining impulses which normally pass to the spinal cord from the brain.

The knee-jerk and other similar reflexes serve to protect joints and ligaments from injury when a sudden strain occurs which tends to separate the joint surfaces or to stretch ligaments ; and the extreme rapidity of the reflex is no doubt associated with this protective function.

Muscular Tone.—The production of the knee-jerk and other tendon reflexes is dependent on the fact that, when they are not carrying out active movements, the skeletal muscles are normally in a state of slight, but steady, contraction, which is spoken of as *muscular tone*. Consequently, when a muscle is thrown into active contraction, it is able to pull upon its attachment at once without the delay which would occur if it had to " take in slack " ; the presence of muscular tone, therefore, adds to the effectiveness of muscular contraction. The condition of tone is due to the continuous discharge of impulses from the spinal cord to the muscles, as is shown by the following observation. When the brain of a frog is pithed and the animal is suspended by its head, the muscles do not become flaccid and the limbs remain very slightly flexed owing to the greater tone of the flexor muscles.

When the spinal cord is destroyed or the posterior roots of the spinal nerves are divided, the muscles lose their tone, and the limbs hang down completely extended.

In mammals, muscular tone is lost when the skeletal muscles are cut off from the central nervous system, or during deep anæsthesia. The normal maintenance of this tone is really a reflex action, the afferent impulses originating, in the mammal, chiefly in the muscles themselves, and the centre, or centres, being in the brain or spinal cord. It is abolished, therefore, not only by section of motor nerves, but also by section of the posterior nerve-roots containing the afferent fibres coming from the muscles. Impulses passing down the spinal cord from the brain also control and modify muscular tone; and this is sometimes greatly increased when the passage of these impulses is prevented by injury to the spinal cord in animals or by disease of the pyramidal tract in man.

The afferent impulses passing from muscles to the spinal cord not only bring about reflex actions, but also, owing to their influence upon muscular tone, play an important part in the co-ordination of reflex actions brought about by external stimuli. If the afferent nerves from the muscles of a limb are divided, the movements of that limb are inco-ordinate (ataxic), even though cutaneous sensation is not interfered with. On the contrary, division of the cutaneous nerves has but little effect upon the co-ordination of muscular movements, provided the afferent muscular nerves are intact. For instance, a cat, even after the division of all the cutaneous nerves to its four paws, is still able to balance itself almost as accurately as a normal animal.

The Visceral Spinal Reflexes.—Local centres exist in the spinal cord associated with reflexes connected with the blood-vessels and sweat glands.

Centres also exist in the lumbo-sacral region of the spinal cord for the functions of micturition, defæcation, erection, and parturition. All these centres are normally controlled to a greater or less degree by the higher centres, but the reflex function of each can be carried out when all connection with the higher centres has been severed.

SPINAL SHOCK

This is a condition, following transverse section of the spinal cord, in which the reflex functions of the cord are abolished in the part posterior to the lesion. It is seen in its simplest form in the frog. If the spinal cord of a frog is divided just posterior

to the medulla, the muscles of the limbs become flaccid, and remain in this condition for about half an hour. During that time no reflex can be elicited in the limbs. As the shock passes off, muscular tone returns, the animal resumes a fairly normal position, and reflex muscular contractions can once more be evoked. In mammals the condition of spinal shock is more prolonged. Section of the spinal cord results in loss of muscular tone and of vascular tone in the part of the body posterior to the lesion. The sphincters of the anus and bladder are relaxed, the reflexes for defæcation and micturition are abolished, and muscular reflexes cannot be elicited. In the lower animals the condition lasts for a few days or weeks, at the end of which time the blood-vessels and muscles have regained their tone, the sphincters of the anus and bladder are contracted, defæcation and micturition take place normally, and it is possible to evoke muscular reflexes. In man, the loss of function after complete transection of the spinal cord is extremely prolonged. In some cases, however, the part of the spinal cord below the lesion regains its functions to such an extent that micturition and defæcation take place as reflex actions and even the knee-jerk may reappear.

The condition of spinal shock is not due to the effect of the operation, nor to the fall of blood-pressure, for it affects only the region of the cord posterior to the lesion. It is believed to result from the cutting off of impulses which are continually reaching the cord from the higher centres.

SECTION VI

THE BRAIN

There are three main divisions of the brain, named respectively the fore-brain, mid-brain, and hind-brain. The fore-brain consists of the cerebral hemispheres and most of the structures bounding the third ventricle, the mid-brain includes the corpora quadrigemina and the cerebral peduncles, and the hind-brain consists of the cerebellum, pons, and medulla oblongata. The cerebral peduncles, corpora quadrigemina, pons, and medulla oblongata together form the "brain-stem," which connects the fore-brain with the spinal cord.

THE BRAIN-STEM

The brain-stem may be looked upon as a continuation upwards of the spinal cord, considerably modified in structure, and divided at its upper end into the right and left cerebral peduncles, each

of which runs into the cerebral hemisphere of its own side. Like the spinal cord the brain-stem is made up of (1) conducting tracts composed of medullated nerve-fibres, and (2) grey matter, associated mainly with the inflow and outflow of nerves.

The conducting tracts have been traced by the methods already described in connection with the tracts of the spinal cord. They are as follows:

The *pyramid*, or motor tract, arises in the cortex of the cerebral hemisphere. It enters the cerebral peduncle of the side of its origin, and runs down the brain-stem in a ventral position to the lower part of the medulla oblongata, where the greater part of it crosses the middle line to become the crossed pyramidal tract of the spinal cord. The fibres which do not cross in the medulla oblongata constitute the direct pyramidal tract.

The *rubro-spinal tract* arises from the red nucleus of the mid-brain. It crosses the middle line close to its origin, and is continued in the lateral region of the brain-stem to the spinal cord.

The fasciculus gracilis and fasciculus cuneatus from the spinal cord terminate in the lower part of the medulla oblongata in the nucleus gracilis and nucleus cuneatus respectively. Axons from the cells of these nuclei cross to the opposite side, forming the supra-pyramidal or sensory decussation, and run upwards, dorsal to the pyramid, as the *fillet* or *lemniscus*. This, the chief sensory tract, is joined by the spino-thalamic tract, the fibres of which have already crossed in the spinal cord. The fillet terminates in the thalamus, thalamo-cortical fibres conveying impulses thence to the cortex of the cerebral hemisphere of the same side.

The *posterior longitudinal bundle* (*medial longitudinal fasciculus*) extends from the thalamus above to a variable distance into the spinal cord below. Its fibres arise from (1) the cells of the nucleus of Deiters in the pons, the original axons dividing into ascending and descending fibres, (2) cells in the anterior corpus quadrigeminum, and (3) a group of cells close to the thalamus. Many of the fibres end in round cells of the nuclei of the 3rd, 4th and 6th cranial nerves; others end in relation with cells in the grey substance of the spinal cord.

Cerebro-cerebellar fibres arise from the cortex of the cerebral hemisphere, enter the cerebral peduncle of the same side in two bundles, one medial, the other lateral, to the pyramid. The fibres terminate in the nuclei pontis, from which other fibres arise and cross the middle line transversely (the transverse fibres of the pons) to become the *middle peduncle of the cerebellum*. By means of these fibres the cerebral hemisphere of one side is connected with the cerebellar hemisphere of the opposite side.

The *inferior peduncle of the cerebellum*, or restiform body, conveys the direct cerebellar tract, and other fibres from the medulla oblongata, to the cerebellum.

The ascending antero-lateral tract runs in the lateral region of the brain-stem from the spinal cord to the mid-brain, and turns there into the *superior peduncle of the cerebellum*, which connects the mid-brain with that organ.

The cerebellar peduncles will be described more fully later.

The **grey matter** of the brain-stem is collected for the most part into small masses which constitute the "nuclei" of the cranial (cerebral) nerves (fig. 33). Some of these give rise to efferent nerves, and are called motor nuclei, the others receive the terminal arborisations of afferent fibres, and are known as sensory nuclei.

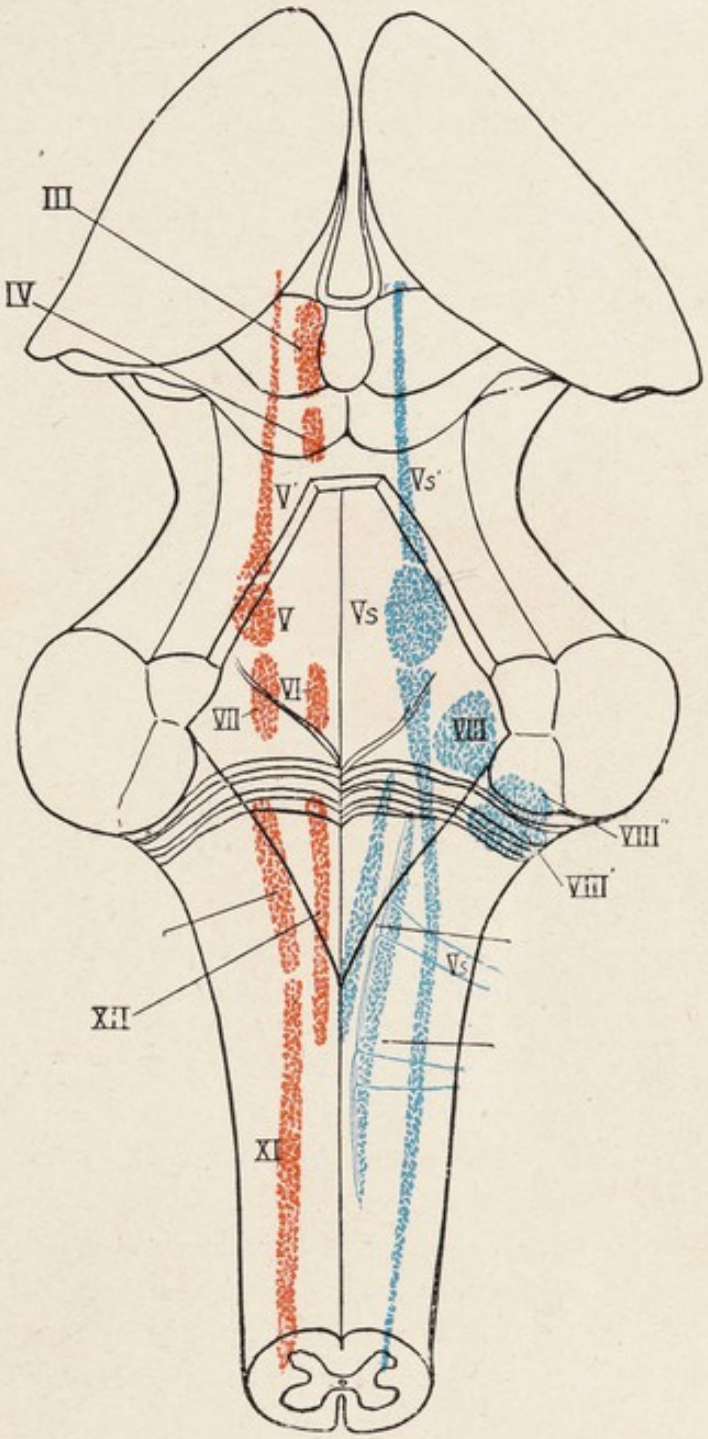


Fig. 33.—A diagram showing the arrangement of the nuclei of the cranial nerves in the brain-stem. Motor nuclei (red); sensory nuclei (blue). From Gray's *Anatomy*.

The *motor nuclei* form two irregular columns of grey matter on each side. The outer column, or *nucleus ambiguus*, is continuous with the head of the anterior cornu of grey matter in the spinal cord, and gives origin to the cranial portion of the 11th cranial nerve, and to the efferent fibres of the 10th, 9th, 7th and 5th cranial nerves. The inner column, continuous with the base of the

anterior cornu, gives rise to the 12th, 6th, 4th and 3rd cranial nerves.

The *sensory nuclei* are also arranged in two columns. The outer column, continuous with the apex of the posterior horn of grey matter in the spinal cord, forms the sensory nucleus of the 5th cranial nerve, and extends from the thalamus above into the spinal cord below. The inner column, mainly confined to the medulla oblongata, consists of the sensory nuclei of the

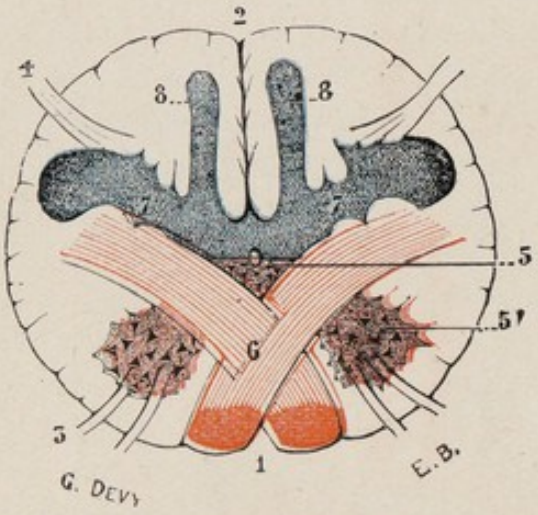


Fig. 34.—Section of the medulla oblongata at the level of the decussation of the pyramids. (Testut.) From Gray's *Anatomy*.

1, Anterior median fissure; 2, posterior median sulcus; 3, motor roots; 4, sensory roots; 5, base of the anterior horn, from which the head (5′) has been detached by the crossed pyramidal tract; 6, decussation of the pyramids; 7, posterior horns (in blue); 8, gracile nucleus.

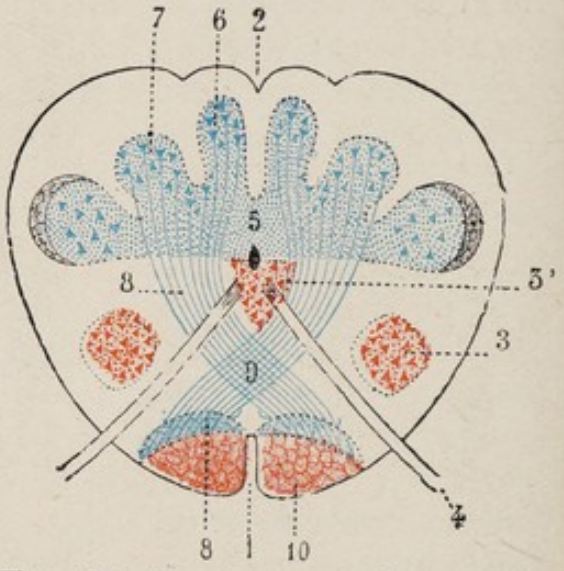


Fig. 35.—Transverse section passing through the sensory decussation. (Schematic.) (Testut.) From Gray's *Anatomy*.

1, Anterior median fissure; 2, posterior median sulcus; 3, 3′, head and base of anterior horn (in red); 4, hypoglossal nerve; 5, bases of posterior horns; 6, gracile nucleus; 7, cuneate nucleus; 8, 8, lemniscus; 9, sensory decussation; 10, pyramid.

9th and 10th cranial nerves. It is continuous with the base of the posterior horn.

In addition, three special nuclei are situated laterally to the outer column, at the junction of the medulla oblongata and pons. Two of these belong to the acoustic division, and the third to the vestibular division of the 8th nerve.

The central canal of the spinal cord is continued upwards in the brain-stem. It comes to the dorsal surface about the middle of the medulla oblongata, and opens out there into the 4th ventricle of the brain. The broadest part of the 4th ventricle lies at the junction of the medulla oblongata and pons. From this level the ventricle narrows to form the cerebral aqueduct in the mid-brain, in which it lies under the corpora quadrigemina. Above this, it opens out into the 3rd ventricle of the fore-brain.

The differences in structure in the brain-stem are best studied by means of transverse sections at different levels.

(1) At the level of the decussation of the pyramids, the medulla oblongata resembles the spinal cord, the anterior horn of grey matter, however, being divided on each side by the decussating bundle, so that the head of the horn takes up a lateral position to become the *nucleus ambiguus*. The posterior horn lies almost transversely, and on its dorsal aspect there appear the nucleus gracilis and nucleus cuneatus projecting into the corresponding fasciculi (fig. 34).

(2) A section at the level of the sensory decussation shows the bundles of fibres arising from the nucleus gracilis and nucleus cuneatus passing ventrally and across the middle line, and separating the head from the base of the posterior horn. The head forms the receptive nucleus for fibres of the fifth nerve (fig. 35). The pyramid occupies a ventral position on each side.

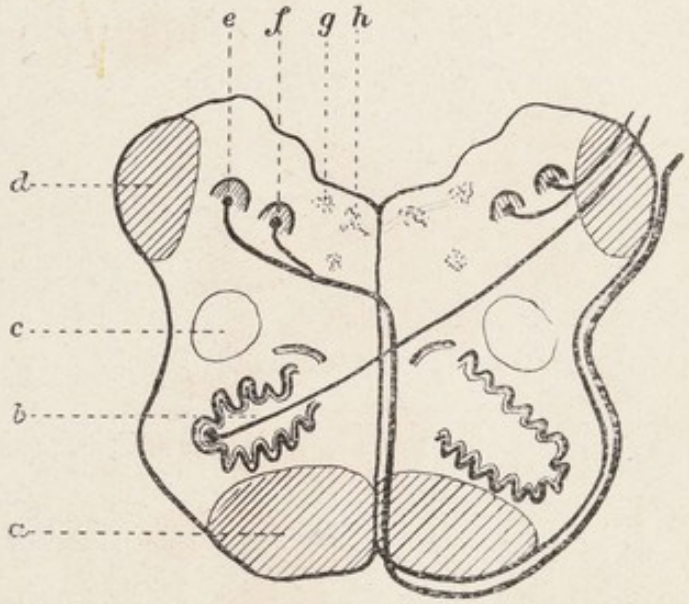


FIG. 36.—Diagram of transverse section of upper part of medulla oblongata.

a, Pyramid; *b*, fibre from olivary nucleus; *c*, spino-thalamic fibres and ventral spino-cerebellar tract; *d*, restiform body; *e*, nucleus cuneatus; *f*, nucleus gracilis; *g*, sensory nucleus of vagus; *h*, nucleus of hypoglossal nerve.

(3) In a section across the upper part of the medulla oblongata the pyramid occupies the same position as in (2) (fig. 36). The fillet is not well-defined, but is dorsal to the pyramid. Dorsal to the pyramid on each side is a section of a wavy sheet of grey substance, like an open bag in shape, the opening being on the medial side. This is the olivary nucleus, fibres from which pass into the restiform body of the opposite side. Dorsal and lateral to the olivary nucleus are the spino-thalamic and ascending antero-lateral (ventral spino-cerebellar) tracts. More dorsally are the nucleus ambiguus and the posterior longitudinal bundle. In the floor of the fourth ventricle are seen the nucleus of the twelfth nerve, close to the middle line, and, lateral to it, the sensory nucleus of the tenth nerve. Lateral to the ventricle is the inferior peduncle of the cerebellum.

(4) A section through the broadest part of the fourth ventricle shows the same structures as in (3), with the exception of the olivary nucleus. In addition, there are seen the nuclei of the eighth nerve. The auditory portion is described on p. 102 (fig. 45). The vestibular portion passes backwards to the vestibular nucleus in the lateral part of the floor of the fourth ventricle, its fibres giving collaterals to the adjacent nucleus of Deiters. It is described on p. 169.

(5) A section through the pons shows the conducting tracts in the relative positions already mentioned. It is characterised by the

presence of a large number of fibres running transversely across its ventral part, and breaking up the pyramid into a number of small bundles (fig. 37). These transverse fibres arise from scattered groups of nerve-cells, the *nuclei pontis*, and form part of the cerebro-cerebellar path (p. 78). At the upper part of the pons, the superior cerebellar peduncle is seen lying dorso-laterally, and the posterior longitudinal bundle is visible as a compact bundle of fibres just ventral to the fourth ventricle.

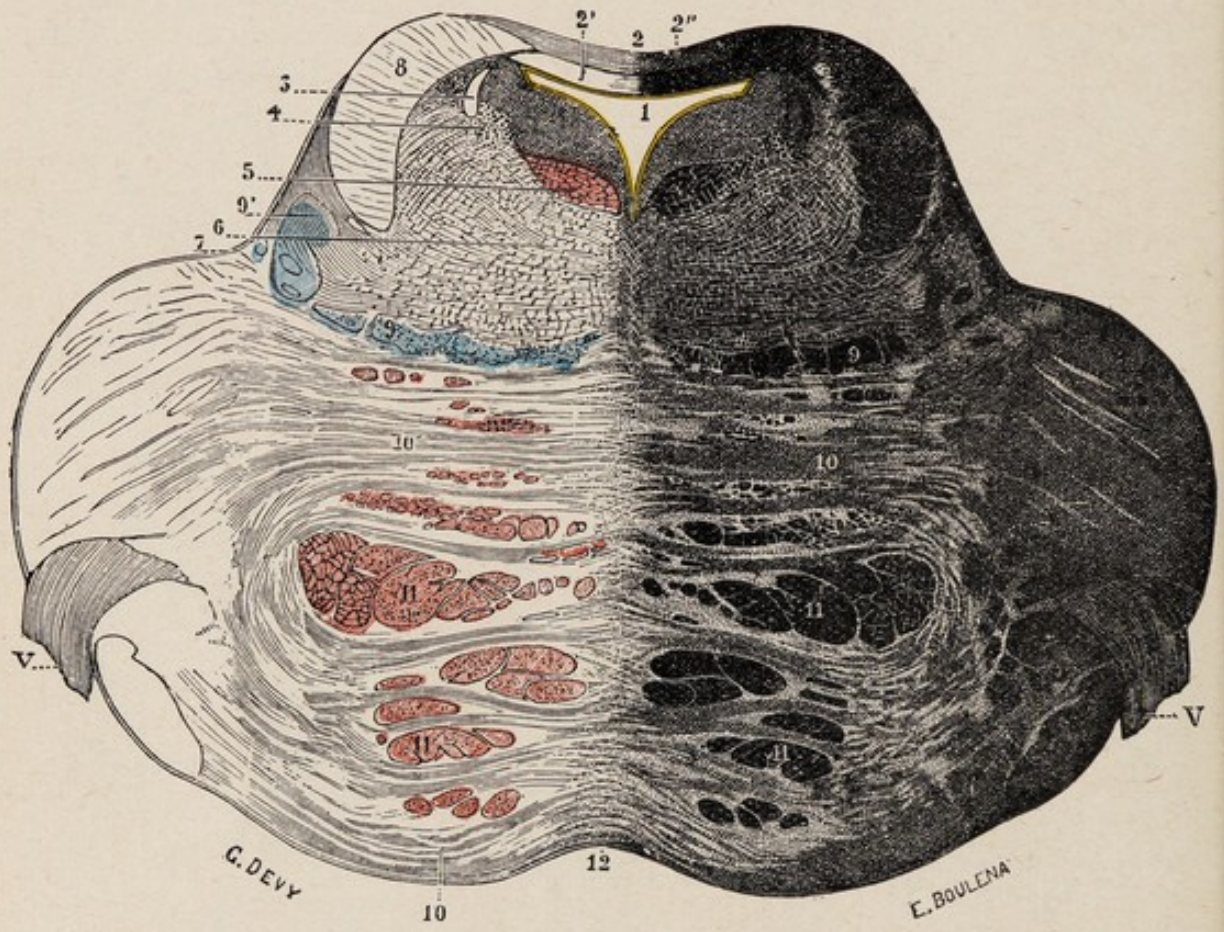


FIG. 37.—Coronal section of the pons, at its upper part. (Testut.)
From Gray's *Anatomy*.

1, Fourth ventricle; 2, anterior medullary velum; 3, mesencephalic root of fifth nerve; 4, nerve-cells associated with this root; 5, posterior longitudinal bundle; 6, formatio reticularis; 7, lateral sulcus; 8, section of superior peduncle; 9, medial fillet; 9', lateral fillet; 10, 10, transverse fibres of pons; 11, 11, pyramid; 12, raphe; V, exit of fifth nerve.

(6) In a coronal section through the mid-brain at the level of the posterior corpora quadrigemina, these structures form the dorsal part of the section, and the cerebral peduncles are situated ventrally (fig. 38). Each cerebral peduncle is divided by a horizontal sheet of grey matter, the *substantia nigra*, into a ventral part, called the crusta or pes, and a dorsal part, the tegmentum. The *crusta* is composed of white fibres running longitudinally, those forming the middle three-fifths being the pyramid, while the medial and lateral fibres are the cerebro-cerebellar fibres running from the cerebral cortex to the pons.

The *tegmentum* contains the fillet, which here consists of a medial and a lateral part. The lateral fillet is mainly made up of fibres running

from the auditory nuclei to the inferior colliculi. Dorsal to the fillet are the posterior longitudinal bundle and the nuclei of the third and fourth cranial nerves, the latter lying in the floor of the cerebral aqueduct. The superior cerebellar peduncle lies lateral to the aqueduct.

(7) A section through the superior colliculi shows the same features as (6), with the addition of a mass of grey matter lying in the tegmentum and known as the red nucleus. Both pairs of corpora quadrigemina are composed of grey matter, but the anterior corpora quadrigemina are covered by a layer of white fibres.

It has been suggested that the red nucleus may form a cell-station on an indirect motor path from the cerebral hemisphere to the spinal

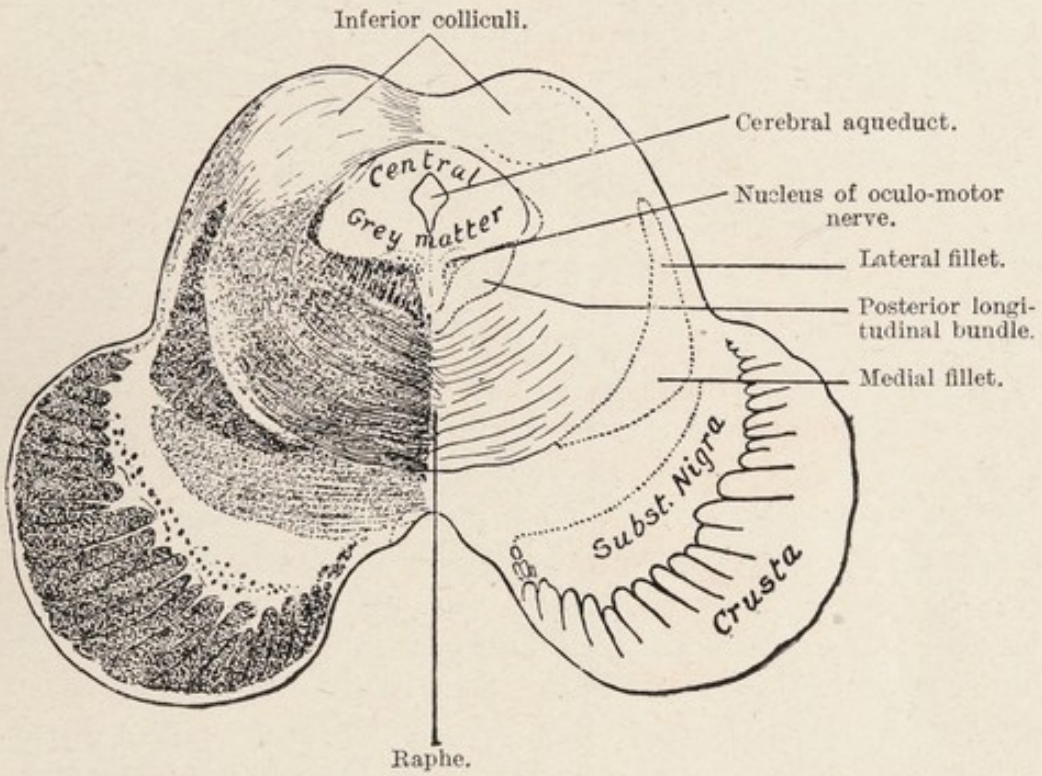


FIG. 38.—Transverse section of mid-brain at level of inferior colliculi. (Gray's *Anatomy*.)

cord, the route being by way of the cerebro-cerebellar path through the pons to the cerebellum, then by the superior peduncle to the red nucleus, and from the latter to the spinal cord by the rubro-spinal tract.

THE FUNCTIONS OF THE BRAIN-STEM

The brain-stem has two important functions. It forms a conducting path for the impulses passing to and from the cerebral hemispheres, and it is concerned in the carrying out of reflex actions. The brain-stem contains a number of groups of nerve-cells, known as " centres," which control and regulate the respiratory movements, the frequency of the pulse, the calibre of the arterioles, and the movements and secretory activity of the

alimentary tract ; and the activity of these centres is influenced by impulses reaching the brain-stem from the viscera, the lungs, and the heart. It also serves, chiefly through the intermediation of the posterior longitudinal bundle, as a centre for reflex movements of the head and eyes in response to impulses from the visual and auditory organs. Further, the brain-stem takes a share in co-ordinating the reflex activities of the body into a harmonious whole.

It is clear, therefore, that the presence of the brain-stem, in addition to the spinal cord, greatly increases the variety and complexity of the reflexes which an animal can display, and that the greater part of the nervous machinery concerned in carrying out reflex actions is situated in the brain-stem and spinal cord.

SECTION VII

THE CEREBELLUM

The cerebellum is connected with the medulla oblongata and with the vestibular nuclei of the pons by the restiform body or inferior cerebellar peduncle on each side, with the pons by the two brachia pontis or middle cerebellar peduncles, and with the mid-brain by the two brachia conjunctiva or superior cerebellar peduncles. It consists of a middle lobe or vermis and two lateral lobes. The surface of the cerebellum is thrown into numerous folds, and the superficial layer, consisting of grey matter, is thus much increased in extent. The interior of the cerebellum is mainly composed of white matter, but it also contains some masses of grey matter, known as the nucleus dentatus, nucleus emboliformis, nucleus globosus, and nucleus fastigii.

The *cortical substance* consists of two layers with a single row of large nerve-cells lying between them (fig. 39). These large cells are known as the cells of Purkinje. They are flask-shaped, the axon coming from the base, and the dendrons from the apex, of each cell. The dendrons branch extensively, and the branches all lie in a plane across the direction of the fold or leaflet, so as to resemble a tree trained against a wall.

The inner (nuclear) layer contains a large number of small, rust-coloured nerve-cells. The dendrites of these are short, and the axons pass into the outer layer, where they divide in a T-shaped manner, the divisions running in the direction of the surface fold, and thus crossing the dendrons of the cells of Purkinje at right angles. Afferent fibres from the white matter arborise round the cells of the nuclear layer, and are called moss-fibres because of the appearance of their terminations.

The outer layer of grey matter, or molecular layer, contains the dendrons of Purkinje's cells, the axons of the small cells of the internal layer, scattered nerve-cells, and the terminations of

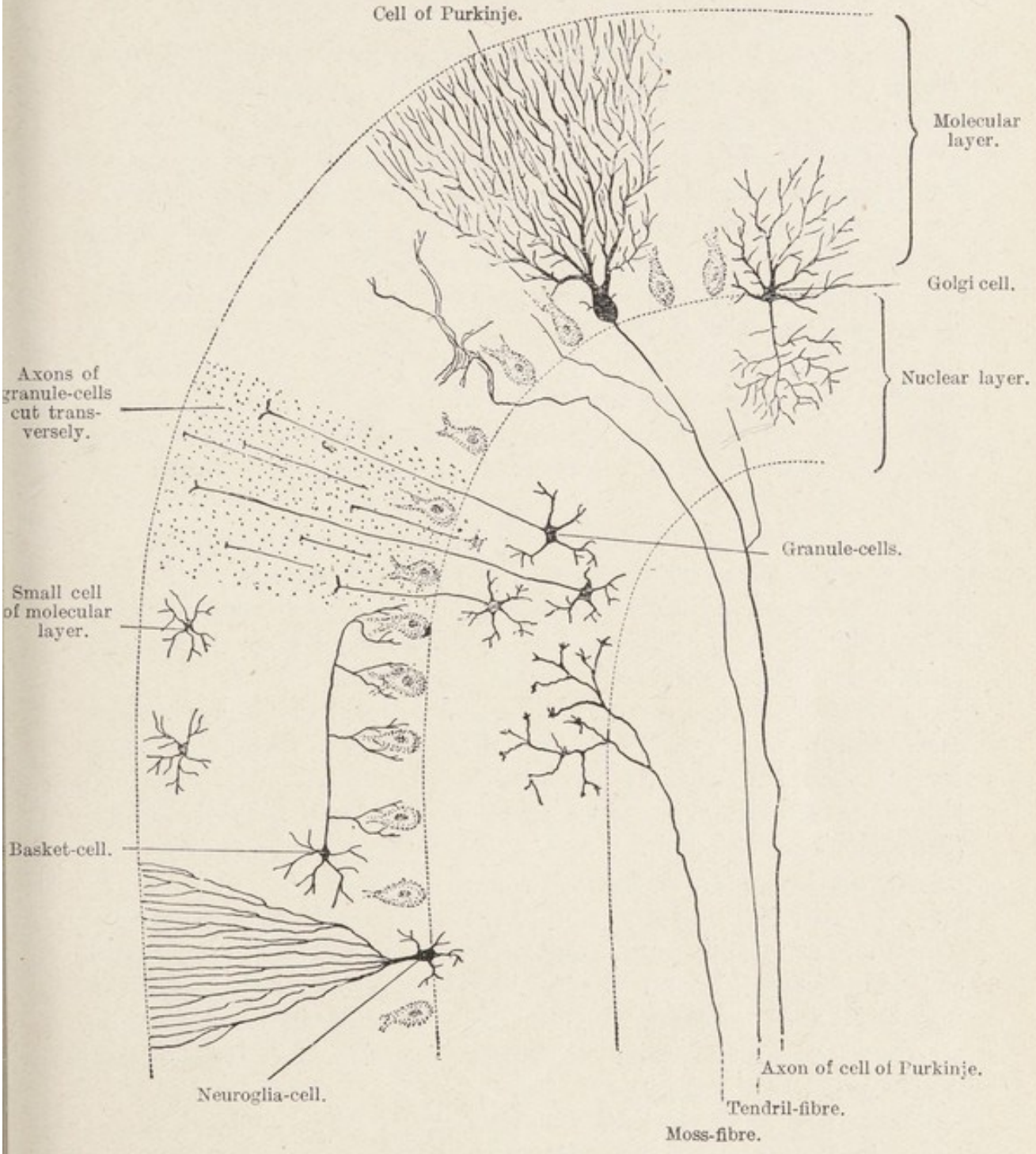


FIG. 39.—Transverse section of a cerebellar folium. (Diagrammatic, after Caja and Kölliker.) From Gray's *Anatomy*.

afferent fibres from the white matter. The principal nerve-cells of this layer are called "basket-cells," from the fact that their axons, and the collaterals from the axons, terminate round the cytons of the cells of Purkinje in a basket-like fashion. The afferent nerve-fibres which reach the molecular layer arborise in apposition with

the dendrons of the cells of Purkinje, and are hence known as climbing or "tendril-fibres." The Purkinje cells receive, therefore, three sets of afferent impulses, namely (1) from the axons of the cells of the granular layer, (2) from the basket-cells, and (3) from the tendril-fibres.

The axons of the cells of Purkinje end in the nucleus dentatus, from which the impulses they transmit are passed on by other neurons.

The *superior peduncles* (brachia conjunctiva) pass to the mid-brain and run under the inferior colliculi. Each contains two sets of fibres. (1) Axons of cerebellar cells; these cross the middle line and divide into ascending and descending branches. The ascending divisions end chiefly in the red nucleus, though some run to the thalamus, and others to the nuclei of the oculo-motor nerves. The descending divisions are believed to reach the anterior columns (funiculi) of the spinal cord. (2) Fibres which are afferent to the cerebellum; these include the antero-lateral ascending tract of the same side running to the vermis.

The *brachia pontis*, or middle peduncles, form part of the connecting path between the cerebral hemispheres and the hemispheres of the cerebellum, the connection being a crossed one (p. 78). The fibres are chiefly afferent, but some are efferent.

The *restiform bodies*, or inferior peduncles, contain both efferent and afferent fibres. The efferent fibres run from the nucleus fastigii and the dentate nucleus to the nucleus of Deiters and the medulla oblongata, and thence into the antero-lateral column (funiculus) of the spinal cord. The afferent fibres are (1) the direct cerebellar tract from the same side of the spinal cord to the vermis; (2) fibres from the medulla oblongata, (*a*) from the nucleus gracilis and nucleus cuneatus of the same and the opposite sides, (*b*) from the olivary nucleus of the opposite side (fig. 36), and (*c*) from the formatio reticularis of both sides; (3) fibres from the chief vestibular nucleus and from Deiters' nucleus.

The afferent fibres to the cerebellum are thus derived from (1) the spinal cord, some through the restiform body, others by way of the superior peduncles, (2) cell-stations in the medulla oblongata, (3) the cerebral hemispheres, and (4) the vestibular nuclei. But whereas the connection with the cerebral hemispheres is a crossed one, that with the spinal cord is for the most part uncrossed.

The efferent fibres from the cerebellum are (1) those which run in the superior peduncles (brachia conjunctiva) to the mid-brain and thalamus, (2) fibres in the middle peduncles to the

nuclei pontis, and (3) those which run in the restiform bodies to the vestibular nuclei and the medulla oblongata.

THE FUNCTIONS OF THE CEREBELLUM

A knowledge of the cerebellar functions has been obtained partly by observation of the results of disease in man and partly by experiments on animals. When the normal impulses from the cerebellum are wanting in man, there is defective co-ordination of muscular movements (known as *ataxia*) as well as defective muscular tone. As a result, the power of maintaining the equilibrium of the body is impaired and the gait is staggering, though consciousness and sensation are not affected. Voluntary movements are carried out in a clumsy fashion and are accompanied by muscular tremor.

The effects of removal of the cerebellum, or any part of it, in animals, vary according to the length of time that has elapsed since the operation was performed. The immediate effect of complete removal is chiefly a condition of ataxia or inco-ordination. If a pigeon, for example, shortly after removal of its cerebellum, attempts to fly, it only succeeds in making exaggerated and inco-ordinated movements of its wings. The attempts of a dog to walk, in these circumstances, are equally futile. After some weeks or months, the animal regains the power of co-ordinated movement to a certain degree. The pigeon is able to fly and the dog to walk, but the power of movement is still greatly impaired. In the dog, progression is unsteady and is only effected with the legs wide apart (abducted) ; the animal maintains its balance with some difficulty and is apt to fall over. The tone of the muscles is lessened (*atonia*), there is some muscular weakness (*asthenia*), and pronounced tremor of the muscles develops, resulting in unsteadiness of movement (*astasia*). The tremor is hardly noticeable in the resting animal, but becomes very obvious as soon as any voluntary movement is attempted ; it is therefore known as " intention " tremor.

If one lateral half only of the cerebellum is removed, the weakness and tremors are limited to that side of the body. For two or three weeks the animal is unable to stand, and lies on the affected side with its head turned to the side of the lesion, and with its trunk curved so that the concavity is toward the lesion (fig. 40). Later, it succeeds in standing and walking by abducting the limbs of the weak side, or by availing itself of the support of a wall.

Although the effects of partial or complete removal of the cerebellum never disappear entirely, they may ultimately become

very trivial owing to the fact that the co-ordination of movements, previously effected by the cerebellum, is now carried out through the cerebral hemispheres, this involving voluntary effort and attention. In this way the cerebral mechanism compensates for the loss of cerebellar functions. A similar process of compensation also occurs in congenital absence of the cerebellum, and is so complete that the individual may appear perfectly normal.

These experiments and observations show that the cerebellum is a centre for the maintenance of muscular tone, and for the co-ordination of muscular movements. Afferent impulses are constantly streaming into the cerebellum from the muscles and joints and from the semicircular canals, and, in response to these, it sends out efferent impulses which adjust the tone of the muscles. It is especially concerned with the maintenance of the position of the body in relation to gravity, and with the co-ordination of the movements of the body as a whole.

FIG. 40.—Dog with right half of its cerebellum removed. (From Sharpey Schafer's *Text-Book of Physiology*.)

The trend of recent evidence is against the existence of localisation of function in the cerebellum; and the "forced movements" which may follow almost immediately on injury to the cerebellum appear to be due to the irritative effects of the lesion.

Summary.—The cerebellum receives afferent impulses (1) by way of the vestibular nerve from the labyrinth of the ear, the end-organs in which are affected by changes in the position of the head, and (2) by the afferent nerves from the muscles, from the end-organs which are connected with muscular sense. Both these sets of impulses are known as *proprioceptive* to distinguish them from the exteroceptive impulses set up by stimuli external to the body. The cerebellum discharges efferent impulses which maintain muscular tone during rest, and which co-ordinate muscular movements during activity. These functions are especially of importance in the maintenance of equilibrium. The absence of the cerebellum is therefore attended by loss of tone and power in the muscles, as well as by a condition of inco-ordination or ataxia. Cerebellar ataxia is associated with muscular weakness, whereas spinal ataxia, due to disease of the posterior nerve-roots, is associated with exaggerated muscular movements.

SECTION VIII

THE FORE-BRAIN

The fore-brain consists of the two cerebral hemispheres, together with certain masses of grey matter and other structures situated around the third ventricle, and comprising the thalami, the corpora geniculata, the hypophysis or pituitary body, and the pineal gland. The thalami and geniculate bodies are composed of grey matter. Each thalamus forms the lateral boundary of the third ventricle on its own side. The internal (medial) and external (lateral) geniculate bodies lie ventral to the thalamus on each side, and are in close relation with the superior colliculi.

The pineal gland lies immediately above the superior colliculi. It contains no nerve structure, being composed of alveoli with earthy phosphates in their interior, and it has not, so far as is known, any function. It is supposed to be the homologue of the pineal eye of the lizards.

THE CEREBRAL HEMISPHERES

The cerebral hemispheres constitute the largest part of the brain. Each consists of an external layer of grey matter, thrown into folds or convolutions, with white matter internally. A mass of grey matter, known as the *corpus striatum*, lies in the interior of each hemisphere, lateral to the thalamus and separated from it by a sheet of white matter, the internal capsule. Each hemisphere also contains in its interior a lateral ventricle, which is in communication with the third ventricle.

The grey matter consists of nerve-cells and nerve-fibres, arranged in layers. The axons of the nerve-cells become medullated and run into the white matter. Other (afferent) fibres from the white matter terminate by arborisation in the grey matter. Most of these are axons of cells in the thalamus, but some are axons of cells in other parts of the cortical layer.

The structure of the grey matter varies in different regions of the cerebral hemisphere, but, whatever the local modifications, the general plan is the same in all parts, and shows an arrangement in five layers (fig. 41). These layers are named as follows :—

(1) The outer fibre-lamina, or molecular layer.
(2) The outer cell-lamina (pyramidal layer).
(3) The middle cell-lamina, or granule layer.
(4) The inner fibre-lamina.
(5) The inner cell-lamina, or layer of polymorphic cells.

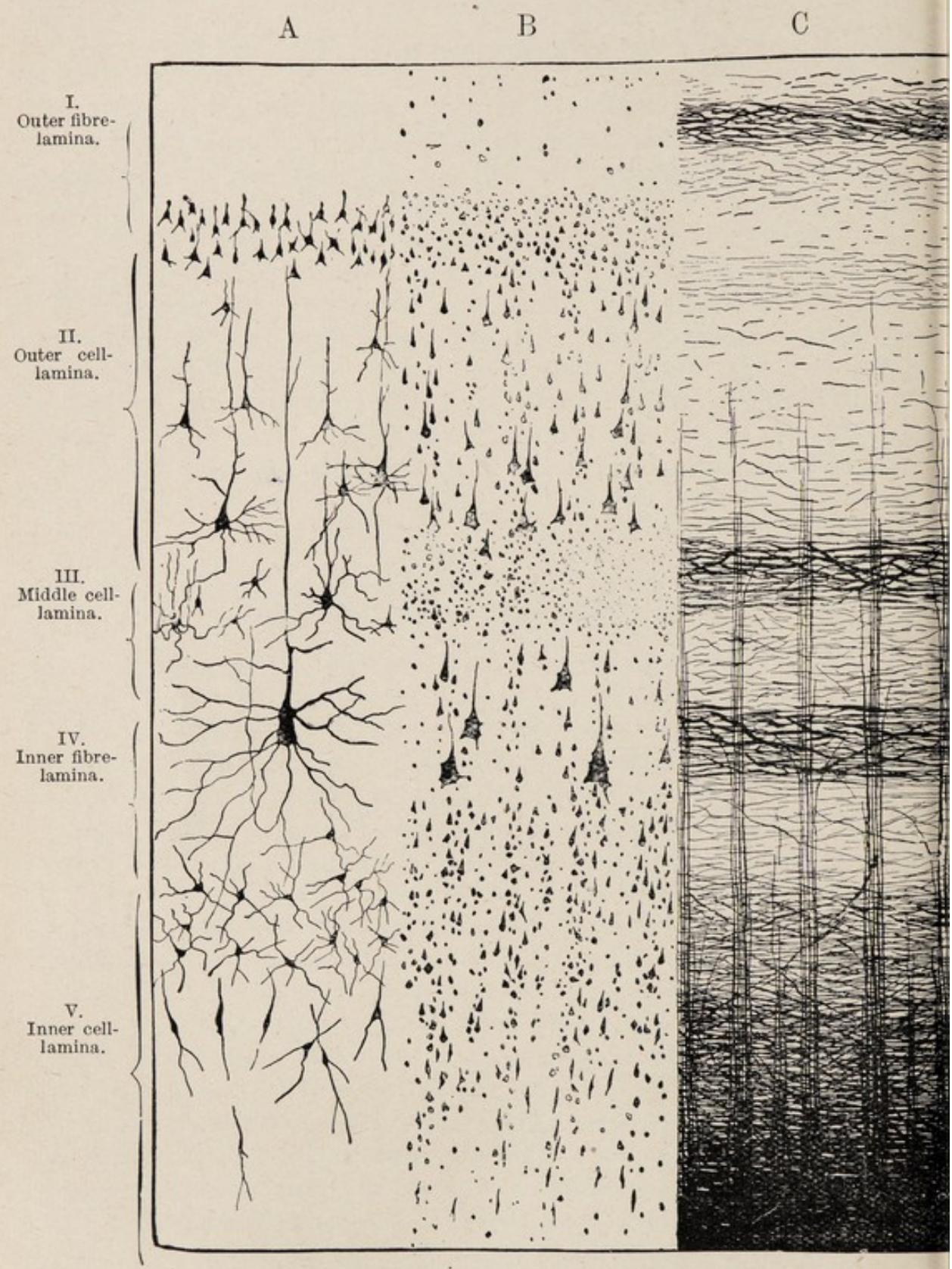


FIG. 41.—Diagram to show the layers of cells and fibres in the grey matter of the cortex of the human cerebral hemisphere, stained by three different methods: A, Golgi; B, Nissl; C, Weigert. From Luciani's *Physiology* (Macmillan & Co.).

A convenient modification of this description is to speak of the layers in their relation to the middle cell-lamina or layer of granules. This arrangement gives (1) a supragranular layer, consisting of a fibre-lamina and a cell-lamina ; (2) the granule-layer itself ; and (3) an infragranular layer, consisting of a fibre-lamina and a cell-lamina.

The outer fibre-lamina contains medullated nerve-fibres running horizontally, a few scattered nerve-cells, and the dendrons of many of the cells of the next layer.

The outer cell-lamina contains pyramidal nerve-cells, and may be subdivided into layers of small, medium, and large pyramids, the small pyramids being most superficial and the large pyramids most deeply situated.

The middle cell-lamina contains pyramidal cells, but is especially characterised by the presence of a large number of stellate cells.

The inner fibre-lamina consists of medullated nerve-fibres, running horizontally, but in the motor area it also contains large, and often solitary, pyramidal nerve-cells, called Betz-cells, the apical dendrons of which may extend to the outer fibre-lamina.

The inner cell-lamina contains a large number of irregular or polymorphic cells, as well as some pyramidal cells, the apices of which point centrally, while the axons pass towards the surface.

The Functions of the Cell-Layers.—Information may be obtained as to the function of the different cell-layers of the grey matter in three ways : (1) by observing the order of their development in the fœtus ; (2) by a comparison of their relative proportion in man and in the lower animals ; (3) by a comparison of the different regions in the human adult cerebrum, and by observations of the structural differences in persons suffering from amentia or dementia.

(1) The study of development of the cortex shows that the inner cell-lamina is the first to appear, and that it has attained three-fourths of the adult depth at the sixth month of fœtal life. It is followed by the middle cell-lamina, which, however, has only one-half of the adult depth at the sixth month of fœtal life. The outer cell-lamina is the last to appear, and develops slowly after birth. The outer fibre-lamina is well developed at birth and is associated in its further growth with that of the outer cell-lamina. The inner fibre-lamina is well developed at birth, attaining its adult depth almost at once (fig. 42).

(2) The inner cell-lamina is the first to appear in the evolution of the cerebral cortex, and is well developed in the lower mammalia ; in the mole, for example, it forms the greater part of the

depth of the cortex (fig. 42). It is followed by the middle cell-lamina, the outer being the last to appear, and attaining a low degree of development in all animals below man. The

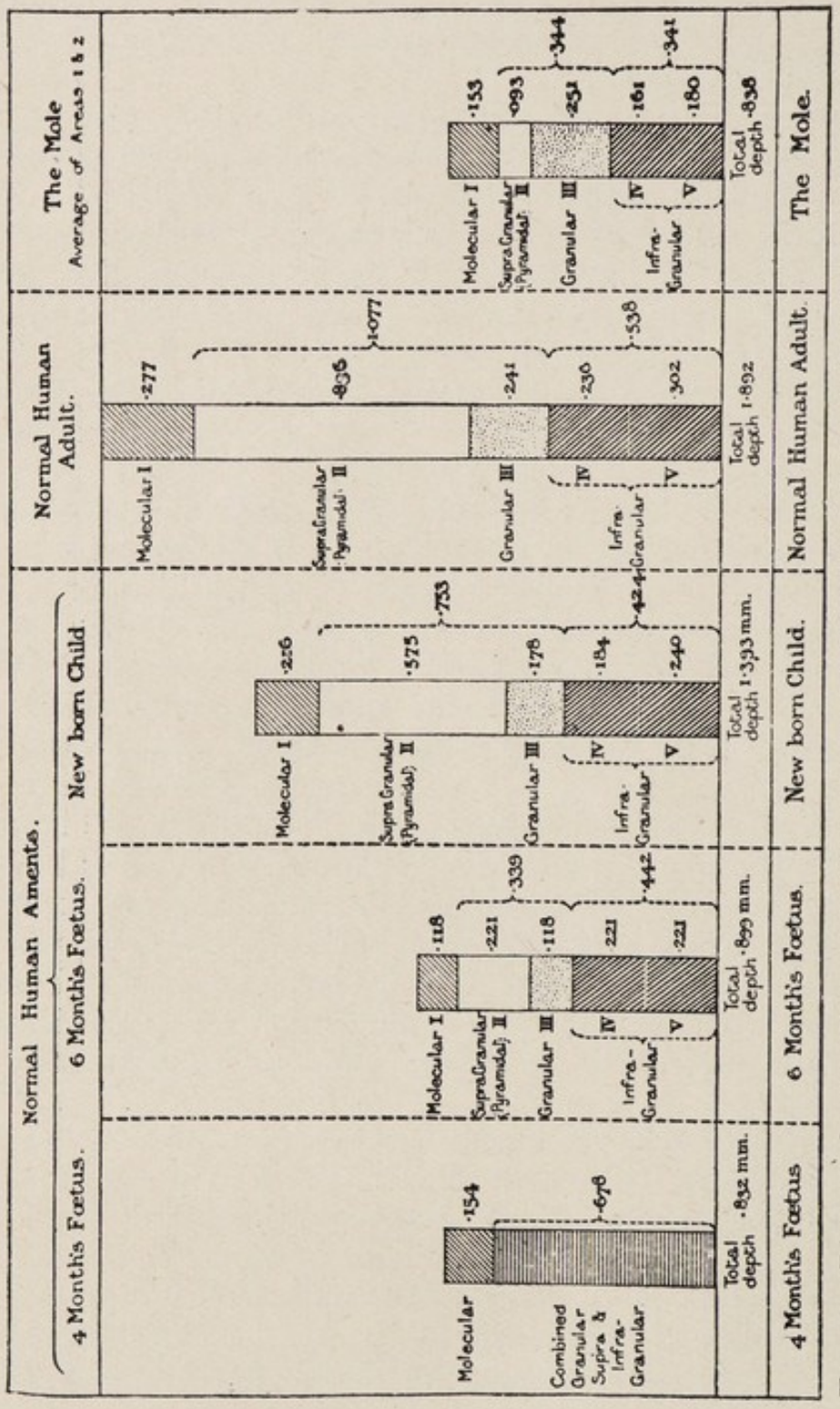


FIG. 42.—Diagram showing (1) successive stages in the development of the layers of grey matter in the human cerebral cortex, and (2) the relative thickness of the different layers in man and in the mole. The layers are numbered I–V, I being the outer fibre-layer. The figures represent the thickness of the layer in millimetres. (J. S. Bolton.) From *Further Advances in Physiology* (Edward Arnold).

outer cell-lamina, however, increases progressively in depth from the insectivora through the rodents and ungulates to the carnivora.

(3) The least developed portion of the human cerebral cortex is the grey matter of the hippocampus, in which the only cell-

laminæ represented are the middle and inner. The ascending frontal convolution (motor area) is characterised by the presence of Betz-cells in the inner fibre-lamina, and by the absence, or very slight development, of the granule-layer. The visuo-sensory area, situated in the occipital lobe, is distinguished by an increase in depth of the middle cell-lamina. The outer cell-lamina is most highly developed in what are known as the association-areas. These are three in number :. the posterior, occupying the posterior part of the parieto-temporal region ; the middle, in the island of Reil ; and the anterior, which lies in that part of the frontal lobe known as the pre-frontal region. The pre-frontal region is the highest zone of association, and in it the outer cell-lamina undergoes the greatest development, this varying considerably, however, in different individuals. The depth of the outer cell-lamina in this region varies with the mental development of the individual. It is imperfectly developed in idiots and imbeciles, and its cells are atrophied in cases of dementia.

On the basis of these facts, J. S. Bolton ascribes different functions to the three cell-laminæ. The polymorphic layer subserves the instinctive activities concerned with obtaining food and shelter, with seeking protection from danger, and with the functions connected with sex. The middle cell-lamina is concerned with the reception and transformation of afferent impulses. The outer cell-lamina is psychic or associational, and has to do with the mental processes, especially with those included under the terms " voluntary attention " and " inhibition."

THE TRACTS OF THE CEREBRAL HEMISPHERES

The nerve-fibres of the white matter of the cerebral hemispheres are either projection-fibres or they are associational in character, including under the latter term the commissural fibres which connect the two hemispheres. The projection-fibres are those which connect the cerebral cortex with the lower parts of the central nervous system, and they are either afferent or efferent. The association-fibres link up different parts of the cortex. The fact that nerve-fibres acquire their myelin sheaths at the time at which they become functionally active has been made use of by Flechsig in studying the nerve-tracts of the cerebral hemispheres, and, from his observations, he has come to conclusions as to the functions of the different areas of the cortex which are as a whole identical with those based upon the study of the variations in the structure of the grey matter in different

regions of the adult cortex. The first fibres to become myelinated in the cerebral hemispheres are those afferent projection-fibres which are distributed to the sensory areas of the brain. The last to acquire a myelin sheath are those which are connected with the higher centres of association.

The Projection-Fibres.—The *efferent* projection-fibres are the pyramidal (cerebro-spinal) and the cerebro-cerebellar. The *pyramidal fibres* are the axons of the Betz-cells in the pre-central convolution or motor area. They converge towards the base of the hemisphere, and occupy the genu and the anterior two-thirds of the posterior limb of the internal capsule (fig. 47). From this situation they descend in the pes of the cerebral peduncle and through the pons and medulla oblongata to the spinal cord in the manner already described.

The *cerebro-cerebellar fibres* are the fronto-pontine from the frontal lobe and the temporo-pontine from the temporal lobe. These descend, the former in the anterior limb of the internal capsule, the latter in the posterior third of its posterior limb, to the base of the cerebral peduncle, after passing through which they reach the pons to arborise round the cells of the nuclei pontis.

The *afferent projection-fibres* are the thalamo-cortical, the optic radiation, the auditory radiation, and some fibres of the superior cerebellar peduncle.

The *thalamo-cortical* fibres are axons of cells in the thalamus and form the final relay on the path of afferent impulses from the lower centres to the cortex of the cerebral hemisphere ; they are distributed to all parts of the cortex. The chief tract passes from the thalamus into the posterior part of the posterior limb of the internal capsule and terminates in the post-central gyrus of the parietal lobe. It conveys impulses from the skin and muscles. Lying behind this group of fibres in the internal capsule are thalamo-temporal fibres, which enter into the formation of the *auditory radiation*. Posterior to the auditory tract are thalamo-occipital fibres which form part of the *optic radiation*. Thalamo-frontal fibres run towards the frontal lobe in the anterior limb of the internal capsule.

Some of the fibres of the superior cerebellar peduncle, coming from the cerebellum, have cell-stations in the thalamus, but others are believed to pass through the posterior end of the internal capsule without interruption to end in the cortex in the neighbourhood of the central sulcus or fissure of Rolando.

The Association-Fibres.—The *short association-fibres* lie immediately under the cortex and connect the grey matter of adjacent convolutions. The *long association-fibres* form tracts

which unite areas of the cortex at some distance from each other.

One tract, the superior longitudinal fasciculus, runs between the frontal and occipital lobes; another, the inferior longitudinal fasciculus, connects the temporal and occipital lobes; a third, the uncinate fasciculus, connects the frontal and temporal lobes; a fourth connects the parietal and occipital lobes; while a fifth runs from the anterior perforated space (substance) over the corpus callosum to the hippocampus.

The *commissural fibres* connect the two cerebral hemispheres and are grouped in the corpus callosum, and the anterior, posterior, and hippocampal commissures. The corpus callosum contains fibres from all parts of each cerebral hemisphere except the olfactory bulb and parts of the temporal lobe. The olfactory lobes are connected by the anterior and hippocampal commissures, the anterior commissure also containing fibres which connect the two temporal lobes. The relationships of the posterior commissure are unknown.

THE FUNCTIONS OF THE CEREBRAL HEMISPHERES

The ascent of the animal scale is marked by a progressive increase in the size and development of the cerebral hemispheres, and in man these structures are both absolutely and relatively larger than in any of the lower animals. The increase in size is associated with a corresponding increase in functional importance, the higher centres acquiring a more marked control over those in the spinal cord. This fact becomes more apparent when the results of removal of the cerebral hemispheres in different animals are compared. In the case of the frog, when the animal has recovered from the shock of the operation, there is at first sight little difference from the normal condition. The posture is normal, equilibrium is maintained, and is regained if the frog is placed on its back. When the animal is placed in water, it swims to the margin and crawls out; if it is placed on an inclined plane, it crawls to the top and balances itself there. If, however, it is not stimulated in any way, it will remain in the same attitude until it dies. The complicated reactions known as volitional impulses are wanting, and the frog shows no spontaneous movements.

Similar phenomena may be observed in a pigeon from which the cerebral hemispheres have been removed. There is the same maintenance of posture unless the animal is disturbed; and the power of equilibration is not affected. The pigeon flies in a normal manner if it is thrown in the air, but it soon alights

and resumes its resting attitude. It pecks at the ground if it is hungry, but does not feed itself.

The removal of the cerebral hemispheres in mammals is usually followed by a fatal result, but the operation has been more or less completely performed in dogs by carrying it out in successive stages. One animal remained alive for a year and a half after the operation. Temporary paralysis followed the operative procedures, but was recovered from, and thereafter, in marked contrast with the frog and pigeon in similar circumstances, the dog showed a tendency to be in continual restless movement. It even learned to feed itself when food was placed near its nose. It responded to stimuli, if painful, by growling or barking and turning its head towards the stimulated spot, though it showed no sign of recognition of the persons who fed it, and gave no indication of fear when threatened or of pleasure when caressed.

The absence of the cerebral hemispheres, therefore, in the frog, pigeon, and dog is associated with a condition in which the animal responds to stimuli in a more direct and simple fashion than is the case when the brain is intact. In the normal animal the effect of a stimulus is modified by impulses arising out of the memory of previous experiences. When the cerebral hemispheres have been removed, the memory records are absent, and the response to the stimulus is simplified; in other words, there is an absence of intelligence, of volition, and of emotion. But the machinery for the carrying out of muscular movements in a co-ordinate manner still remains, and can be set in action by a suitable stimulus.

The function of the cerebral hemispheres is largely associative, combining the effects of immediate with those of past stimuli, and giving out efferent impulses based on such combinations. The grey matter of the cortex is not only excited by stimuli, but the stimuli produce a permanent record in its substance, known as memory, which exercises an important influence on all subsequent actions.

Decerebrate Rigidity.—When the cerebral hemispheres of an animal are removed, or cut off from the lower centres by a section through the mid-brain, the extensor muscles of the neck, limbs, and tail acquire a temporarily increased tonus, and the limbs become rigidly extended, and are only flexed with difficulty. The condition is known as "decerebrate rigidity." Section of the afferent nerve-roots connected with a limb abolishes the rigidity in that limb. These facts demonstrate very clearly not only the reflex nature of muscular tone, but also the inhibitory influence of the cerebral hemispheres on that tone.

THE LOCALISATION OF FUNCTION IN THE CEREBRAL HEMISPHERES

It has already been pointed out that histological and embryological researches have indicated that different areas of the cortex subserve different functions, and both observation of the results of disease in man and experimental studies in connection with animals have confirmed and extended these conclusions. Injuries and tumours of different parts of the human cortex give rise to muscular paralysis, blindness, deafness, aphasia, or mental deficiency, according to the site of the lesion. Experiments carried out on animals, either of the nature of stimulation of various parts of the surface of the cerebral hemispheres or of removal of localised portions, have given results parallel with those derived from the study of disease and injury in human beings; and, as a consequence, it has been possible to map out the surface of the hemispheres into areas, each of which possesses a definite function. The pre-central convolution is motor in function, the post-central is sensory and is especially concerned with the reception of impulses concerned with tactile discrimination and kinæsthetic impulses, that is, impulses from muscles, tendons, and joints. The medial aspect of the occipital lobe, or that part of it which lies on the borders of the calcarine fissure, is visuo-sensory, while the convolutions immediately adjacent to the visuo-sensory area are visuo-psychic. The audito-sensory area and the audito-psychic area are situated in the superior temporal convolution. The area for taste and smell is in the hippocampal convolution. No special area has been discovered for the senses of heat, cold, pain, and tactile localisation. The parieto-temporal region, the island of Reil, and the pre-frontal region form the three special association-areas (fig. 43).

The Motor Area.—Stimulation of either the grey matter or of the underlying white matter of the pre-central convolution gives rise to muscular movements on the opposite side of the body. The latent period is longer for stimulation of the grey matter than when the white fibres are excited, but a stronger stimulus is required to elicit movement from the white matter than from the grey. In either case the resulting movements are co-ordinated, groups of muscles being affected, and contraction of a particular group being accompanied by reciprocal relaxation of the corresponding antagonistic group. In other words, "movements, not muscles," are represented in the cortex. Further, stimulation of a particular point in the pre-central convolution is invariably followed by the same movement, so that, for example, excitation of one point will result in extension of the thigh, of

another in flexion of the thigh, of another in flexion of the leg, and so on. The representation of the movements of the leg, trunk, arm, and face is in that order on the convolution from above downwards, and each of these sub-areas may be further subdivided into points for the movements of particular groups of muscles.

Correlated with the development of the cerebral cortex is the increased size of the pyramidal tract, which in monkeys, and still more in man, is the principal path for the rapid conduction of voluntary impulses to the motor neurons of the spinal cord. Other motor paths from the cerebral cortex probably exist in

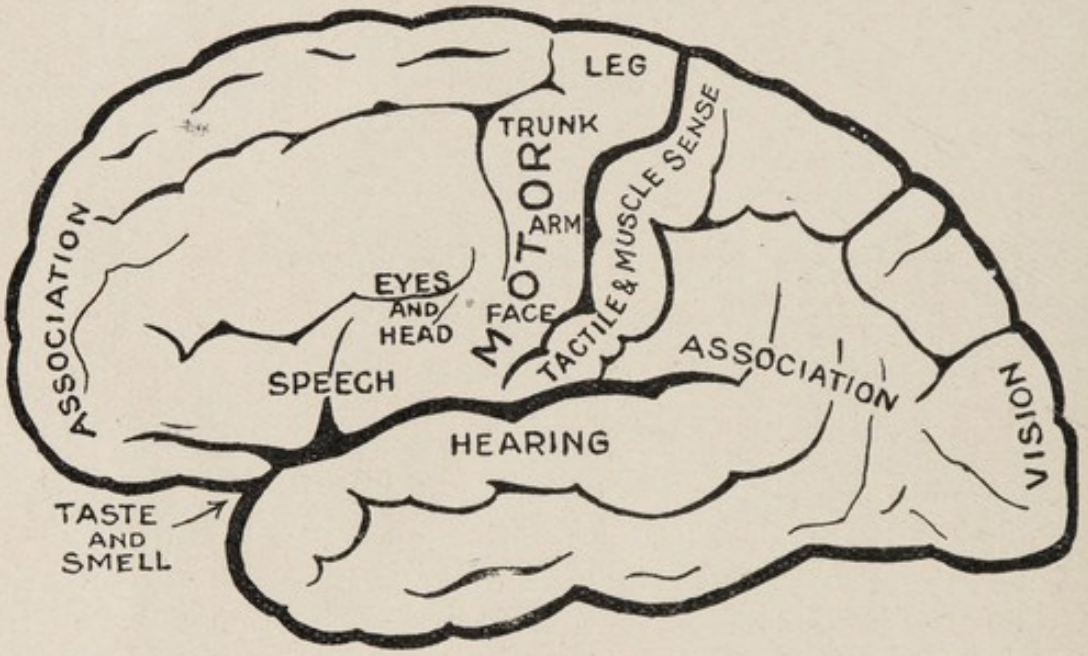


FIG. 43.—Diagram showing localisation of function in the cortex of the left cerebral hemisphere.

the human nervous system, but have fallen into disuse, and it is for this reason that the effects of lesions of the cortex, or of the pyramidal tracts in any part of their course, are so much more severe and permanent in man than in the lower animals.

It must not be supposed that the motor area of the cerebral cortex is the actual seat of voluntary impulses. On the contrary, its activity is aroused by impulses from other parts of the brain, and represents only a small fraction of the total process of which it forms a part. Generally speaking, the movements produced are on the opposite side of the body to that stimulated, but in some cases muscles on both sides of the body may be simultaneously affected ; for example, stimulation of a point concerned with the movements of the eyes will result in both eyes being turned towards the opposite side. If the right side be stimulated, the eyes are turned to the left by the contraction of the right

internal rectus and the left external rectus, with simultaneous relaxation of the right external, and left internal, recti. Similarly the areas for the trunk and neck govern movements of both sides of the body. In all cases in which a movement is carried out by the combined action of muscles on the two sides of the body, the muscles of both sides are bilaterally represented in the cortex.

The application of an effective stimulus to a " motor point " on the cortex excites a definite movement, as, for example, flexion of the thumb. If a stronger stimulus is applied to the same point, the excitation will spread to adjacent areas, just as irradiation occurs in the spinal cord. By increasing the strength of the stimulus it is possible to throw all the muscles of the body into convulsive contractions. A similar phenomenon is exhibited in Jacksonian epilepsy, in which a localised irritation of a motor area, such as that due to the pressure of a spicule of bone, causes a general convulsion beginning in the part of the body represented at the site of the lesion.

The motor area has been stimulated in conscious human beings ; the stimuli elicited movements without any sensation other than a consciousness of the movements which took place. There is therefore no reason to ascribe any sensory function to the pre-central convolution, and it must be considered as purely motor.

The effect of removal of the motor area varies in different animals. In all cases the immediate effect is paralysis of the muscles on the opposite side of the body. In the dog recovery takes place, and the power of movement becomes almost as complete as it was before the operation. In the monkey recovery is less complete, and a certain degree of weakness may remain as a permanent result. When the motor area, or any part of it, is destroyed by disease in man, recovery is still less complete. In the ascent of the animal scale the functions of the nervous system become more and more transferred to the higher centres ; hence, injury of these centres in the higher animals, and especially in man, is productive of more serious interference with the neuro-muscular mechanism than is the case in animals lower in the scale.

The Area for Cutaneous and Muscular Sense.—It is obviously a matter of considerable difficulty to locate the area for tactile and muscular sensibility, inasmuch as stimulation of a sensory area in animals is followed by no objective phenomena, and opportunities rarely arise for observation of the results of stimulation in conscious human beings. There are, however, recorded cases of stimulation of the post-central convolution in conscious individuals, and, in these, sensations of numbness and touch at

the periphery of the body were evoked. Moreover, the site of the sensation varied with the part of the convolution stimulated ; and the results showed that sensory representation of the limbs, trunk, and head, occurs in the post-central gyrus in the same order as the motor representation of these parts in the pre-central gyrus. Apart from stimulation, the localisation of the sensory areas rests upon the effects of removal of different cortical regions and upon histological and clinical observations.

Stimulation of the post-central convolution in animals is followed by muscular movements, but a stronger stimulus is required to elicit these than is necessary if the pre-central convolution is stimulated, and the latent period is longer in the case of the post-central gyrus, indicating that the impulse has to traverse a larger number of neurons. This result is what might be anticipated, as it is probable that the post-central and pre-central convolutions are connected by short association-fibres and that, when the post-central gyrus is stimulated, the impulse passes from it to the pre-central gyrus and thus gives rise to movement.

Removal of the post-central convolution in monkeys is said to result in ataxia, without paralysis, of the muscles of the opposite side of the body. But Graham Brown has excised a part of the post-central convolution opposite the arm area of the pre-central in a young chimpanzee, and records that, after a short period of weakness of the opposite fore-limb, there was no appreciable permanent motor defect.

The thalamo-cortical fibres are distributed not only to the post-central convolution but also to the temporal, frontal, and occipital lobes, and therefore sensory impulses are distributed to a much wider area of the cortex than that from which motor impulses arise. The chief tract of thalamo-cortical fibres, however, terminates in the post-central gyrus.

The available evidence indicates that the post-central gyrus is a sensory area specially connected with cutaneous sensibility, that the whole of the parietal area is concerned with muscular sense, and that the senses of heat, cold, and pain have a wider distribution in the cortex of the cerebral hemisphere.

The Visual Area.—The visual area comprises a central region (the visuo-sensory area), to which the fibres of the optic radiation are distributed, and a zone surrounding this, called the visuo-psychic area, not related directly to any system of projection-fibres, but linked up with the visuo-sensory area by association-fibres. The visuo-sensory area occupies the greater part of the medial aspect of the occipital lobe ; the visuo-psychic area extends on to the lateral aspect of the lobe.

Extirpation of both occipital lobes results in total blindness; extirpation of one lobe leads to blindness of the homolateral half of each retina. Stimulation of the visuo-sensory area is followed by movements of the eyes, and, from the direction in which the eyes are turned in response to stimuli applied to various parts of the area, it may be inferred that the retinal impulses are projected on to the cortex according to a definite plan. Thus, stimulation of the upper part of the occipital lobe is followed by a downward movement of the eyes, while stimulation of a lower point of, say, the right lobe leads to a deviation of both eyes towards the left. In the former case the movement is that which would normally follow the excitation of the upper part of the retina, in the latter it is that which would occur from excitation of the right side of either retina. The fovea centralis, or part of the retina concerned with distinct vision, is represented bilaterally.

Impulses are transmitted from the retinæ to the occipital lobes by the optic nerves, optic tracts, and optic radiations (fig. 44). Each optic nerve, consisting of the axons of nerve-cells in the retina, divides at the chiasma, the fibres from the medial side of the retina crossing to the opposite side to take part in the formation of the optic tract of that side. Thus each optic tract is made up of fibres from its own side of each retina. The tract-fibres terminate by arborisation round nerve-cells in the pulvinar of the thalamus, the external geniculate body, and the superior colliculus of the corpora quadrigemina. The fibres which enter into the optic radiation arise in the thalamus and external geniculate body, and are distributed to the cortex of the occipital lobe (fig. 44). The relay-fibres from the superior colliculus are distributed to the oculo-motor nuclei, and appear to be concerned with the function of equilibration and with reflex contraction of the pupil.

The Auditory Area.—The localisation of the auditory area is less definite than that of the visual area, largely owing to the difficulty of ascertaining the degree of deafness produced in animals by experimental lesions. A partial decussation of the auditory tracts occurs, similar to that of the optic nerves, so that each cerebral hemisphere receives impulses from both ears.

The auditory area comprises an audito-sensory region, to which the auditory projection-fibres are distributed, and an audito-psychic region, connected with the receptive district by association-fibres. The audito-sensory area is located in the temporal lobe, and has been supposed to be limited to the middle region of the superior temporal convolution, the audito-psychic area being adjacent to it. The superior temporal convolution

is probably the chief centre for hearing, but there may be subsidiary areas outside it, since Schafer has shown that removal of the superior temporal convolutions alone from both sides in monkeys does not result in complete deafness. Stimulation of the superior temporal convolutions in monkeys is followed by

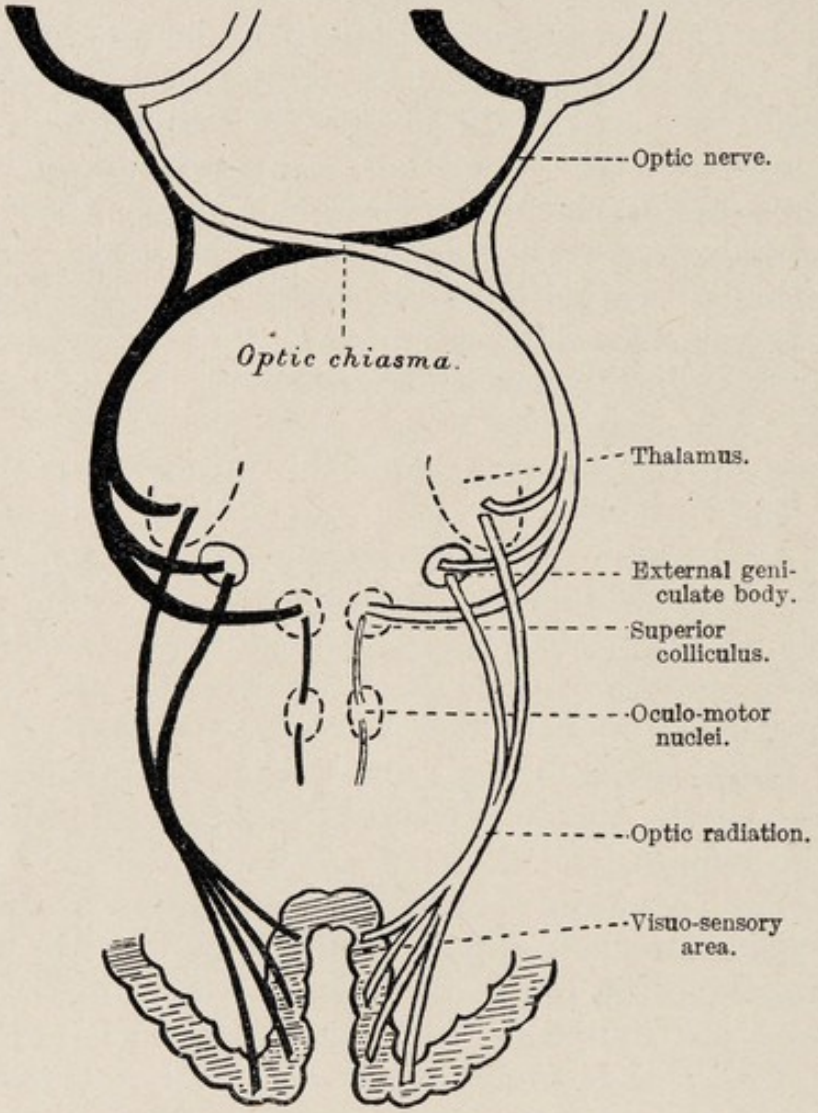


FIG. 44.—Diagram showing the path of the visual impulses.

The oculo-motor nuclei are connected by commissural fibres (not shown in figure).

pricking of the opposite ear and turning of the head towards the opposite side.

Impulses pass from the cochlea to the auditory centre by the cochlear division of the eighth nerve, the auditory tract, and the auditory radiation. The fibres of the cochlear nerve are derived from the spiral ganglion, and terminate in the tuberculum acusticum and the accessory nucleus. The axons from the tuberculum acusticum turn over the restiform body to become the *striæ acusticæ* (*striæ medullares*) in the floor of the fourth

ventricle. These dip into the substance of the pons at the middle line, some passing to the trapezoid nucleus and the superior olivary nucleus of the same side, others to the corresponding nuclei of the opposite side. Some fibres terminate in these nuclei on each side, others are continued directly into the lateral fillet. The fibres from the accessory nucleus constitute the trapezium, and also enter into the formation of the lateral fillet (fig. 45). Many of the trapezoid fibres have cell-stations in the trapezoid and superior olivary nuclei. The lateral fillet terminates in the inferior colliculus and internal (medial) geniculate body; from the latter new fibres arise to be distributed to the superior temporal convolution as the auditory radiation.

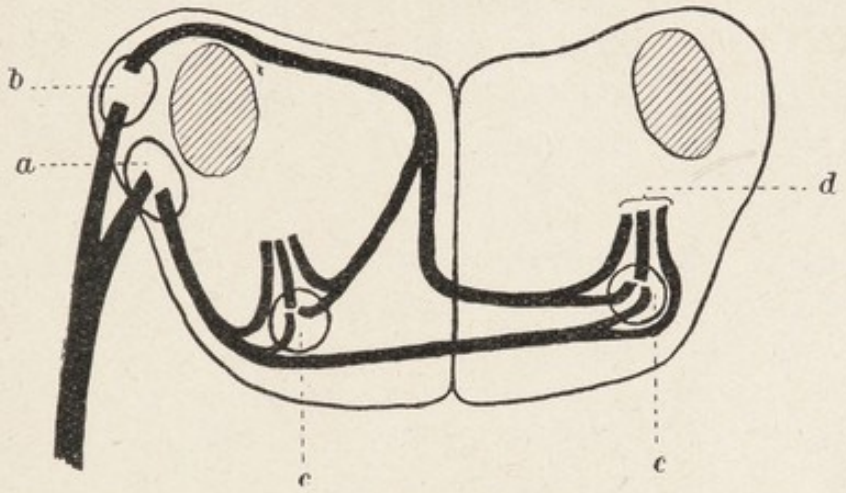


FIG. 45.—Diagram showing the path for auditory impulses in the pons.

a, Accessory nucleus; *b*, tuberculum acusticum; *c*, trapezoid nucleus; *d*, lateral fillet.

The Area for Smell and Taste.—The area for smell and taste is located in the hippocampal convolution and the neighbouring structures. This region of the brain is relatively large in animals which have a highly developed sense of smell. Extirpation of the area has not yielded definite results. Stimulation causes movements of the lip and nostrils on the same side, such as would be caused by a disagreeable or irritating odour applied to the nostril.

The olfactory nerve-fibres are non-medullated processes of cells in the olfactory mucous membrane, and terminate in structures, known as glomeruli, in the olfactory lobe in relation with the dendrites of certain "mitral" cells, the axons of which convey the impulses transmitted to them by the olfactory fibres to the hippocampal region of the same or the opposite side (fig. 46).

The nerves of taste are the chorda tympani to the anterior two-thirds, and the glossopharyngeal to the posterior third, of

the tongue. The taste-fibres of both nerves terminate in a column of cells in the pons, which also receives afferent fibres from the fifth nerve. The conducting tract from this nucleus to the cortical area for taste has not been traced.

The Association-Areas.—There are three great association-areas: the posterior in the parieto-temporal region, the middle in the island of Reil, and the anterior or pre-frontal. Stimulation of these areas gives rise to no obvious motor response, but disease or imperfect development of them in man is accompanied by various forms of mental deficiency. The pre-frontal area is the highest associational centre; it is the last to develop and the first to

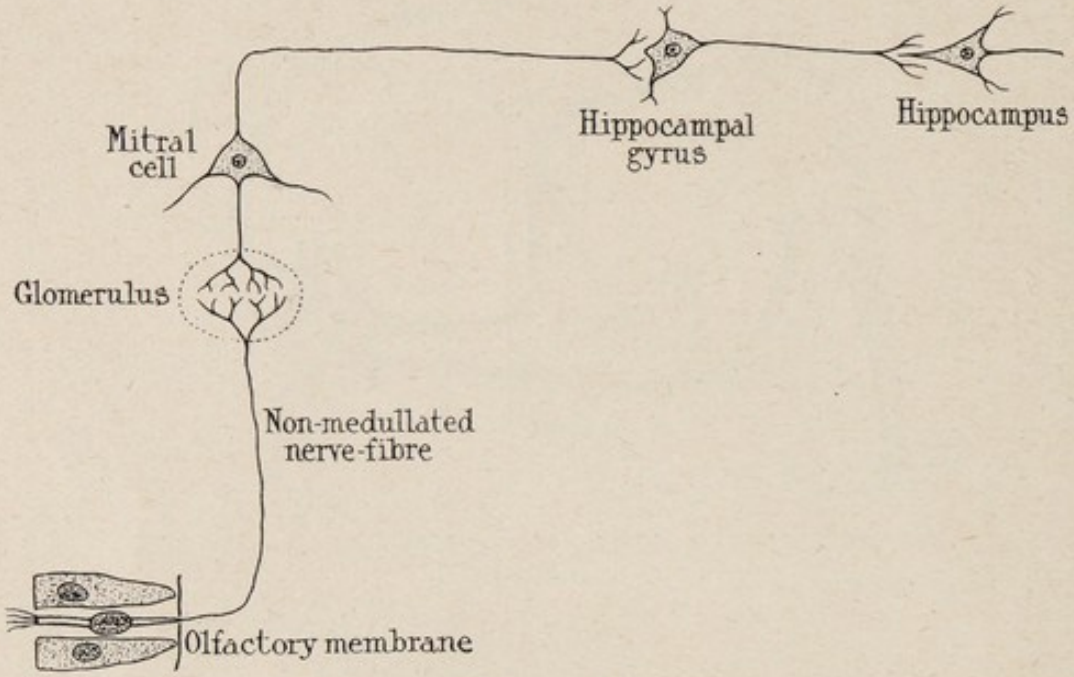


FIG. 46.—A diagram of the path for olfactory impulses.

retrograde. In it the outer cell-lamina attains its greatest depth, and atrophy of the cells of this lamina is found in cases of dementia. The posterior association-area, lying between the visuo-psychic and the audito-psychic areas, is concerned with mental images, especially with the processes involved in the perception of spoken and written language. Lesions of this area are accompanied by interference with the appreciation of words, and give rise to the different forms of sensory aphasia.

The human brain is characterised by the great development of the association-areas. They represent the material basis for the memory of past stimuli, and for the comparison of one set of stimuli with another. In other words, they are the anatomical structures concerned with knowledge, intelligence, and, still further, with the faculties of inhibition and voluntary attention, which find their highest development in man.

SPEECH AND APHASIA

The pre-eminence of man is intimately associated with the power of speech. The production of spoken or written words is of course only a specialised use of the muscular system; but, for the appreciation of language, the existence of word-hearing and word-seeing centres has sometimes been assumed. Language constitutes the basis, or the instrument, of thought; and words, when heard or seen, awaken the memory of past stimuli and associations. Speech is merely the expression of thought. Interference with the language mechanism produces *aphasia*, and this may be either motor or sensory or both. In motor aphasia the power of forming words is lost, in sensory aphasia there is inability to comprehend spoken or written language.

Motor aphasia is due to the loss of power of performing the co-ordinated muscular movements concerned with the production of speech. It may be caused by a lesion of the third left frontal convolution (Broca's area), in which case there is also slight and temporary impairment of the power of appreciating the meaning of words. Destruction of the subcortical fibres in the neighbourhood of the lenticular nucleus gives rise to the condition known as *anarthria*, in which there is loss of power of articulate speech without any impairment of intelligence. In consequence of the unilateral situation of the speech-centre, motor aphasia is found associated with right-sided paralysis caused by a lesion of the motor projection-fibres in the internal capsule of the left side (see below). In left-handed persons Broca's centre is situated on the right side of the brain, and in such individuals motor aphasia is associated with paralysis of the left side of the body caused by a lesion in the right internal capsule.

Sensory aphasia may take the form of word-blindness or word-deafness. In word-blindness, vision may be perfect and the words on a printed page may be distinctly seen, but they are as meaningless as if they were in an unknown language, and there is no power of associating the written symbol with past stimuli. Similarly in word-deafness, hearing may be perfect, but spoken words are unintelligible sounds. Sensory aphasia is always accompanied by some degree of mental deficiency, especially in the case of word-deafness. It is due to a lesion in the parieto-temporal region of the cerebral hemisphere. The most common form of aphasia is a combination of anarthria with sensory aphasia.

THE THALAMUS AND INTERNAL CAPSULE

The thalamus forms the lateral boundary of the third ventricle. It is a large ganglionic mass, and receives the terminations of the fibres of the fillet. The outgoing fibres from the thalamus are distributed to all parts of the cortex of the cerebral hemisphere, and cortico-thalamic fibres also run from the cortex to the thalamus.

On the lateral aspect of the thalamus is the internal capsule, to, and from, which fibres radiate from, and to, all parts of the cortex. In a horizontal section, the internal capsule is seen to consist of a short anterior limb pointing outwards and forwards, and a longer posterior limb directed outwards and backwards; the junction of the two limbs is termed the genu. The lateral aspect of the internal capsule is bounded by the lenticular nucleus of the cerebral hemisphere. The anterior limb is bounded on its medial aspect by the head of the caudate nucleus of the hemisphere. The anterior limb of the internal capsule contains the fronto-pontine fibres. The genu and the anterior two-thirds of the posterior limb contain the pyramidal fibres for the head, arm, trunk, and leg in the order mentioned from before backwards. Behind the pyramidal fibres are, in order, the fillet, the auditory radiation, the temporo-pontine fibres, and the optic radiation (fig. 47).

The lenticular and caudate nuclei together form the corpus striatum, which is believed to co-ordinate movements of a less highly organised kind than those represented in the cerebral cortex.

THE PATHS BETWEEN THE CEREBRAL HEMISPHERES AND THE SPINAL CORD

Afferent impulses enter the spinal cord by the posterior nerve-roots. Those for muscular sense and tactile discrimination travel by the posterior column to the nucleus gracilis and nucleus cuneatus in the medulla oblongata. From these nuclei fibres arise and cross to the opposite side, where they form part of the fillet. The fillet passes through the pons, mid-brain and internal capsule to terminate in the thalamus, from which the impulses are conveyed to the cortex of the cerebral hemisphere by the thalamo-cortical fibres (fig. 26). The paths for touch, tactile localisation, pain, heat, and cold cross in the spinal cord very shortly above the entrance of the posterior roots by which they were conveyed. They travel up by the spino-thalamic tract, or possibly by short segmental tracts, to the medulla oblongata,

and there join the fillet, their subsequent course being that just described.

The pyramidal (cerebro-spinal) fibres take origin as the axons of the Betz-cells in the motor area, pass through the white matter of the cerebral hemisphere, through the internal capsule, the

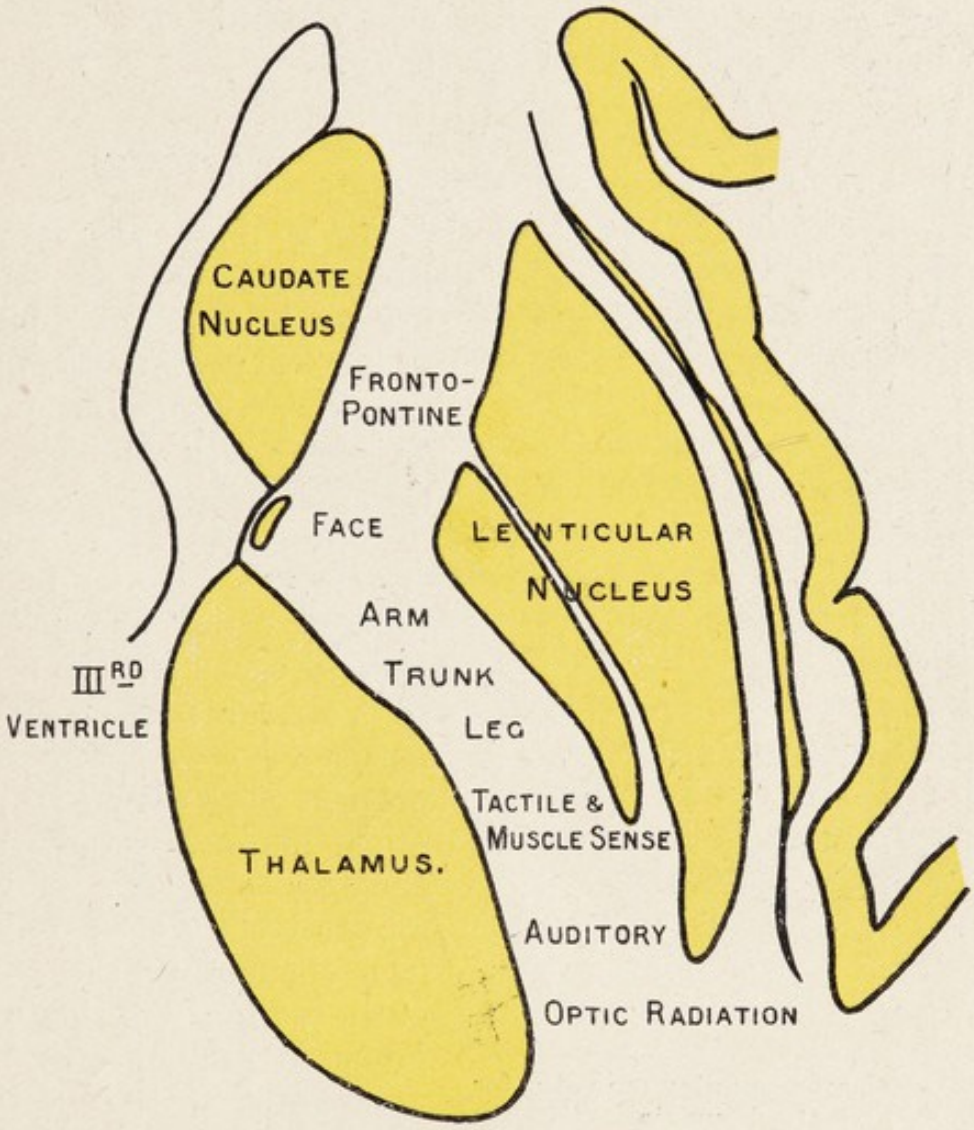


FIG. 47.—Diagrammatic representation of the right internal capsule, as seen in horizontal section.

pes of the mid-brain, and the pons, to become the pyramid of the medulla oblongata. Most of these fibres cross in the pyramidal decussation to form the crossed pyramidal tract, and terminate by turning into the grey matter of the spinal cord, where they pass their impulses on, probably through an intermediate neuron, to the cells of the anterior horn, the axons of which become the motor fibres of the nerves to the skeletal muscles (fig. 48). The pyramidal fibres which do not cross in the medulla oblongata form the direct pyramidal tract of the spinal cord, and cross

by degrees to the grey matter of the opposite side to come into relation with the cells of the anterior horn. Some of the uncrossed fibres join the crossed pyramidal tract of the same side, and their further course is unknown. The pyramidal fibres from each cerebral hemisphere convey impulses to the contralateral side of the body.

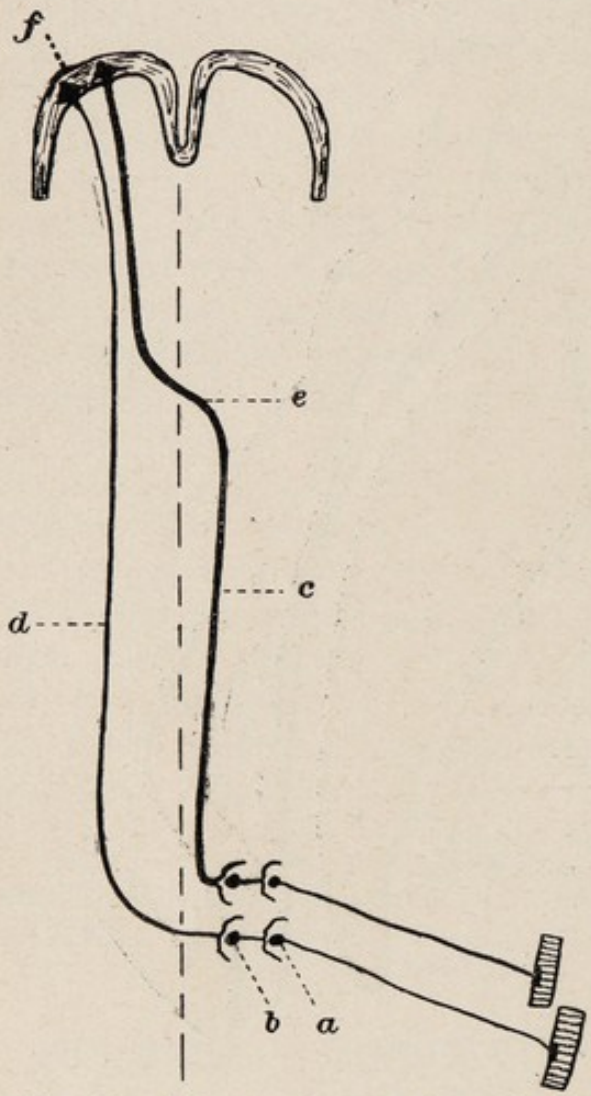


FIG. 48.—Diagram showing the paths for motor impulses.

a, Cell in anterior horn of grey matter; *b*, cell in posterior horn; *c*, crossed pyramidal tract; *d*, direct pyramidal tract; *e*, decussation of pyramids; *f*, motor area in cortex.

FATIGUE

In a muscle-nerve preparation fatigue is shown first of all in the end-plates (p. 51). In the intact animal, however, the causation of fatigue is very complex, and the most important factor is the central nervous system. Even the fatigue brought about by muscular exercise usually has its origin to a larger extent in the nervous system than in the muscles themselves, the part of the nervous system which becomes fatigued being in all probability the synapses. The changes in the nerve-cells which are brought about by prolonged exercise also indicate that fatigue is partly nervous in origin. It must be remembered, moreover, that the sense of fatigue does not always correspond with the degree of fatigue as measured by the capacity of the muscles to do work; and the effect of psychical influences in lessening or abolishing the sense of fatigue is well known.

SLEEP

Every active tissue of the body has alternating periods of activity and rest. Thus the ventricles of the heart have a period of contraction of three-tenths of a second, followed by a period

of relaxation of five-tenths of a second. In the case of the other muscular tissues and of the glands, the periods are longer and are often irregular, but the same general principle holds good. The active phase of the cells in the cerebral cortex which subserve consciousness coincides with the waking period, while the resting phase is the period of sleep. During sleep consciousness is in abeyance, and the activity of all the vital processes is lowered; respiration is slower, the rate of the heart-beat is reduced, glandular secretions are diminished in quantity, metabolic changes generally are less active, and the temperature falls. Histological observations on the nerve-cells in sparrows show that certain spindle-shaped, clear bodies (Nissl-spindles) disappear from the cells during the activity of the day and are restored during the night's rest. It may be concluded that katabolic changes exceed anabolic changes during the waking hours, and that the reverse is the case during sleep.

The cause of sleep has been much discussed, and it is generally agreed that it is associated with a diminished supply of oxygen to the brain; the cells of the cerebral cortex are undoubtedly peculiarly susceptible to a deficiency of oxygen. Further, there is evidence to show that the blood-flow is side-tracked during sleep so that the brain receives a smaller supply than it does in the waking hours. If a limb be enclosed in a plethysmograph, it is found that the volume of the limb increases during sleep owing to dilatation of its blood-vessels. As a result, the supply of blood to the brain is diminished, but this is probably secondary to the diminution in functional activity; and the causation of sleep is still urknown.

SECTION IX

THE CEREBRO-SPINAL FLUID

The cerebro-spinal fluid forms a water-cushion by which the brain and spinal cord are protected from jarring shocks during any sudden movement of the body; it serves also as the medium for the conveyance of oxygen and nutritive material to the brain and cord, and into it are discharged the metabolic products formed by these organs. It occupies the space between the membranes of the brain and spinal cord, and fills the ventricular cavities of the brain and the central canal of the cord. The fluid lying in the ventricular cavities communicates with that which fills the space between the membranes at the foramen of Majendie and at two other foramina, one of which lies at each side of the recess of the fourth ventricle.

The cerebro-spinal fluid resembles lymph, but is much less concentrated than that fluid. It is clear and limpid, and has a specific gravity of 1002 to 1007. It contains glucose, urea, and small amounts of the other organic constituents of blood-plasma, proteins being present in traces only. Its inorganic constituents correspond with those of plasma.

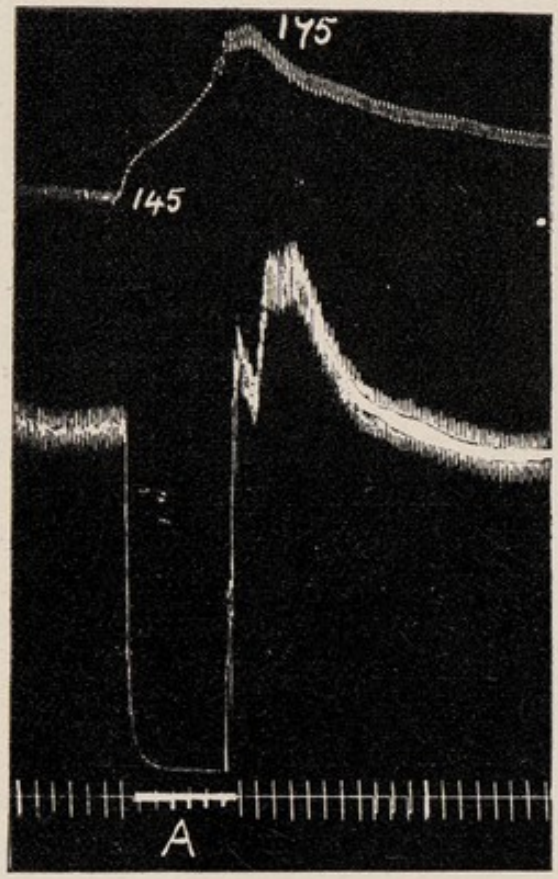


FIG. 49.—Tracing showing the effect of stimulation of the peripheral end of the vagus nerve on the pressure of cerebro-spinal fluid (upper curve) and on the arterial pressure (lower curve). Vagus stimulated at A. The cranial venous pressure (not shown in the figure) also fell. The figures on the upper curve indicate pressure in mm. water. (Dixon and Halliburton.)

If the dura mater is punctured the cerebro-spinal fluid escapes from the opening, showing that it is under a certain degree of pressure, which can be measured by inserting a cannula into the subarachnoid space and connecting it with a manometer. It is found that the pressure corresponds roughly with the venous blood-pressure, and that it varies to a slight extent with variations in arterial and venous pressure.

If the cerebro-spinal fluid is allowed to escape, it is rapidly replaced. This is shown in cases in which the escape continues for some time, either in conditions experimentally produced in animals or in such accidental circumstances as fracture of the base of the skull in man. A loss of 100 c.c. or more per hour has been known to continue for weeks in a human being.

The cerebro-spinal fluid is derived from the choroid plexus, and there is evidence that it is formed by a process of secretion. It has been found that a saline extract either of the choroid plexus or of brain-tissue, if injected into the circulation, brings about an increased flow of cerebro-spinal fluid, which may be collected by means of a cannula. This observation suggests that the extract contains some active substance, of the nature of a hormone, which acts as a chemical stimulus to the secretory activity of the choroid plexus. The hormone contained in the

extract is not destroyed by boiling and is soluble in alcohol. It is not a protein, but must have a relatively large molecule, since it will not pass through a Chamberland filter.

The flow of cerebro-spinal fluid is also increased if the air breathed by an animal is either deficient in oxygen or contains an excess of carbonic acid, whereas it is diminished when the air breathed contains an excess of oxygen.

That the fluid is not formed by filtration is suggested by experiments in which a fall of blood-pressure is accompanied by an increased production of the fluid, as is shown by a rise of pressure recorded by a manometer connected with the subarachnoid space in the skull. For example, if one vagus nerve is divided and the peripheral portion stimulated, the blood-pressure may fall nearly to zero both in the carotid artery and in the cranial veins, while at the same time the pressure of the cerebro-spinal fluid shows a very marked rise (fig. 49). The explanation of this rise is found in the diminished supply of oxygen to the brain and the local accumulation of carbonic acid.

The secretion of cerebro-spinal fluid must be balanced, under normal conditions, by a corresponding degree of absorption, and experiments have shown that the absorption takes place directly into the veins.

SECTION X

THE AUTONOMIC SYSTEM

In contradistinction to skeletal muscle, the unstriped muscle which is found in the walls of the heart, arterioles, digestive tract, uterus, bladder, and elsewhere, is not under the control of the will, though its contraction is regulated by impulses arising in the central nervous system. The nerves which supply these structures, and also those to the secretory glands, form the autonomic system. The characteristic feature of this system is the existence of a cell-station on every nerve-path between the central nervous system and the effector-organ (muscle or gland). The synapse is situated in a ganglion, and the autonomic path thus consists of a *pre-ganglionic fibre*, a *synapse*, and a *post-ganglionic fibre* (fig. 50).

The autonomic system includes (1) branches of the third, fifth, seventh, ninth and tenth cranial nerves, and fibres issuing from the anterior roots of the second and third sacral nerves, and known as the pelvic visceral nerves or nervi erigentes; these together constitute the *parasympathetic* nervous system; and (2) the *sympathetic* system, the pre-ganglionic

fibres of which leave the spinal cord in the anterior roots of all the spinal nerves from the first thoracic to the fourth lumbar.

The pre-ganglionic nerve-fibres are medullated and small, varying in diameter from 2 to 4 μ; each ends by arborisation round a nerve-cell which lies in a sympathetic, or other, ganglion. The axon of the nerve-cell forms the post-ganglionic fibre, and is usually non-medullated. The nervous impulse issuing from the central nervous system along a pre-ganglionic fibre normally passes across the synapse to the ganglion-cell, and then along the post-ganglionic fibre to muscle or gland.

Although the entire autonomic system is built up on this general plan, the actual anatomical distribution of the fibres and the situation of the cell-stations are very varied. The fibres issuing from the brain and from the sacral region of the spinal cord have their cell-station close to, or actually within, the organ which they supply. The fibres of the sympathetic system take a different course. Lying along each side of the vertebral column is a chain of ganglia which forms the lateral sympathetic chain (fig. 51). As a rule there is one ganglion corresponding with each spinal nerve-root, but in the dog the upper four thoracic ganglia are fused into one larger mass, the stellate ganglion. In the cervical region there are in most animals only two ganglia, inferior and superior, united by the cervical sympathetic nerve. The pre-ganglionic sympathetic fibres leave the anterior roots in the thoracic and upper lumbar regions as a series of small nerves, the white *rami communicantes*, each of which enters the corresponding ganglion of the lateral sympathetic chain. Some of these fibres, including those which carry impulses to the blood-vessels of the skeletal muscles and skin and to the hairs and sweat-glands, have their cell-stations in one or other of the ganglia of the lateral sympathetic chain; and the post-ganglionic fibres form small nerves (called grey rami communicantes), one of which joins each of the spinal nerves. The sympathetic fibres which supply the blood-vessels and other structures of the head leave the spinal cord by the first to the fourth or fifth thoracic white rami, and pass through the stellate ganglion up the cervical sympathetic nerve to the superior cervical ganglion; their cell-stations lie in this ganglion, and the post-ganglionic fibres leaving

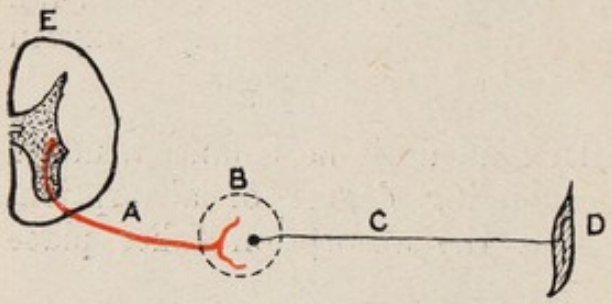


FIG. 50.—Diagram to show relation between pre-ganglionic and post-ganglionic fibres.

E, Spinal cord; A, pre-ganglionic fibre; B, cell-station; C, post-ganglionic fibre; D, unstriped muscle-fibre.

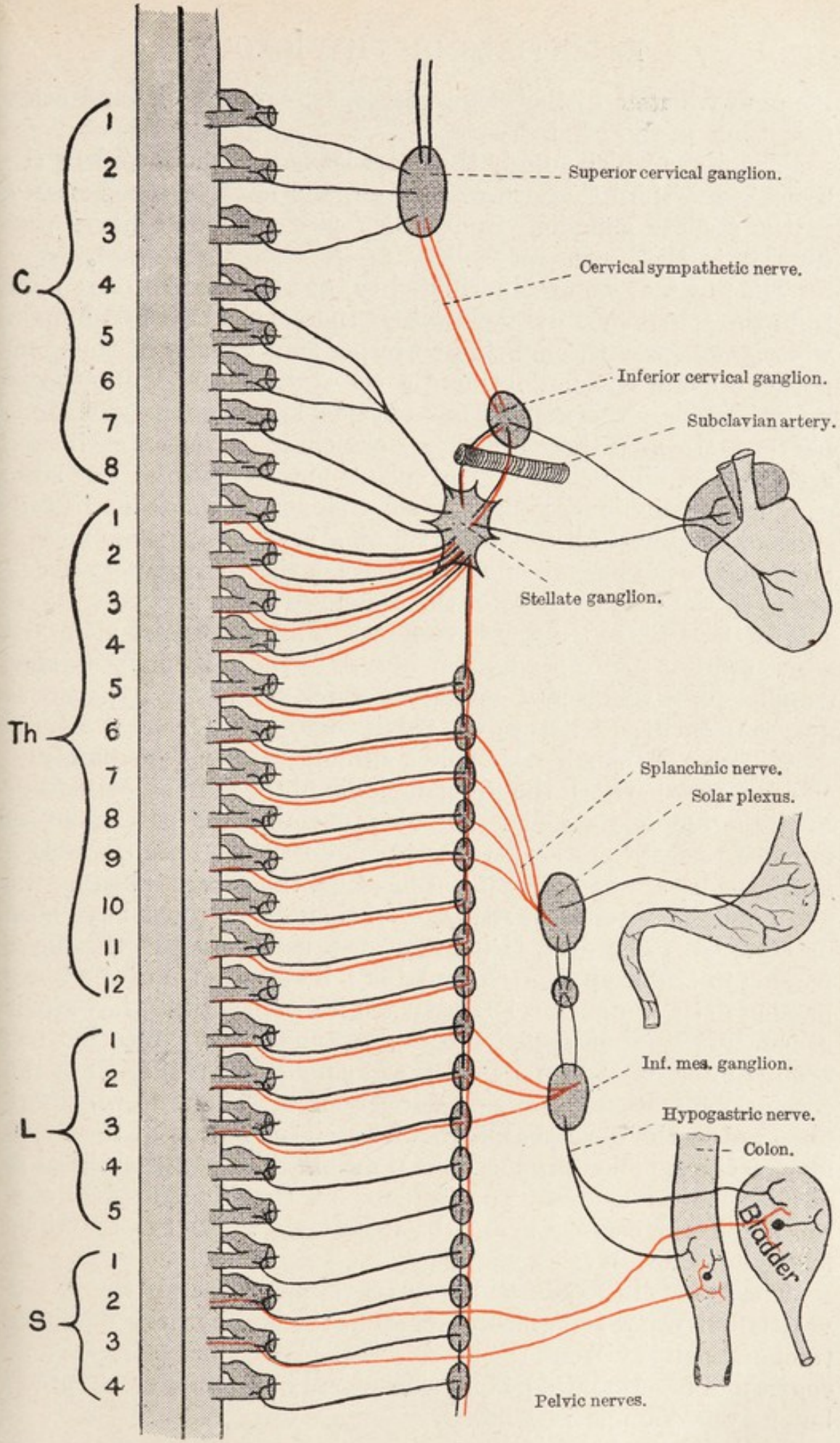


FIG. 51.—Diagram of mammalian autonomic nervous system (excluding cranial nerves).

Pre-ganglionic fibres, red ; post-ganglionic, black.
The fibres forming the lesser and lowest splanchnic nerves in man are omitted in the diagram.

it are distributed to the blood-vessels, salivary glands, and other structures in the head.

The fibres which supply the heart leave the spinal cord by the second and third thoracic white rami, and have their cell-station in the stellate ganglion, from which post-ganglionic fibres pass directly to the heart.

The fibres which are distributed to the abdominal viscera issue from the spinal cord by the lower six thoracic and the first lumbar white rami, pass through the corresponding ganglia of the sympathetic chain without forming a cell-station, and are gathered up into two large nerves, one on each side, known as the splanchnic nerves. (In man there are three splanchnic nerves on each side, great, lesser, and lowest.) The splanchnic nerves enter two large ganglia, the semilunar ganglia or solar plexus, in which lie the cell-stations of almost all the fibres running in the splanchnic nerves. Some of the post-ganglionic fibres leaving these ganglia are distributed to the blood-vessels of the abdominal viscera, while others supply the walls of the digestive tract. Fibres also pass along the white rami of the upper lumbar nerves to the inferior mesenteric ganglia, from which post-ganglionic fibres run in the hypogastric nerves to be distributed to the pelvic organs.

Nicotine, in small doses, first stimulates and then paralyses the synapses between the pre-ganglionic fibres and the nerve-cells in the autonomic ganglia, thereby preventing the passage of an impulse through the cell-stations ; it does not affect the nerve-fibres themselves. By means of nicotine, the course taken by the autonomic fibres and the situation of their cell-stations have been determined. The drug is painted on a ganglion, and the fibres passing to and from it are stimulated ; if stimulation of the fibres passing to the ganglion is ineffective, it is clear that they have their cell-station in that ganglion. For example, when nicotine has been painted on the superior cervical ganglion, stimulation of the cervical sympathetic nerve produces none of the effects which are observed in the normal animal, whereas stimulation of the fibres leaving the ganglion produces the same effect after the application of nicotine as before. The experiment shows that the fibres running in the cervical sympathetic nerve have their cell-stations in the superior cervical ganglion.

The fibres of the autonomic system supply not only the blood-vessels but other structures, including the walls of the digestive tract and pelvic viscera, the heart, sweat-glands, and hairs. Their course and function will be fully considered in subsequent chapters, but may be summarised here.

I. *Cranial autonomic fibres.*

Third nerve.—The autonomic fibres pass to the ciliary ganglion,

where they have their cell-station, and supply the ciliary and sphincter pupillæ muscles of the eye.

Seventh and ninth nerves.—The autonomic fibres supply vaso-dilator fibres to the tongue, and secretory and vaso-dilator fibres to the salivary glands.

The vagus sends inhibitory fibres to the heart, motor fibres to the muscular coats of œsophagus, stomach, small intestine, and bronchioles, and secretory fibres to the stomach and pancreas; the cell-stations probably lie in the walls of the structures supplied by the different fibres.

II. *Sacral autonomic fibres.*—These supply dilator fibres to the blood-vessels of the penis, and motor fibres to the muscles of the rectum and bladder.

III. *Sympathetic fibres.*

(1) The fibres to the head leave the spinal cord in the first five thoracic white rami, and run in the cervical sympathetic nerve; this contains vaso-constrictor fibres for the blood-vessels, secretory fibres for the salivary glands, and fibres for the dilator pupillæ.

(2) The fibres to the heart have their cell-station in the stellate ganglia, and convey accelerator and augmentor impulses.

(3) The fibres to the abdominal viscera leave the spinal cord in the lower six thoracic and the first lumbar white rami. Most of them have their cell-stations in the semilunar and superior mesenteric ganglia, from which they are distributed. They convey constrictor impulses to the blood-vessels of the stomach, small intestine, kidneys, and spleen, inhibitory impulses to the muscular walls of the stomach and small intestine, and motor impulses to the ileo-colic sphincter.

(4) The pelvic viscera are supplied from the white rami of the last thoracic and the upper lumbar nerves, the cell-stations being in the inferior mesenteric ganglia. The nerves convey constrictor impulses to the blood-vessels of the pelvic organs, motor fibres to the uterus, and inhibitory impulses to the muscular coats of the colon and bladder.

(5) All the white rami also contain fibres which have their cell-stations in the lateral chain of ganglia, the post-ganglionic fibres passing usually, but not always, into the corresponding spinal nerve to be distributed to the blood-vessels of the muscles and skin, and to the sweat-glands and hairs in the area supplied by that nerve.

It will be noticed that many organs are supplied by two sets of fibres, parasympathetic and sympathetic, having opposing functions.

FUNCTIONS OF THE GANGLIA

The cells of the ganglia serve as distributing centres, and each pre-ganglionic fibre arborises round a number of cells, so that the post-ganglionic fibres are much more numerous than the pre-ganglionic fibres.

At one time various reflex actions were attributed to the sympathetic ganglia, but these have been proved to be not true reflexes, but pseudo- or axon-reflexes. For example, when the nerves connected with the inferior mesenteric ganglion are divided, with the exception of the left hypogastric nerve to the bladder, stimulation of the central end of the right hypogastric nerve causes contraction of the left half of the bladder (fig. 52). This

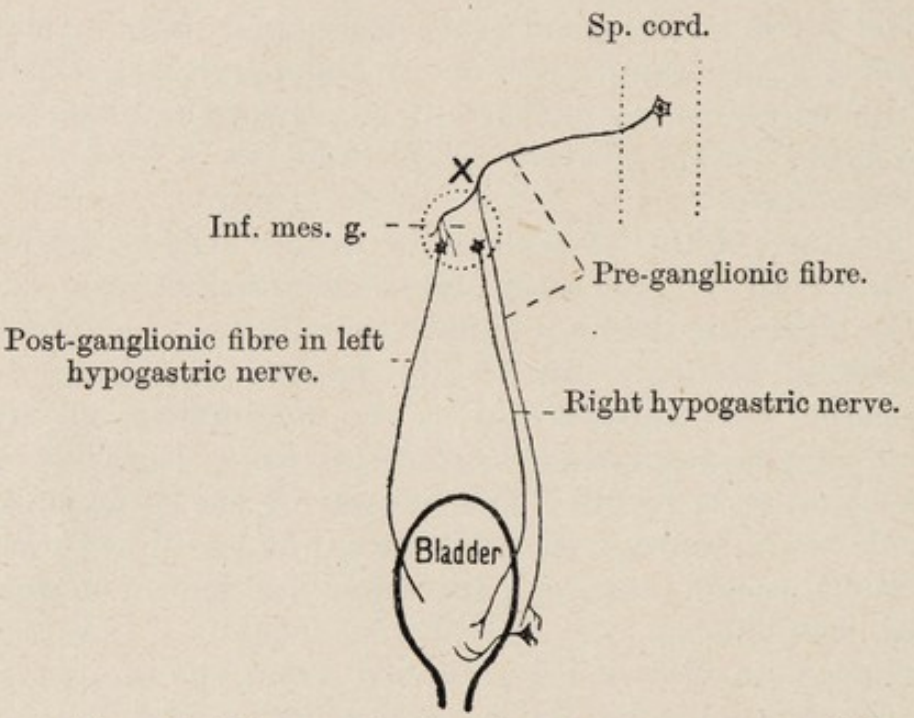


FIG. 52.—Diagram showing the structures concerned in the "axon-reflex" referred to in the text. (Starling's *Principles of Physiology*.)

is due to the fact that certain pre-ganglionic fibres arising in the spinal cord pass through the inferior mesenteric ganglion to form synapses with nerve-cells in the wall of the bladder. In their course through the ganglion each gives off a collateral fibre, which arborises round nerve-cells in the ganglion itself. From these cells post-ganglionic fibres pass to the bladder. Thus, in the above experiment, the ascending impulse set up by the stimulus passes by the collateral fibre in the ganglion to the cell of origin of a post-ganglionic fibre which is distributed to the opposite half of the bladder. This effect is called an *axon-reflex*.

AFFERENT FIBRES IN AUTONOMIC SYSTEM

The autonomic system also contains afferent fibres, though these are less numerous than the efferent fibres ; in the splanchnic and hypogastric nerves about one-tenth of the fibres are afferent. The stimulation of these fibres by abnormal processes in the abdominal organs may give rise to pain. The pain is usually referred, however, not to the organ itself, but to the surface of the body ; for instance, afferent impulses from the stomach may give rise to pain which is referred to an area of skin at the lower border of the ribs, and this area may actually be tender to touch. The explanation of this phenomenon is that, where two areas of unequal sensibility are connected with the same spinal segment, any stimulation of the nerve of less sensibility is referred to the area supplied by the nerve of greater sensibility ; and the sensibility of the skin is greater than that of the viscera. The position of the referred pain and of tender cutaneous areas has proved of value in man as a means of localising disease of the internal organs.

CHAPTER V

THE ORGANS OF SENSE

SECTION I

The structures concerned in the production of any particular sensation are arranged in a system, made up of (1) an end-organ, (2) a chain of neurons for the transmission of impulses from the end-organ, and (3) sensory, psychic, and association-areas of the cerebral cortex, in which the impulse is received, and in which the sensation is excited. The system is described as *exteroceptive* when the end-organ is situated at the surface of the body and receives impulses from without; as *enteroceptive* when the end-organ is in the viscera; and as *proprioceptive* in the case of end-organs affected by the position of the body, or by the degree of tension of a muscle. Thus, the exteroceptive system includes the structures which have to do with sensations of touch, taste, smell, sight, and hearing; the enteroceptive system includes the mechanisms for hunger and thirst; and the proprioceptive system has to do with variations in the position of the head and limbs and in the degree of muscular contraction.

The end-organs for each sense are structurally adapted to receive only the stimulus for that particular sense, this being known as the *adequate stimulus*. Thus, the rods and cones of the retina are stimulated by vibrations of the ether, but not by vibrations of the air, while the hair-cells in the cochlea of the ear are excited by waves of air, but not by those of the ether. The nerve-fibres which transmit the impulses, on the contrary, appear to be able to transmit any variety of stimulus, and they all give the same type of electrical variation when stimulated by an electric current.

Although the various sense-organs differ widely in structure, certain general principles can be formulated as regards their function, which are applicable to them all.

(1) Stimulation of the end-organs of any particular sense gives rise to the sensation peculiar to that sense, and to that sensation only; in other words, each sense has its own specific quality or

modality. This is the "law of specific irritability." The quality of the sensation aroused might be determined by the nature of the receptive end-organ, by the conducting apparatus, or by the area of the cortex to which the impulse is transmitted. Direct stimulation of the central portion of a divided sensory nerve gives rise to the specific sensation, so that the modality is not determined by the end-organ. For example, pressure on the ulnar nerve-trunk excites a pricking sensation referred to the area of distribution of the nerve, and section of the optic nerve in a conscious patient is accompanied by the sensation of flashes of light. Again, there is no reason to believe that the conducting nerve-fibres have any more influence on the nature of the impulse they convey than an electric wire has in determining the nature of a telegraphic message. It is, therefore, in the cortex of the cerebral hemisphere that the explanation of the specific character of the sensation is to be sought, and this conclusion is supported by the fact that sensations may be aroused in the absence of any stimulation of the end-organs, for example, during dreams or in hallucinations.

(2) In the case of each sense a certain minimal strength of stimulus, known as the *threshold stimulus*, is necessary to evoke a sensation. The exact strength of the threshold stimulus for any particular sense varies in different individuals, and also in the same individual at different times. A succession of subliminal stimuli, that is of stimuli each of which is below the threshold value, may excite a sensation by a summation effect, just as the summation of subminimal stimuli may excite a reflex action. The threshold value will vary with the condition of the sense-organ and of the area of the cerebral cortex with which it is associated. For example, the mechanism may be fatigued, and will then be less responsive to stimulation. This is well illustrated in the case of smell. The air of a closed room, which is occupied, becomes disagreeable, but the occupants of the room do not notice the unpleasant smell, although this is at once apparent to anyone coming in from the outer air. The threshold value also varies with the state of adaptation of the sense-organ. Thus, an eye which has been exposed to light is said to be light-adapted, while one that has been in darkness for a time is dark-adapted. The threshold value of the light stimulus for the dark-adapted eye is much lower than, actually about one-fiftieth of, that required to produce a sensation in the light-adapted eye.

(3) The increase of stimulus necessary to cause a difference in the degree of sensation bears a constant proportion to the strength of the original stimulus. If the eye is being stimulated by the light of one hundred candles, the extra stimulation required to produce the sensation of more light can be derived from one more

candle. If, however, the original stimulus came from one thousand candles, then ten more candles would be required for a difference to be detected.

Similarly, if a weight of 30 grams is held in one hand, one more gram must be added to excite a sensation of increased weight, and a smaller increase would not be noted. If the original weight is 60 grams, 2 grams must be added for the difference to be perceptible. So also in the case of sound, the stimulus must be increased by one-seventh to lead to the perception of increased volume of sound. In all cases this relationship, which is known as Weber's law, only holds good within certain definite limits, the limits for the sense of pressure, for example, as tested by weights, lying between 50 and 1000 grams.

CUTANEOUS SENSATIONS

The sensations aroused by the application of different varieties of stimuli to the skin are those of touch or light pressure, heat, cold, and pain. These various sensations are independent, and do not result from different forms of stimulation applied to the same set of nerve-endings. The evidence that tactile sensation, heat, cold, and pain are distinct senses is (1) histological, (2) the existence of independent spots in the skin, stimulation of each of which gives rise to one variety of sensation only, and (3) the fact that the conducting path for one set of impulses, for example, those giving rise to pain, may be blocked, while those for the other senses are unaffected. The sensation excited by heavy pressure is not a cutaneous one, but depends upon the stimulation of sensory nerve-endings in the deeper structures, such as subcutaneous tissue and muscle.

Histological. The End-organs in the Skin.—The peripheral fibres of the cells in the spinal ganglia, or the homologous ganglia of the cerebral nerves, terminate in the skin in various ways. The termination may be free, or it may be protected.

Free nerve-endings are found in the anterior epithelium of the cornea; the axis cylinders of the nerve-fibres lose their myelin sheaths at the periphery of the cornea and, after entering into the formation of a plexus in the corneal substance, terminate between the epithelial cells in the form of fine varicose fibrils. Similar terminations are found in the epidermis, and fibrillar nerve-endings occur also around the hair-follicles.

The *protected nerve-endings* are all formed on the same general plan. There is a central, soft core surrounded by a variable amount of fibrous tissue, arranged sometimes irregularly, and sometimes, as in the Pacinian corpuscles, in laminæ. The nerve-

fibre loses its myelin sheath and runs into the core of the end-organ, where it ends in one or more knob-like extremities. Such endings are the *end-bulbs* found in the conjunctiva, penis, clitoris, and in the synovial membrane of some joints ; the *touch-corpuscles of Meissner* in the connective tissue papillæ of those parts of the skin which are most sensitive to contact stimuli, that is, in the hand and front of the forearm, the lips, the foot, and the mammary papilla : the *Pacinian corpuscles* found in the subcutaneous tissue of the hand, foot, and genital organs, and in the mesentery and some organs, such as the pancreas : the *corpuscles of Golgi and Mazzoni* and the *corpuscles of Ruffini*, found in the subcutaneous tissue of the fingers.

The Sensory Spots in the Skin.—If a cooled, metal point is drawn gently along the skin of the forearm or back of the hand, a sensation of cold is produced at certain definite spots, which may be marked out with coloured ink. If the point is warmed and the experiment repeated, it is found that other spots, quite distinct from those for cold, respond, and give the sensation of heat. Similarly, by using the prick of a needle as the stimulus, another series of spots may be marked out which give rise to pain. Lastly, by testing the sense of touch with a bristle, a fourth set of spots may be located. The most numerous spots in the skin are those for pain ; next in order are the touch-spots, those for cold being less numerous, and the heat-spots fewest of all.

The specific character of the different nerve-endings is confirmed by the effect of other stimuli. The application of menthol to the skin, for example, stimulates especially the nerve-endings for cold, and gives rise to a sensation of coolness. If the arm be held in a jar of carbonic acid gas, there is a sensation of warmth, the nerve-endings for heat being especially affected. Electrical stimulation of the various spots excites a specific sensation, namely, warmth in a heat-spot, pain in a pain-spot, and so on.

Additional evidence as to the independence of the sensations is derived from the effect of cocaine on the surface of the eyeball. Under normal conditions suitable stimulation of the conjunctiva excites the sensations of heat, cold, or pain, whereas stimulation of the cornea gives rise to the sensation of pain only. The application of cocaine to the eye paralyses the nerve-endings for pain, but does not effect those for heat or cold.

The Conduction of Cutaneous Impulses.—The nerve-fibres which convey the cutaneous impulses are bound together in common trunks. Prolonged pressure on these trunks sets up a block to the conduction of impulses, and occasionally cases occur in which, by the pressure of a bony outgrowth or otherwise, a partial block is produced, whereby the senses of pressure and

temperature are lost, while that of pain is retained, or *vice versa*. A similar partial block occurs at times in the disease known as syringomyelia, in which there is pressure on the conducting paths in the spinal cord owing to distension of the central canal.

The cutaneous senses are therefore independent and are subserved by different nerve-fibres, but the further question as to whether each sense has a specific nerve-ending cannot be so decisively answered. Special functions can, however, be ascribed to some of the nerve-endings in the skin with a reasonable degree of probability.

The fact that any stimulus applied to the cornea gives rise to pain indicates that interepithelial, fibrillar nerve-endings are associated with the pain-sense. In this connection it may also be noted that stimulation of a sensory nerve in its course gives rise to the sensation of pain. The skin areas most sensitive to touch are those, like the palmar surface of the fingers, where the touch-corpuscles of Meissner are most abundant. Where hair is present, the touch-spots immediately surround the point of emergence of the hair. It may therefore be concluded that the touch-corpuscles in hairless regions and the fibrillar nerve-endings around the hair-follicles are the peripheral terminations of the touch-fibres. Finally, the position of the Pacinian corpuscles and of the corpuscles of Golgi and Mazzoni, and of Ruffini, makes it clear that these structures can only be affected by deep pressure.

THE DISTRIBUTION OF THE CUTANEOUS SENSORY NERVE-ENDINGS

Reference has already been made to the fact that the cornea is richly supplied with nerves for pain, and that the skin of the palmar surface of the fingers is markedly endowed with the sense of touch. The distribution of the various sensory nerves is therefore unequal, and investigations have been made, especially in connection with the pressure-sense, to determine (1) the degree of pressure which can be detected at different parts of the skin surface, and (2) the relative acuteness, in different areas, of tactile discrimination, that is, of the power of appreciating two separate pressure stimuli applied simultaneously.

(1) Von Frey's method of estimating the degree of pressure on the skin which can be appreciated is to use hairs of different thickness, the pressure required to cause each to bend being known. In this way he found that the skin of the nose and lips and the mucous membrane of the tongue are most sensitive

to pressure, while the skin of the region of the loins has a very low degree of sensitivity. The minimum stimulus which could be detected in different areas is shown in the following table :—

Area.	Grams per sq. mm.
Tongue and nose	2
Lips	2·5
Finger-tip and forehead	3
Palm, arm, thigh	7
Forearm	8
Back of hand	12
Abdomen, outside of thigh	26
Back of forearm	33
Loins	48

(2) Tactile discrimination is measured by means of the *æsthesiometer*, an instrument somewhat resembling a pair of compasses, one limb of which can be moved along a scale on which the distance between the two points can be read off. When the two points, armed with small pieces of cork, are applied to the skin a sufficient distance apart, the resulting sensation is of two separate stimuli. When the two points are approximated, the degree of approximation varying for different parts of the skin surface, the double stimulus is productive of a single sensation. The minimal distance apart at which the points give rise to separate sensations is shown in the following table :—

Region.	Distance in mm.
Tip of tongue	1·1
Volar surface of finger-tip	2·3
Palm of hand	11·3
Back of hand	31·6
Middle of back, upper arm, thigh	67·1

These figures have no reference to the distances which separate the actual pressure-spots, but include on an average about ten such spots in each case between the limbs of the æsthesiometer.

LOCAL SIGN

Just as a localised stimulus of a definite kind applied to the skin invariably evokes the same reflex, so also, in a conscious individual, a stimulus applied to a particular area of the skin is referred to the stimulated spot. There must therefore be a specific quality in the impulse conveyed to the association-centres according to the area of the skin in which it originates,

and this quality is called "local sign." It has been supposed by some authorities that local sign is due to a recognition of the muscular reflexes which are, or may be, evoked as a result of the stimulus, but it is more probable that it is developed as the result of experience. If the index and middle fingers be crossed, and a pea be placed between them in this position (Aristotle's experiment), the sensation produced will be of two peas, because the individual has no previous experience of a single stimulus applied in this way.

PROTOPATHIC AND EPICRITIC SENSIBILITY

After section of a cutaneous nerve, examination of the area of skin supplied by the nerve reveals (1) a central zone in which all cutaneous sensations are absent, and (2) a peripheral zone in which sensation is either blunted or altered in character, a light touch, for example, exciting a different sensation from that aroused by touching normal skin. Sensations caused by deep pressure are unaffected, showing that these depend largely upon stimulation of afferent fibres in the muscles. During regeneration of the divided nerve, the first sensations to return are those of pain, of heat for temperatures above 38° C., and of cold for temperatures below 24° C.; and these sensations present two unusual features. In the first place, a stronger stimulus is required to elicit the sensation (*e.g.* that of pain) than in the case of normal skin, but the sensation, when once aroused, is intense, persistent, and peculiarly unpleasant in character. In the second place, the power of localising the position of the stimulus is very imperfect.

Some weeks or months later, the sense of touch, the senses of heat and cold between 24° C. and 38° C., and the power of localisation of touch and of pain return, and sensation becomes normal in all respects.

Head considers that these phenomena are due to the existence of two kinds of sensibility, namely, (1) protopathic, and (2) epicritic. Protopathic sensation, which is the more primitive, returns first, and includes the sense of pain and that of temperature above 38° C. or below 24° C. Epicritic sensation returns much later, and includes the sense of touch, with tactile localisation, and the senses of heat and cold between 38° C. and 24° C.; it may be looked upon as the latest and highest development of the tactile sensory mechanism. This interpretation of the events occurring during regeneration of a sensory nerve is not accepted by all authorities.

SECTION II

THE SENSES OF TASTE AND SMELL

The Sense of Taste is localised in the mucous membrane of the mouth and fauces, especially in that covering the tongue. The end-organs concerned are widely distributed in the mucous membrane; they lie in the epithelial layer, and are known as taste-bulbs. A taste-bulb is an oval body bounded externally by spindle-shaped cells, and containing in its interior other cells which are fusiform; each of the latter terminates at its peripheral extremity by a hair-like process, which projects through an aperture called the gustatory pore. The terminations of the fibres of the nerves of taste penetrate the other pole of the taste-bulb, and end by arborisation round the fusiform cells, which are the end-organs for the sense of taste. Many taste-bulbs occur in connection with the vallate papillæ found at the base of the tongue, on both sides of the fossa which surrounds each papilla. Serous glands lie in the connective tissue subjacent to the vallate papillæ, and their ducts open into the lower part of each fossa.

The substances which act as stimuli for the sense of taste must be in true solution; substances in colloidal solution are tasteless. Ordinary foodstuffs possess both taste and flavour, the appreciation of the latter depending on the sense of smell, so that, if the nose be firmly held to prevent air-currents reaching the olfactory membrane while food is in the mouth, flavours are not appreciated. There are only four true sensations of taste—*sweet*, *bitter*, *salt*, and *sour*. Any other sensation excited in the mouth, for example, astringency, is due to stimulation of the nerves of common sensibility.

Different nerve-fibres are concerned in the different sensations of taste. This is shown (1) by the fact that some areas of the tongue are more sensitive than others to the different stimuli, and (2) by the effect of drugs. Thus the tip of the tongue is most sensitive to substances giving rise to the sensation of sweetness, the base to those which arouse a bitter sensation, the sides and upper surface to sourness, while a salt taste may be excited over the surface generally. There are, moreover, substances which give different sensations of taste according to the part of the tongue on which they are placed. Bromsaccharin, for example, excites a sweet sensation if placed on the tip of the tongue, but only a bitter sensation if placed on the posterior part. Further, the individual papillæ have been tested, with the result that some are found to be more sensitive to substances which give rise to a sweet sensation, others to those which excite the other taste

qualities, while most are sensitive to more than one quality. Further evidence for the existence of specific nerves for the various sensations of taste is derived from the effect of drugs. Cocaine applied to the papillæ has no effect on the production of salt sensations, but it abolishes the other three qualities in a definite order, bitter being the first and sour the last to disappear. Gymnemic acid, from the leaves of *Gymnema sylvestre*, abolishes only the production of sweet and bitter sensations, the former going first.

The nerves of taste are the chorda tympani to the anterior two-thirds, and the glossopharyngeal to the posterior third of the tongue. The taste-fibres have their central termination in each case in the column of grey matter which forms the sensory nucleus of the nervus intermedius and the glossopharyngeal nerve.

The Sense of Smell.—The end-organs for the sense of smell are limited in their distribution to the upper part of the nasal cavities. The membrane lining this region is yellow in colour, and consists of a characteristic epithelium lying on a connective tissue layer, The epithelial layer is formed of a superficial layer of columnar. supporting cells, and of several layers of nerve-cells ; the latter are elongated in shape, and each possesses a nucleus. The prolongation of the cell peripheral to the nucleus lies between the columnar cells, and terminates at the surface in six to eight hair-like processes ; the central prolongation is continued as a non-medullated nerve-fibre to the olfactory lobe, where it arborises in the manner already described (p. 103). The connective tissue layer contains small alveolar glands, known as Bowman's glands, the secretion of which moistens the surface of the membrane.

The adequate stimulus for the sense of smell must be in the gaseous form, or in the condition of excessively minute particles. Further, the gases or particles must be soluble both in water and in lipoid substances. They are conveyed to the lower, or respiratory, portion of the nasal cavities by the air-currents due to the respiratory movements. From the respiratory passage they reach the olfactory region by diffusion.

No satisfactory classification of odours has been arrived at, and it is usual to describe them as pleasant or unpleasant. Other sensations excited in the nasal mucous membrane, such as the irritation produced by ammonia, are due to stimulation of the endings of the fifth nerve.

The chief characteristics of the sense of smell are (1) its extreme delicacy, and (2) the ease with which it may be fatigued. (1) The delicacy of the sense of smell is indicated by the dilution of a

substance which can still be perceived. Musk can be detected in a dilution in air of one in eight millions; mercaptan in a dilution of one in twenty-five billions. (2) The fatiguability of the olfactory sense is shown by the insensibility of a person sitting in a closed room to the fact that the air has become vitiated, and also by absence of sensation from a particular perfume after it has been inhaled for a short time.

The estimation of the threshold stimulus for the sense of smell is made by means of the olfactometer of Zwaardemaker. This instrument consists of a porous cylinder which is impregnated with the odorous substance. A tube is inserted into the cylinder for varying distances, so that a greater or less part of the cylinder is exposed to the air passing through the tube (fig. 53). The end of the tube outside the cylinder is placed in a nostril, and the

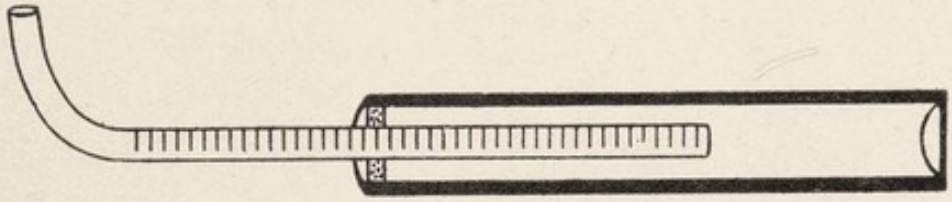


FIG. 53.—Diagram of Olfactometer.

smallest amount of exposed cylinder surface which will give a sensation indicates the threshold stimulus for the substance tested.

The olfactory sense is developed to a varying extent in different animals. Generally speaking, it is present to a greater degree in many of the lower animals than in man; in the dog, for example, it is highly developed.

SECTION III

THE SENSE OF SIGHT

The end-organs of the sense of sight are situated in the eyeball, which is protected from injury by its situation in the orbital cavity, and also by the eyelids. The surface of the eyeball is kept moist by the tears secreted by the lachrymal gland. Loss of moisture occurs through evaporation from the surface of the eyeball, and superfluous tears are drained away through the *puncta lachrymalia* at the inner end of the eyelids into the lachrymal sac, and thence by the nasal duct into the nasal cavity. The lachrymal secretion is slightly alkaline, and contains sodium chloride.

THE EYEBALL

The eyeball consists of three coats surrounding the transparent media which constitute the dioptric apparatus. It is covered in front by the conjunctiva, a connective tissue membrane with a superficial layer of stratified squamous epithelium. The conjunctiva is reflected over the posterior surfaces of the eyelids, and is represented on the cornea only by the layer of stratified epithelium.

The **outer coat** of the eyeball consists of the sclera and cornea. The *sclera* forms five-sixths of the coat, and is protective in function. It is opaque, and is made up of dense fibrous tissue with some elastic fibres and flattened cells, a few of which are pigmented. The *cornea* forms one-sixth of the outer coat, and has a somewhat greater convexity than the sclera. It is transparent, and is made up of parallel lamellæ of white fibrous tissue, with spaces between. In the spaces lie flattened, branched cells, the corneal corpuscles. The cornea is covered in front by stratified squamous epithelium, which rests on a homogeneous-looking membrane composed of closely woven fibrils, and known as the anterior elastic lamina. The posterior surface of the cornea is covered by a single layer of flattened cells, resting on an elastic, homogeneous membrane, called the posterior elastic lamina. In the inner part of the sclera, close to its junction with the cornea, is a vein, the canal of Schlemm (*sinus venosus sclerae*), which encircles this part of the eyeball. Behind the sinus is a projecting ridge of the sclera, the scleral spur, which forms the point of origin of the radial fibres of the ciliary muscle. At the margin of the cornea the posterior elastic lamina breaks up into trabeculæ, some of which are attached to the anterior surface of the scleral spur, while the others form the *ligamentum pectinatum iridis*, which is continuous with the substance of the iris. The angle between the cornea and the iris is known as the filtration-angle, because here the aqueous humor drains between the fibres of the ligamentum pectinatum iridis into the canal of Schlemm.

The **middle coat** of the eyeball consists of the choroid, ciliary processes, and iris, together forming the vascular tunic of the eyeball. The *choroid* is separated from the sclera by a lymph-space, which, however, is traversed by strands of non-vascular fibrous tissue, constituting the *lamina suprachoroidea*, and forming the outer layer of the choroid itself. Internal to the lamina suprachoroidea is a layer containing the larger blood-vessels, and internal to that is another layer, the *chorio-capillaris*, which contains a network of capillaries ; the capillary layer is bounded

internally by a structureless membrane, the *lamina basalis*. Scattered throughout the choroidal tissue are numerous pigment-cells.

The choroid lines the sclera to within a short distance of the sclero-corneal junction, and is continued forward from that point as the *ciliary processes*, about seventy in number, which, when viewed from behind, appear as a circle of radially arranged, vascular projections. The posterior surface of the ciliary processes is covered by a double layer of cubical pigment-cells, forming the forward prolongation of the retina, and called the *pars ciliaris retinæ*. The substance of the ciliary processes consists of connective tissue with pigment-cells and blood-vessels, together with the *ciliary muscle*. The latter is composed of smooth muscle-fibres, and consists of a radial and a circular portion. The radial fibres arise from the scleral spur and pass backwards to be inserted into the ciliary processes and choroid ; the circular fibres form a bundle which lies internally to the radial portion.

The *iris* is continued forward from the ciliary processes and is incomplete in front, leaving a circular aperture, the *pupil*. The iris is composed of connective tissue, with a variable number of pigment-cells and numerous blood-vessels. In dark eyes the pigment-cells are numerous ; in blue eyes they are fewer in number. The fibres of the ligamentum pectinatum iridis connect the iris with the posterior elastic lamina of the cornea. The anterior surface of the iris is covered by a single layer of flattened cells, continuous over the ligamentum pectinatum with that of the posterior surface of the cornea. The posterior surface is covered by a double layer of cubical pigment-cells (the uveal layer) continuous with the pars ciliaris retinæ. Circularly arranged, smooth muscle-fibres lie close to the margin of the pupil, forming the *sphincter pupillæ*, and radially arranged, smooth muscle-fibres, the *dilator pupillæ*, lie close to the posterior surface of the iris.

The **internal coat** of the eye consists of the *retina*, a delicate, semi-transparent membrane lining the posterior three-fourths of the eyeball, and ending abruptly just behind the ciliary processes in a jagged margin, the *ora serrata*. The retina consists from without inwards of the following layers (fig. 54) :—

1. The layer of pigment-cells.
2. The layer of rods and cones.
3. The outer nuclear layer.
4. The outer molecular layer (outer plexiform layer).
5. The inner nuclear layer.
6. The inner molecular layer (inner plexiform layer).
7. The layer of ganglionic nerve-cells.
8. The layer of nerve-fibres (stratum opticum).

The structures forming these layers are supported by the fibres of Müller, which extend from the level of the bases of the rods and cones to the inner surface of the retina. The ends of Müller's fibres are expanded and fused together to form the outer and inner limiting membranes, the former lying between the layer of rods and cones and the outer nuclear layer, and the latter bounding the retina internally. Each fibre has a nucleus at the level of the inner nuclear layer.

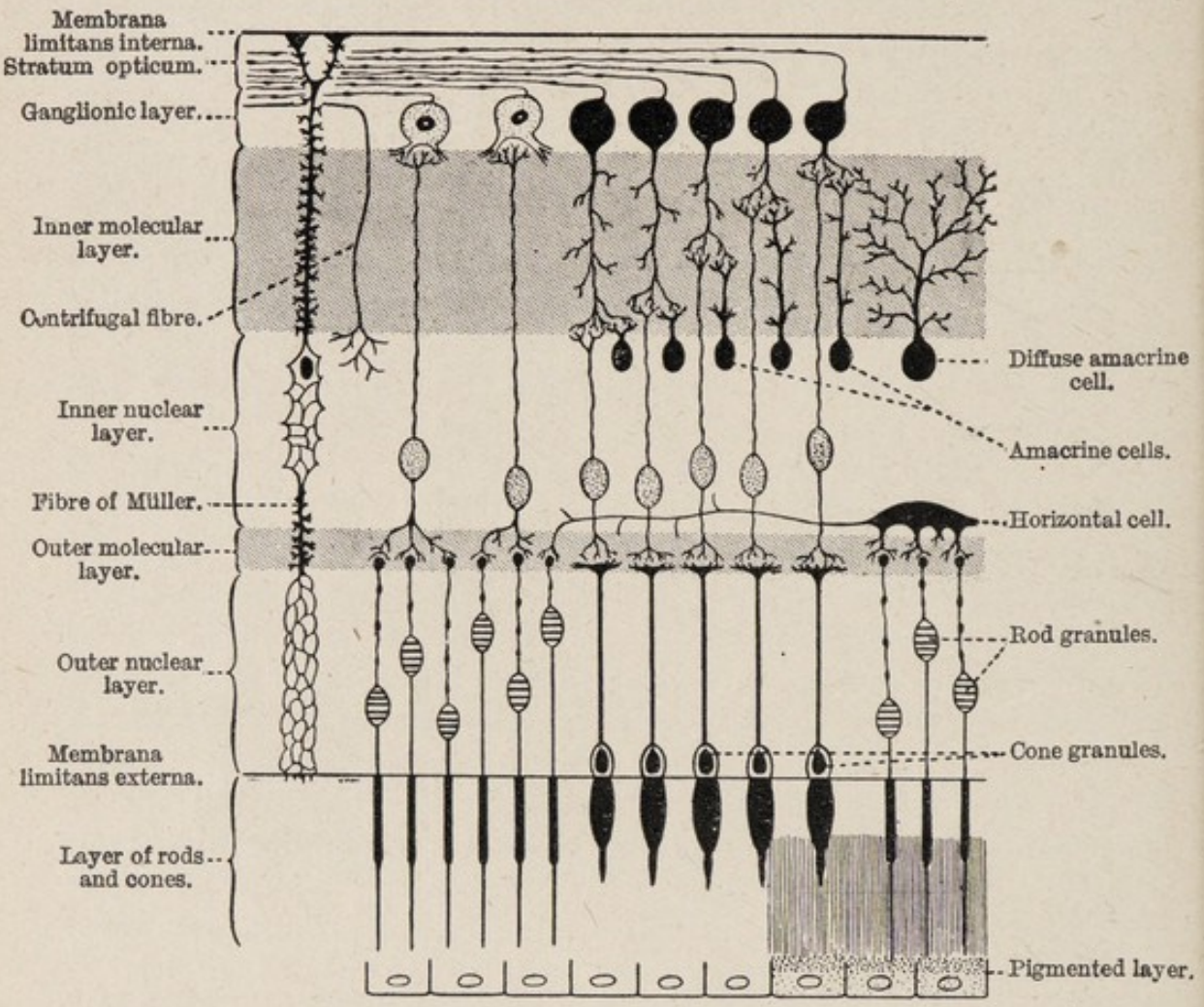


FIG. 54.—Plan of retinal neurons. (After Cajal.) From Gray's *Anatomy*.

(1) The cells of the pigment-layer are hexagonal on surface view, and, when seen from the side, they exhibit an outer non-pigmented portion containing a nucleus, and an inner pigmented part with delicate processes running between the rods and cones.

(2) and (3) The layer of rods and cones and the outer nuclear layer together form one layer of neurons. Each *rod* consists of (*a*) an outer cylindrical segment which is transversely striated and which, in a dark-adapted retina, contains visual purple or rhodopsin, and (*b*) an inner fusiform segment, vertically striated in its outer fourth and granular in the remaining three-fourths. Each rod is prolonged into the outer nuclear layer as

a varicose fibril, in the course of which is a nucleus. The nucleus in some animals is transversely striated. The fibril ends in a knob in the outer molecular layer, the knobs of several adjacent rod-neurons coming into relationship with the dendritic arborisation of a single rod-bipolar cell of the inner nuclear layer. The *cones* are shorter and thicker than the rods, and each consists of an outer and an inner segment. The outer segment is conical and is transversely striated. The inner segment is vertically striated in its outer two-thirds and granular in its inner third. The continuation of the cone in the outer nuclear layer is a comparatively thick fibre which contains a nucleus immediately under the outer limiting membrane. The cone-fibre terminates in the outer molecular layer by a branched extremity, which is in relationship with the dendritic arborisation of a single cone-bipolar cell of the inner nuclear layer.

(4) and (5) Most of the nuclei of the inner nuclear layer belong to bipolar nerve-cells, one fine process from the nucleus passing into the outer molecular layer, the other towards the inner surface of the retina. The outer process ends in a dendritic arborisation in relation either with the knobs of several rod-neurons (*rod-bipolars*), or with the terminal branching of a cone-neuron (*cone-bipolars*). The inner process of a rod-bipolar arborises round the cyton of a cell in the ganglionic layer; that of a cone-bipolar arborises in the inner molecular layer in relation with the dendrons of a ganglionic cell. In the outer part of the inner nuclear layer are *horizontal cells*, the dendrons and axons of which arborise in the outer molecular layer, so that these cells have an associational function. In the inner part of the layer are cells which were at one time believed to have no axons, and were therefore called *amacrine cells*. The dendrons of these cells arborise in the inner molecular layer in relation with the dendrons of the ganglionic cells. Their axons run into the layer of nerve-fibres.

(6), (7), and (8) The cells of the ganglionic layer are arranged in a single row in the greater part of the retina. Each has branched dendrons which extend into the inner molecular layer, where they terminate at different levels in relation with the terminal arborisations of the axons of the cone-bipolars. The axons of the ganglionic cells are continued as non-medullated nerve-fibres in the *stratum opticum*. Some of the fibres in the stratum opticum have a centrifugal course and run into the retina, to terminate by arborisation in the inner nuclear layer.

Three parts of the retina require a special description—the macula lutea, the place of exit of the optic nerve, and the ora serrata.

The *macula lutea* is the part of the retina concerned with distinct vision. When an object is "looked at," its image is formed on the macula, or, more particularly, on the *fovea centralis*, a small depression in the centre of the macula. At the fovea there are no rods, and the cones are longer than in the remainder of the retina. The cones and their nuclei are the only retinal structures present in the fovea, and the cone-fibres are inclined away from the fovea towards the inner nuclear layer. In the peripheral region of the macula the ganglionic layer is several cells deep, and cones are more numerous than rods. The proportion of cones diminishes from the macula to the periphery of the retina, and near the ora serrata very few cones are present. The macula is situated slightly to the lateral side of the posterior pole of the eyeball.

The fibres of the stratum opticum converge to a point about 3 mm. to the nasal side of the macula lutea to form the optic nerve, which passes back through a gap in the choroid coat, and through a perforated part of the sclera known as the *lamina cribrosa*. The place of exit of the nerve, as seen from the interior of the eyeball, is a sharply defined pale area, nearly circular in outline, and is called the *optic disc*. At the disc all the retinal layers are absent except the stratum opticum, the fibres of which acquire a myelin sheath as they emerge from the eyeball.

The layers of the retina cease abruptly at the *ora serrata*, and are represented in the ciliary region by two layers of cells, the outer, pigmented layer being a continuation forwards of the pigment layer of the retina, and the inner layer consisting of columnar cells. On the ciliary processes and iris both layers of cells are pigmented.

THE CONTENTS OF THE EYEBALL

The cavity of the eyeball is divided into two unequal portions by the crystalline lens and its suspensory ligament. The larger, posterior space is occupied by the vitreous humor (body); the smaller, anterior space by the aqueous humor.

The *crystalline lens* is a biconvex, transparent structure, and lies immediately behind the pupil. It is composed of concentrically arranged fibrous laminæ, made up of prismatic fibres with serrated edges. The central portion of the lens is firmer and denser than the peripheral portion, which is more jelly-like. The posterior surface is more convex than the anterior surface, and rests in the hyaloid fossa of the vitreous body. The lens is enclosed in a structureless capsule, which is continuous at the margin of the anterior surface with the suspensory ligament

of the lens. The latter is prolonged backwards as the zonula ciliaris, to be attached to the ciliary processes.

The *vitreous humor* is transparent and resembles a thin jelly, containing a few scattered delicate fibres. It is enclosed in a delicate capsule, the hyaloid membrane, which in the neighbourhood of the ciliary processes is thickened to form the zonula ciliaris. The latter splits in front into two layers, the anterior being the suspensory ligament of the lens, and the posterior lining the concavity in the vitreous body, the hyaloid fossa, in which the lens rests. A canal runs through the vitreous humor from the optic disc to the posterior pole of the lens, and is lined by a continuation of the hyaloid membrane. This canal contains the hyaloid artery in the embryo.

The space in front of the lens is divided into an anterior and a posterior chamber by the iris, and contains the aqueous humor, which is a watery fluid, containing salts, chiefly sodium chloride, with a trace of protein.

THE NUTRITION OF THE EYEBALL

The vascular tunic of the eyeball receives the long and short posterior ciliary arteries and the anterior ciliary arteries. The outer layers of the retina receive nourishment by means of lymph derived from the blood-supply to the choroid. The inner layers of the retina have a direct blood-supply through the distribution of the central artery of the retina, which enters the eyeball with the optic nerve. The cornea is supplied with lymph from the blood-vessels surrounding its margin. The veins of the choroid converge to form four or five main trunks, the *venæ vorticosæ*. The blood from the retinal artery is returned by the corresponding retinal vein.

INTRA-OCULAR TENSION

By inserting a cannula connected with a manometer into the anterior chamber of the eyeball, it can be shown that the contents of the globe exert a pressure on the walls equal to about 25 mm. of mercury. If the intra-ocular pressure be recorded on a revolving drum simultaneously with that of the carotid artery, it will be seen that the two tracings run a parallel course. Obstruction of the descending aorta, for example, causes an immediate rise in both curves, and these remain at the new level till the obstruction is removed, when both fall simultaneously.

The chief source of fluid in the eyeball is the vessels of the ciliary processes, and, as the pressure of the intra-ocular fluid

varies with the arterial blood-pressure, it may be assumed that it is derived from the blood-vessels by a process of filtration. Normally, the addition of new fluid is balanced by the draining away of an equal amount, mainly through the filtration-angle (p. 128) into the canal of Schlemm, but also to a very small extent by the posterior lymphatics of the eyeball. The blood-pressure in the capillaries is higher than that in the veins, and thus it is possible for filtration from capillaries and drainage into a vein to occur simultaneously. In certain diseased conditions the drainage is interfered with, and fluid accumulates in the eyeball, causing a rise of intra-ocular pressure. This condition is known as *glaucoma*, and, if it is not promptly relieved, it results in atrophy of the retina from pressure, and therefore leads to blindness.

The mechanism of transudation of fluid from the ciliary processes, and the escape of an equal quantity by the canal of Schlemm and posterior lymphatics of the eyeball, is of importance not only for the nutrition of the non-vascular contents of the eyeball, but also because the state of tension thereby maintained gives the eyeball the degree of rigidity which is necessary if it is to serve any useful purpose as an optical instrument.

THE FUNCTION OF SIGHT

The function of sight, in the commonly accepted sense of the word, involves (1) the formation in the retina of a real image of external objects, (2) changes in the retinal end-organs, (3) the transmission of an impulse from the retina to the cortex of the occipital lobe, (4) the changes in the visuo-sensory and visuo-psychic areas of the cortex which result in a visual sensation, and (5) the associational processes of comparison of the sensation with previous sensations, by which visual judgments are formed.

THE FORMATION OF AN IMAGE IN THE RETINA

The eyeball may be compared with a photographic camera, the cornea, aqueous humor, lens, and vitreous body forming a system of lenses, the choroid coat representing the dark lining of the camera, and the retina acting as the sensitive plate. If a segment of the sclera with the choroid be excised from the back of the eye of a recently killed ox, and the eye be held in front of an electric lamp, an inverted image of the lamp will be seen upon the retina, similar to the image which may be observed on the ground-glass screen of a camera.

In the camera the image is usually formed by means of a single biconvex glass lens. The optical axis of such a lens is a line drawn through its optical centre, and entering and leaving it in a direction perpendicular to the plane of the lens. A ray of light passing along this axis (axial ray) enters and leaves the lens with its direction unchanged, but rays falling upon the lens outside the axial ray and parallel with it are refracted, both on entering and leaving the lens, towards the axial ray, so that they meet it, or come to a focus, at a point which is known as the principal focus of the lens (fig. 55). A pencil of divergent rays falling upon such a lens will, if the lens has a sufficient degree of convexity, be brought to a focus at a point behind the principal focus. If an object, such as an arrow, be placed at some distance from a biconvex lens, the pencil of rays from the tip of the arrow will be brought to a focus behind the lens, and the same will

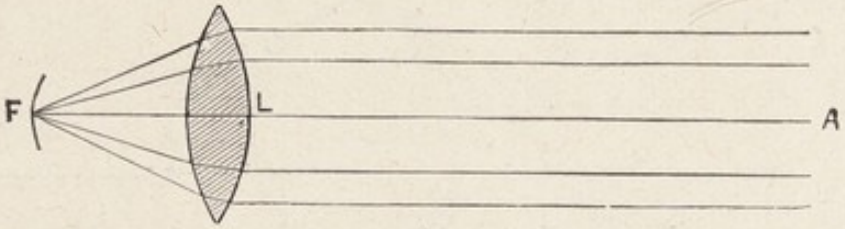


FIG. 55.—Diagram of the course of parallel rays through a biconvex lens (L), by which they are made to converge to the principal focus (F). A, axial ray. (Starling's *Principles of Physiology.*)

hold for rays from the butt and every other point on the arrow. The axial ray of each pencil will pass through the optical centre (nodal point) of the lens with its direction unchanged. The result will be the formation of a real, inverted image of the arrow in the plane in which the rays are focussed.

The formation of an image in the eye is more complicated in that the cornea, aqueous humor, lens, and vitreous body form, not a single lens, but a system of lenses differing in refractive index, so that alteration in the direction of rays of light takes place at the anterior surface of the cornea, anterior surface of the lens, and posterior surface of the lens. It has been calculated, however, that the net result of the refraction in the eye is the same as that which would occur in a uniform medium, the anterior surface of which is 2·3 mm. behind the anterior surface of the cornea, and the nodal point 0·47 mm. in front of the posterior surface of the lens. Such a theoretical arrangement is known as the reduced or schematic eye (fig. 56); and the refraction of rays of light entering the eye is assumed to take place only at the anterior surface of the hypothetical uniform medium,

the axial rays passing through the theoretical single nodal point.

By means of the schematic eye the size of an image on the retina can be ascertained. In the normal, or emmetropic, eye at rest, parallel rays are brought to a focus on the retina, and, for practical purposes, rays proceeding from a point 6 metres or more distant from the eye may be regarded as parallel. If, therefore, a diagram of the reduced eye, and of an object at 6 metres (or a greater) distance, be drawn to scale, and if lines be drawn from the periphery of the object through the nodal point to the retina, like the continuous lines in fig. 56, the size of the retinal image can be measured. As the distance of the nodal point from the retina in an emmetropic eye is known (15·5 mm.), the size of the retinal image of an object will be in the same proportion to the size of the object itself as 15·5 mm. is to the distance of the object from the nodal point. The size of the image of an object nearer the eye than 6 metres can be calculated in the same way, it being assumed that the eye is accommodated for the object.

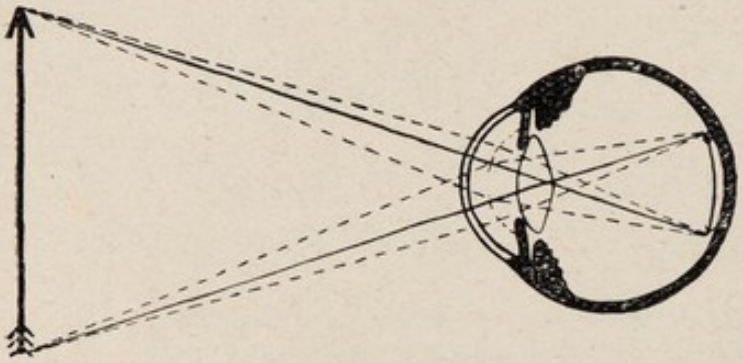


FIG. 56.—Diagram showing formation of an image in reduced eye.

The angle subtended by the object at the nodal point, and therefore that subtended by the image also, is known as the visual angle.

The limit of retinal discrimination corresponds with a visual angle of sixty seconds; that is, in order that two points of light may be distinguished as separate points they must subtend an angle at the nodal point of not less than sixty seconds. A visual angle of this size corresponds with the diameter of a single cone in the fovea centralis; it subtends a base of 4·38 μ on the retina, and the cones in the fovea vary in diameter between 2 and 5 μ.

SIGHT-TESTING.—The acuteness of vision is tested either by means of groups of dots of varying sizes or by means of special test-types. The test-card is usually placed at a distance of 6 metres from the eye to be tested, and the visual acuity is expressed as a fraction, of which the numerator is the distance in metres at which the test is made, and the denominator is the distance at which the smallest type read should be distinguished, as, for example, 6/6 (normal), 6/9, 6/12, and so on. When vision is 6/6 the eye is said to be *emmetropic*.

ACCOMMODATION

In the case of an emmetropic eye at rest parallel rays, that is, rays coming from a distance of 6 metres or more, are brought to a focus on the retina.

Rays from objects less than 6 metres from the eye are divergent, but they too can be brought to a focus on the retina by the act of *accommodation*. The essential part of this act is that the lens becomes more convex, its refractive power being thereby increased, so that divergent rays are focussed on the retina. The nearer the object is to the eye, the more divergent are the rays which pass from any point on it to the cornea, and the greater is the effort of accommodation required to secure distinct vision. There is a limit to the range of accommodation, this limit being fixed by the extent to which the convexity of the lens can be increased. In the young adult an object placed within 10 cm. of the eye cannot be seen distinctly, since the rays proceeding from it to the cornea are so divergent that they cannot be brought to a focus on the retina.

On looking obliquely into an eye which is being accommodated for a near object, the alteration in shape of the lens can be observed. The iris can be seen to move forward because of the increasing convexity of the lens. The alteration in shape is limited to the anterior surface, and this can be demonstrated by means of Sanson's images, which are most conveniently observed with the help of an instrument known as the *phakoscope*. This consists of a triangular box with truncated angles. At one angle is an aperture for the eye of the observer, at another an opening for the observed eye, at the third two trianglar openings for the admission of light. Opposite the observed eye is another opening in which a wire is placed. The person who is being observed first relaxes his accommodation by looking through the aperture opposite to him at an imaginary distant object. The source of light is seen to be reflected from his eye at three positions, namely, the anterior surface of the cornea, and the anterior and posterior surfaces of the lens (Sanson's images). The images reflected from the anterior surfaces of the cornea and lens are erect; that from the posterior surface of the lens is small and inverted. When the person who is being observed looks at the wire, the middle image alters, coming nearer to the anterior image and becoming smaller in size (fig. 57); the other images remain unchanged. This shows that the anterior surface of the lens moves forward in accommodation, and also that it becomes more convex. The absence of movement of the other images

indicates that the cornea and the posterior surface of the lens remain stationary during accommodation.

The Mechanism of Accommodation.—The lens is an elastic structure, and it is enclosed in a capsule which is connected with the ciliary processes by the suspensory ligament. The contents of the eyeball exert a pressure on the coats of the eye, amounting normally to the equivalent of 25 mm. of mercury. In consequence of this tension the suspensory ligament exerts a pull on the capsule of the lens, and the convexity of the anterior surface of the lens is in this way diminished. When the lens is removed from the eye, it assumes a more convex shape in virtue of its elasticity. The same change of shape takes place, with the lens in position, when the tension of the suspensory ligament is diminished during accommodation by the action of the ciliary muscle. Contraction of the radial fibres of this muscle pulls forward the posterior part of the ciliary processes with the attached suspensory ligament, and in this way the latter is relaxed, and the lens becomes more convex anteriorly in virtue of its elasticity (fig. 58). The circular fibres of the ciliary muscle also take part in accommodation, approximating the ciliary processes to the lens by their contraction, and thus aiding the slackening of the suspensory ligament. The effect of contraction of the ciliary muscle may be demonstrated by two experiments: (1) by the action of eserine, and (2) by the movement of a needle inserted into the ciliary processes. (1) When eserine is instilled into the human eye, it causes the ciliary muscle to contract, and the slackening of the suspensory ligament can be shown by oscillations of the lens which take place when the head is quickly moved. (2) When the point of a needle is inserted into the ciliary processes in an animal, and the ciliary muscle is made to contract, the end of the needle outside the eye moves backwards, showing that the point of the needle, which is fixed in the ciliary processes, has been pulled forward.

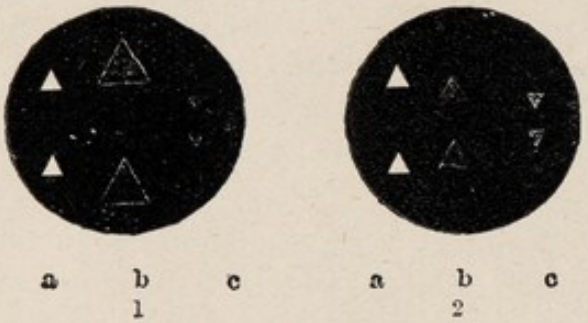


FIG. 57.—Sanson's images, (1) with eye at rest, (2) during accommodation. (Starling's *Principles of Physiology.*)

a, Images from anterior surface of cornea; *b*, from anterior surface of lens; *c*, from posterior surface of lens.

When the ciliary muscle contracts in accommodation, there occur at the same time (1) contraction of the pupil and (2) convergence of the eyes. The contraction of the pupil is effected by the sphincter pupillæ, and is of service in sharpening the

definition of the image formed on the retina, just as the definition of an image in the photographic camera is improved by the use of a small diaphragm. The convergence of the eyes is effected by the contraction of the internal recti, and results in the image of the object looked at being formed on the fovea of each eye.

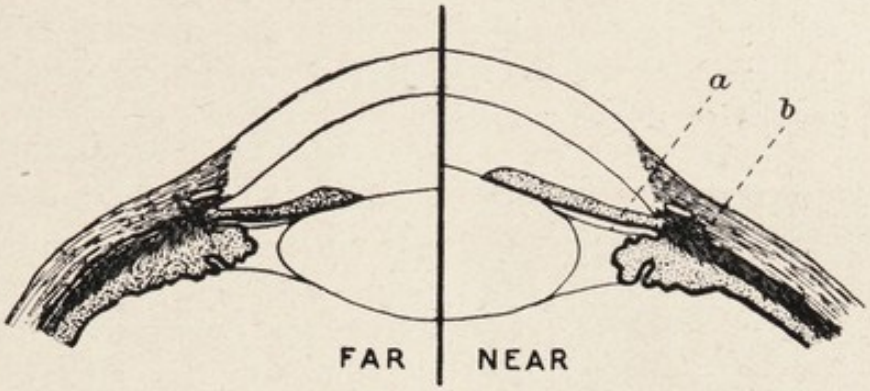


FIG. 58.—Diagram showing mechanism of accommodation. (After Helmholtz and Foster.)

a, suspensory ligament; *b*, radial fibres of ciliary muscle.

In the emmetropic eye the far point (*punctum remotum*) of distinct vision is at infinite distance, while the near point (*punctum proximum*) varies with age. The elasticity of the lens, and consequently the range of accommodation, diminishes steadily as age advances, and the near point therefore gradually recedes. This is shown in the following table :—

Age.	Range of Accommodation in Dioptres.	Near Point.
10	14	7 cm.
20	10	10 ,,
30	7	14 ,,
40	4·5	22 ,,
50	2·5	40 ,,
60	1	100 ,,
70	0·25	400 ,,

In civilised life the power of accommodation is called into play more for reading than for any other purpose, and it will be seen from the table that between the ages of forty and fifty the near point recedes to a greater distance than it is convenient to hold a book. Moreover, it is found that the prolonged effort of accommodation required for reading cannot be kept up if more than three-fourths of the total power of accommodation is being utilised. If is therefore necessary, usually about the age of forty-five, to supplement the mechanism of accommodation for reading or other near work by the use of convex lenses of such

strength as to bring the near point to a range of about 25 cm., or ten inches. The term *presbyopia* is used to indicate the failure of accommodation which occurs about the age of forty-five.

Accommodation is a voluntary act, and is peculiar in that respect in that the ciliary muscle and the sphincter pupillæ are composed of smooth muscle. Both these muscles, as well as the internal recti, are supplied by the third cerebral nerve, and section or paralysis of this nerve makes accommodation impossible. Definite groups of nerve-cells can be localised in the nucleus of the third nerve for each muscle supplied by it, stimulation of particular areas in the nucleus being followed by contraction of particular muscles. The groups of cells for the ciliary muscle, sphincter pupillæ, and internal recti lie close together in the anterior part of the nucleus; and the centre for the internal rectus on each side is connected with that of the sixth nerve of the same side, so that when the internal rectus contracts there is reciprocal relaxation of the external rectus of the same eye.

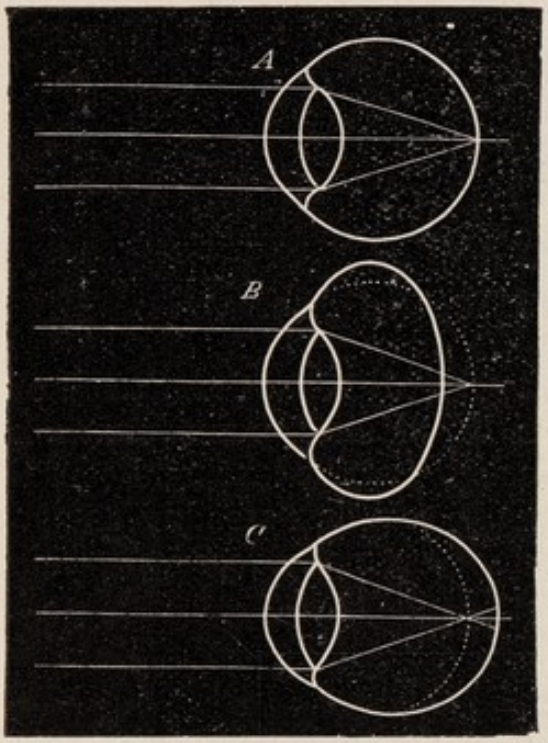


FIG. 59.—Diagram of course taken by parallel rays on entering the eye. (Starling's *Principles of Physiology.*)
A, an emmetropic; B, a hypermetropic; and C, a myopic eye.

AMETROPIA

The condition of the normal or standard eye is called *emmetropia*, and any departure from the standard is known as *ametropia*. When the antero-posterior diameter of the eyeball is too short, so that parallel rays are focussed behind the retina, the condition is called hypermetropia; when the antero-posterior diameter is unduly long, so that parallel rays are focussed in front of the retina, the term myopia is used to indicate the defect (fig. 59); when the rays of light entering the eye in one meridian are refracted to a greater or less degree than those which enter in another meridian, the condition is spoken of as astigmatism (fig. 60).

A moderate degree of *hypermetropia* does not necessarily involve defective vision, because the defect is usually compensated by increased power of the ciliary muscle, so that rays of light are focussed on the retina by an increased use of the

accommodative mechanism already described. The extra strain involved in this compensatory effort, however, often leads to unpleasant symptoms, and it is advisable in many cases of hypermetropia to correct the error by the use of convex spectacles.

Myopia cannot be overcome by any accommodative act, and distinct focus of distant objects can only be obtained in a myopic eye by the use of concave spectacles, which cause the rays of light entering the eye to diverge to such an extent that they are focussed on the retina.

Astigmatism is usually due to unequal curvature of the cornea, the commonest form showing a greater convexity in the vertical than in the horizontal meridian. In other words, the cornea is not spherical, but resembles the back of a spoon. Consequently the rays entering the eye in the meridian of greater curvature are

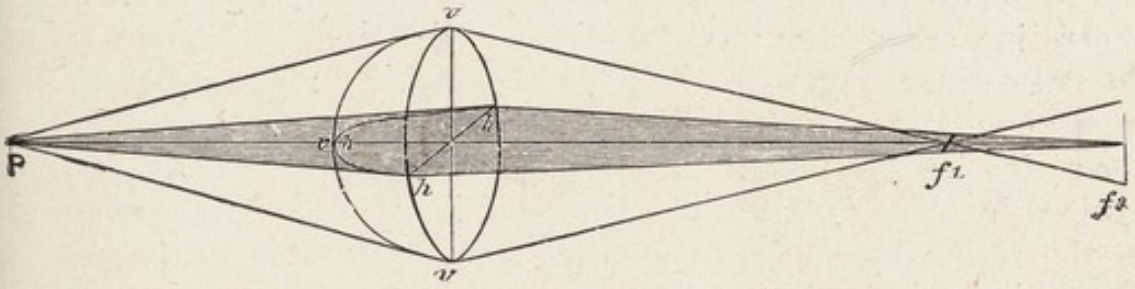


FIG. 60.—Diagram to show the course of rays in an astigmatic eye. (Waller.) From Starling's *Principles of Physiology*.

The rays (from P) in the vertical meridian, *vv*, come to a focus sooner than those in the horizontal meridian, *hh*.

brought to a focus in front of those which enter in the meridian of lesser curvature (fig. 60), and, as a result, the eye cannot focus both bars of a cross simultaneously. The defect is counteracted by the wearing of cylindrical lenses, that is, lenses which resemble a vertical section of the superficial part of a cylindrical glass rod.

The unit of measurement for degrees of refractive error and for the strength of compensating lenses is the *dioptre*. This term indicates a lens of such a strength that by it parallel rays are brought to a focus at a distance of one metre. A 2 dioptre (2D) lens has a focal distance of half a metre, a 3D lens of a third of a metre, a $\frac{1}{2}$D lens of two metres, and so on.

SPHERICAL AND CHROMATIC ABERRATION

The rays of light which pass through the peripheral part of a biconvex lens are refracted to a greater degree than those which are transmitted through the central portion, and are consequently brought to a focus in front of the latter. The crystalline lens exhibits this defect in common with other biconvex lenses, and

there may be a certain blurring of the image formed on the retina from this cause. The unequal refraction which produces this result is known as *spherical aberration*, and it is modified to some extent in the eye (1) by the centre of the lens being denser and more highly refractive than the peripheral portion, and (2) by the iris acting as a diaphragm and cutting off the peripheral rays. The physical error is thus counteracted by the physiological properties of the lens and iris.

By *chromatic aberration* is meant a fault common to all lenses, and shared by the crystalline lens, whereby each sector of the lens acts as a prism, dispersing the coloured rays which are combined in white light. The rays at the violet end of the spectrum are of short wave-length and are more refrangible, and therefore come to a focus sooner than the rays of greater wave-length towards the red end of the spectrum. Consequently the images formed on the retina are surrounded by violet and red haloes. But these do not arouse any sensation, for two reasons: (1) because the rays of medium refrangibility, which are brought to a focus on the retina, are the most luminous, and the effect of the stimulation excited by these is to depress the sensitivity of the adjacent parts of the retina by contrast, and (2) because the visual apparatus is relatively insensitive to the rays at the extreme ends of the spectrum.

THE FUNCTIONS OF THE IRIS

The pupil varies in size with the degree of light entering the eye and with other conditions, becoming smaller when the sphincter pupillæ contracts and wider with relaxation of the sphincter and contraction of the dilator pupillæ. We have seen that the pupil becomes contracted during accommodation, and that the result is improved definition of the image in the retina. The improvement is due to the cutting off of the peripheral rays, with the consequent correction of spherical aberration. Further, the iris regulates the amount of light entering the eye, and so protects the retina from over-stimulation. If the intensity of the light is gradually increased, the pupil does not contract, but, if the increase is sudden, the pupil becomes smaller and afterwards slowly returns to its former size as the retina becomes adapted to the increased stimulus. On the contrary, in a person in a dark room the pupils are widely dilated and remain in this condition until the eyes are once more exposed to light.

The alteration of the pupil with varying degrees of light is due in mammals to a reflex nervous mechanism, the optic nerve conveying the afferent impulses, and the third nerve and sym-

pathetic fibres conveying the efferent impulses to the sphincter and dilator muscles of the pupil respectively.

In man, and in other animals in which there is a partial decussation of the optic nerves, the reflex contraction of the pupil to light is bilateral, that is, light falling on one eye leads to contraction of both pupils. This is due to the fact that, by means of the decussation, each optic nerve forms connections with both superior corpora quadrigemina, and thus with the nuclei of both third nerves. If one optic nerve is atrophied, the pupil of that eye will contract when light falls on the unaffected eye.

The *nerve-supply* of the muscles of the iris forms part of the autonomic system. The pre-ganglionic fibres for the supply of the sphincter muscle lie in the third cranial (cerebral) nerve, and terminate in the ciliary ganglion. Post-ganglionic fibres arise from the cells of the ganglion, and pass to the sphincter muscle by the short ciliary nerves. Section of the third nerve is followed by dilatation of the pupil; stimulation of the third nerve, or of the short ciliary nerves, leads to contraction of the pupil.

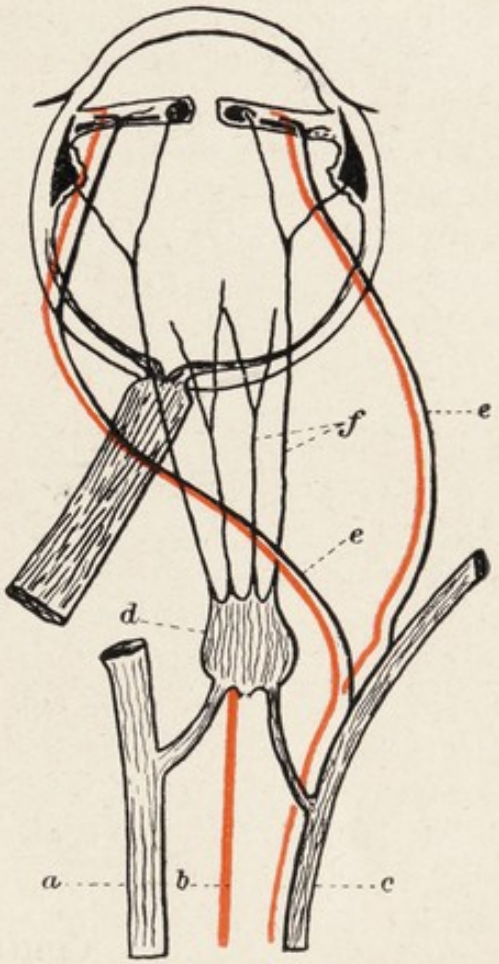


FIG. 61.—Scheme of the nerves of the eye (after Foster).

Sympathetic fibres red. *a*, third nerve; *b*, sympathetic root of ciliary ganglion; *c*, nasal branch of fifth nerve; *d*, ciliary ganglion; *e*, *e*, long ciliary nerves; *f*, short ciliary nerves.

The pre-ganglionic dilator fibres emerge from the spinal cord by the first two thoracic anterior roots, and run up in the cervical sympathetic nerve to the superior cervical ganglion, from which post-ganglionic fibres run along the internal carotid artery to the Gasserian ganglion; here they join the ophthalmic division of the fifth nerve and finally reach the dilator muscle of the iris by way of the long ciliary nerves (fig. 61). Section of the cervical sympathetic nerve is followed by contraction of the pupil, and stimulation of its distal end leads to dilatation. The fact that dilatation of the pupil is due to active contraction of the radial muscle-fibres of the iris, and not merely to relaxation of the sphincter, is proved by two experiments. (1) Localised stimulation

of the periphery of the iris leads to contraction of that part of the iris only, and (2) if a sector of the iris be separated by two radial cuts it will contract, either on local stimulation or on stimulation of the sympathetic nerve in the neck. The sympathetic root of the ciliary ganglion contains vaso-constrictor fibres for the vessels of the eye, but the cell-station for these fibres is not in this ganglion, but in the superior cervical ganglion.

Since section of the third nerve is followed by dilatation of the pupil, it is obvious that, in normal circumstances, constrictor impulses are constantly passing along the nerve to the sphincter; these impulses are called *tonic* impulses, because they keep the muscle in a state of slight, steady contraction. Similar tonic impulses must travel along the sympathetic fibres to the dilator muscle of the iris, since section of these fibres is followed by contraction of the pupil.

Contraction of the pupil occurs not only as a result of the light reflex, but also from other causes. The various factors which bring about diminution in the size of the pupil are :—

1. Light falling on the retina, giving the reflex effect already described.

2. (*a*) Accommodation, (*b*) Sleep. In both of these conditions the contraction of the pupil is an associated process. In accommodation, it occurs simultaneously with the contraction of other muscles supplied by the same nerve as the sphincter pupillæ; in sleep the eyes are rotated upwards and inwards, and the pupils contract in association with the convergence.

3. Drugs. Morphia taken internally, and eserine or pilocarpine, either taken internally or applied directly to the eye, cause the pupil to contract. Contraction also takes place in the third stage of chloroform or ether anæsthesia, that is, the stage of anæsthesia proper.

Dilatation of the pupil occurs :—

(1) On the removal of the light-stimulus from the eye.

(2) As a result of stimulation of sensory nerves.

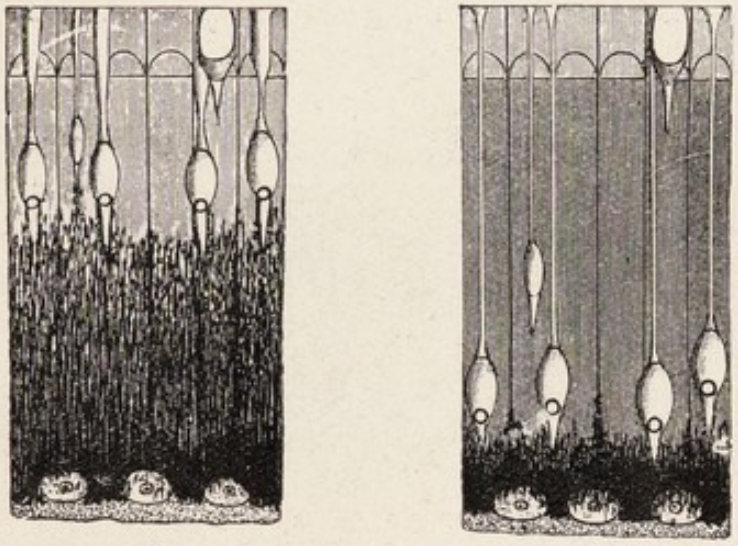
(3) In emotional conditions, such as fear.

(4) From the action of drugs, for example, from the internal administration or local application of atropine, or from the local application or intravenous injection of adrenalin. The pupil is also dilated in the early stages of chloroform or ether anæsthesia, and again when excess of the anæsthetic is administered.

THE RETINAL IMAGE

When light falls upon the eye it excites chemical, histological, and electrical changes in the retina.

The Chemical Changes.—We have seen that the outer segments of the rods contain a substance called rhodopsin or visual purple. Rhodopsin can be dissolved out of the retina by a solution of bile-salts, and it is rapidly decolorised on exposure to light. If an animal be kept in the dark for some time, and then killed and its retina examined, the latter will be of a red colour, which soon fades on exposure to light. If, on the contrary, the eyes have been exposed to bright light the retina is pale. The effect of light in bleaching rhodopsin is in proportion to its intensity, so that, if a rabbit is kept in the dark for a time and then its eye is exposed opposite a window, a picture of the window, called an optogram,



A B

FIG. 62.—Sections of the frog's retina. (From Starling's *Principles of Physiology.*)

A, after exposure to light; B, kept in the dark. (Engelmann.)

is formed on the retina ; in the optogram the window-pane areas are bleached, while the rhodopsin is not decolorised in the shaded parts corresponding with the bars. As visual purple is not present in the cones, the fovea does not show this chemical change.

The Histological Changes.—In an eye which has been exposed to light, fine processes of the pigment-cells of the retina are found to extend between the rods and cones, the processes themselves being laden with pigment-granules, whereas, if the animal has been kept in darkness before the examination of its eye, the cells of the pigment-layer are flat, the processes being retracted. Further, in some animals, for example the frog, the cones are retracted on exposure to light, and extended when the animal is kept in darkness (fig. 62). The cells of the pigment-layer have the power of restoring the visual purple, for, when a retina, which has been bleached by exposure to light, is laid upon the pigment-layer, rhodopsin again appears in the rods.

The Electrical Changes.—When an excised eye is placed in circuit with a string galvanometer, it is found that a current passes through the eye from the posterior to the anterior pole. When light is allowed to fall upon the retina, there is first a small negative variation of this current, followed by a marked positive variation.

THE FUNCTION OF THE RODS AND CONES

The layer of rods and cones is the part of the retina in which the impulses are excited which give rise to visual sensations. This is proved by three facts. (1) In the fovea, which is the area for most distinct vision, cones only are present, the other layers of the retina being absent. (2) No sensation is excited when light falls on the optic disc, where the rods and cones are absent and

FIG. 63.—(Starling's *Principles of Physiology.*)

nerve-fibres only are present. The optic disc is therefore called the blind spot, and it is to be noted that there is no sensation of darkness arising from it, but merely the absence of any sensation at all. The existence of the blind spot can be demonstrated in the following way. If the left eye be closed and the right eye gaze steadily at the cross in fig. 63, and if the book be moved to and fro, it will be found that at a distance of about eight inches from the eye the white circle will disappear. The black background will appear to be continuous, showing that the gap is unconsciously filled up. (3) The level of the layer which is stimulated by light can be determined by means of "Purkinje's images." If, in a darkened room, a strong beam of light is focussed on the sclera just external to the cornea, images of the retinal vessels will be seen by the subject of the experiment. If the position of the light is altered, that of the images will also change. The degree of displacement of the light and that of the displacement of the images, as well as the distance of the latter from the eye, being known, the distance between the retinal vessels and the layer of the retina which is stimulated by the shadows can be calculated ;

and it is found in this way that the structures which are stimulated correspond in position with the layer of rods and cones. The appearance of Purkinje's images is due to the fact that the light, falling from an unusual direction, casts the shadow of the vessels on a part of the retina unaccustomed to such a stimulus.

Inasmuch as the rods and cones differ in structure, it is to be expected that their functions also differ, and there is evidence that this is the case. The cones are most abundant in the central area of the retina, and the rods are in greater proportion in the peripheral part. Associated with this distribution is the fact that central vision is more distinct in ordinary light and peripheral vision more distinct in dim lights. Thus a star which is seen by indirect, or peripheral, vision, may be invisible when the eye is directed towards it. This fact suggests that the cones are adapted for vision in good light, and the rods for use in dim light. It is stated by some authorities that in most birds which go to roost when twilight falls, or even when the sky is obscured by heavy clouds, cones only are present, and that, on the contrary, in owls and bats, which are nocturnal in their habits, there are only rods. Again, the study of the field of vision for colour shows that, whereas the central area of the retina is responsive to all coloured rays, the periphery is colour-blind. Moreover, all parts of the retina are colour-blind in dim light.

It is justifiable, therefore, to believe that the cones are functional in good light, and are responsive to stimulation by both white and coloured light, whereas the rods come into play in dim lights and are unaffected by rays from coloured objects. It may further be assumed that the function of rhodopsin is to sensitise the rods, and so to make them more excitable to the weak stimuli for which they are adapted.

Adaptation.—If two persons enter a room in which there is a moderate degree of light, one from bright daylight, the other after being for some time in a dark room, the former will experience a sensation of comparative darkness, whereas the latter may be dazzled. The eyes in the one case are light-adapted, in the other dark-adapted, and the condition of adaptation determines the degree of sensation produced by the stimulus. In the same way, if one goes out-of-doors from a lighted room at night, at first one must grope one's way, but objects gradually become more distinct as the eyes become more adapted to the darkness. After ten minutes the retina is twenty-five times as sensitive as it was on first leaving the bright light. Further, the dark-adapted eye is colour-blind, and must become light-adapted once again before colours can be recognised.

VISUAL SENSATIONS

Although the sensation of light can be excited by various forms of stimulus applied to the eye, for example by a blow, the *adequate stimulus* consists of the waves in the ether which emanate from luminous bodies. The sensation of white light results from a compound stimulation, for white light can be dispersed into a series of rays of differing wave-length by passing it through a prism, each particular wave-length giving rise to a different quality of sensation, known as colour. The dispersed rays constitute the spectrum of white light, and only some of these act as an adequate stimulus to the retina. The visible rays range from those which give rise to the sensation of red, with a wave-length of 760 millionths of a millimetre, through orange, yellow, green, blue, indigo to violet, with a wave-length of 397 millionths of a millimetre. The infra-red and ultra-violet rays do not excite any visual sensation.

The images formed upon the retina are merely records of light, shade, and possibly colour. Light and shade are due to varying intensity of white light. The fact that certain objects reflect only particular coloured rays depends upon their property of absorbing the rays which they do not reflect. Thus, grass absorbs the rays from both ends of the spectrum and reflects those of the middle, while a scarlet poppy absorbs all the rays of short wave-length, reflecting only the longer waves of the red end of the spectrum.

The invisibility of the ultra-violet rays, or at least of a certain number of them, is due to the fact that they are absorbed by the refractive media of the eye, especially by the lens, and therefore do not reach the retina. After removal of the lens for cataract, visual sensations may be excited by rays of as short a wave-length as 313 millionths of a millimetre. The ultra-violet rays are described as actinic, because they can be detected by their effect on silver salts, for example in a photographic plate.

The infra-red rays, on the contrary, are not appreciably absorbed by the refractive media of the eye, but are invisible because they do not form an adequate stimulus for the end-organs of the retina.

The impulses excited in the retina pass to the occipital lobes of the cerebral hemispheres by the tracts already described (p. 101), those from the left half of each retina reaching the left occipital lobe, and those from the right halves passing to the right lobe. Section of one optic nerve causes complete blindness in that eye.

Section of one optic tract, *e.g.* the right, causes blindness in the corresponding half (right) of each retina. The fovea of each retina is represented bilaterally in the brain.

The impulses conveyed by the optic tracts reach the visuo-sensory area of the cortex, and by means of association-fibres are transmitted first to the visuo-psychic area, and then to the great association-areas. With the aid of the memory of previous visual, tactile, and other sensations, visual judgments are formed as regards size and distance, shape, depth, and other properties of the objects seen.

In connection with the production of visual sensations we have to consider the time required to excite a sensation, the duration of the effect of a stimulus, and the phenomena of colour-vision.

A certain interval must elapse between the application of a stimulus to the rods and cones and the production of sensation. This *latent period* has not been measured, but it has been ascertained that the reaction-time for sight is rather longer than that for hearing or for stimulation of the skin. By reaction-time is meant the time taken to make a voluntary movement in response to a given stimulus. This includes the time taken in the receptor-organ, in the afferent nerve-fibres with their intermediate cell-stations, in the sensory and psychic areas of the cortex, in the association-area and the motor area, and, finally, in the efferent path, and in the effector-organ. The reaction-time for sight is usually about one-fifth of a second, for hearing about one-seventh, and for stimulation of the skin rather less.

More definite information is available as to the *duration of the effect of a stimulus*. If a bright electric light is looked at for a few seconds and then the eyes are closed, the image of the light will persist for a short time and then fade away. This is known as a *positive after-image*, and is best seen on waking from sleep. The same persistence of sensation is the cause of the solid appearance of the spokes in a rapidly revolving wheel. The normal duration of the visual sensation can be measured by means of revolving discs on which are black and white sectors. If the gaze be directed to such a disc while it is revolving slowly, the separate sectors can be distinguished. With an increased speed of revolution the disc appears to be of a uniform shade of grey, at first producing a sensation of "flicker," and later, as the rate of rotation increases and fusion is complete, showing a uniform and steady grey appearance. If the rate of rotation at which complete fusion occurs and the size of the sectors are known, it can be calculated that the duration of each impression on the retina after the withdrawal of the stimulus is about one-

fiftieth of a second. The fusion of sensations is comparable with the fusion of single muscular contractions to produce tetanus.

COLOUR-VISION

The various colour-sensations are due to stimulation of the retina by rays of different wave-lengths, and it has long been a subject of discussion as to whether the various qualities of visual sensation are associated with stimulation of different end-organs, or with different chemical substances in the retina. Many theories have been put forward, but none of these accounts for all the facts, and only two need be mentioned here.

The *Young-Helmholtz theory* postulates the presence in the

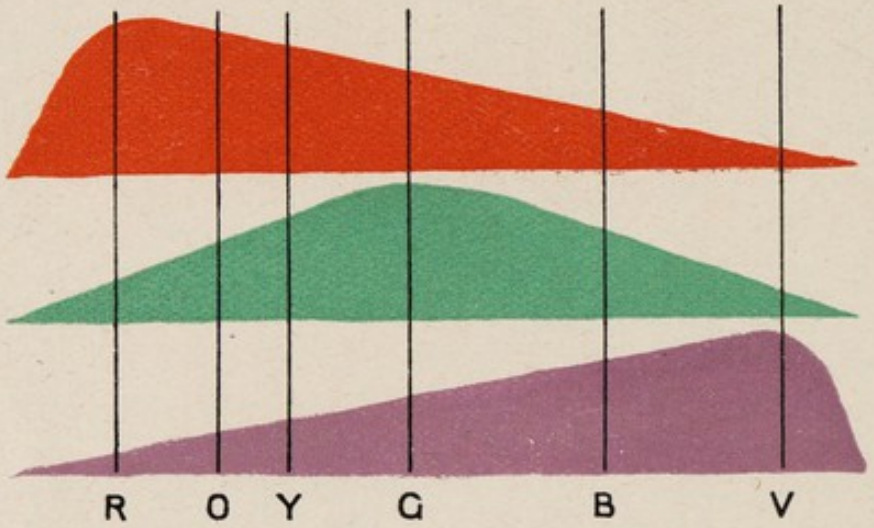


FIG. 64.—Diagram to illustrate the Young-Helmholtz theory of colour-vision.

retina of three photo-chemical substances, one of which is susceptible to stimulation by the spectral red rays, and to a diminishing extent by the other rays from the orange to the violet; a second is affected chiefly by the green rays and to a less extent by those toward either end of the spectrum: while the third is mostly affected by the violet rays, and to a diminishing extent by the remainder of the spectrum from indigo to red (fig. 64). Stimulation of all three substances to an equal extent excites the sensation of white. Stimulation confined mainly to the red substance gives the sensation of red, whereas equal stimulation of the red and green substances with slight affection of the violet substance gives rise to the sensation of yellow. The other colour-sensations are excited in the same way by varying degrees of stimulation of the three substances.

On this theory there are three primary sensations of colour, and the hypothesis finds its chief support in the facts connected with colour-blindness. Total colour-blindness is rare, but about 4 per cent. of European males are partially colour-blind, the

commonest form being an inability to distinguish between red and green. This defect is associated in some cases with an absence of sensation from the rays of the red end of the spectrum, while in others there is no inability to distinguish the spectral red, but the green of the spectrum is seen as a grey band, and gives no sensation of green. Cases of the former type are red-blind, of the latter green-blind, and on the Young-Helmholtz theory they are accounted for by the absence of the red and green elements respectively from the retina.

According to *Hering's theory*, there are four instead of three primary colour sensations—red, green, blue, and yellow. These are arranged in pairs, the two colours in each pair being comple-

FIG. 65.—Diagram to illustrate Hering's theory of colour-vision.

mentary or antagonistic. If a circular disc, coloured one half red and the other half green, is rotated rapidly, the sensations of red and green will be fused, and the resulting sensation will be grey, or absence of colour. The same fact holds for blue and yellow. Red and green on the one hand, and blue and yellow on the other, are therefore antagonistic colours. On Hering's theory there are three photo-chemical substances in the retina, each of which arouses a different sensation according as it is undergoing assimilation or dissimilation. One of these substances is broken down when stimulated by red rays and built up when green rays fall upon it (red-green substance); the second undergoes dissimilation or katabolism under the influence of yellow, and assimilation or anabolism under the influence of blue rays (yellow-blue substance); the third is broken down by white light and built up again in the absence of light (white-black substance) (fig. 65).

According to Hering's theory, the individual should be able

to distinguish neither spectral red nor spectral green in the absence of the red-green substance; but this is not the case. The sensation of spectral red may be normal while that of spectral green is missing, or, conversely, the sensation of green may be normal while that of red is absent. Hence Hering's theory does not account satisfactorily for the phenomena of colour-blindness, but it is supported by the effects of fatigue of the visual apparatus, and by the facts of simultaneous and successive contrast.

Fatigue of the mechanism connected with visual sensations can be demonstrated by looking fixedly at a bright object for a short time and then transferring the gaze to a white surface, when a dark spot or *negative after-image* will be seen, corresponding with the position on the retina of the image of the bright object. Owing to the fatigue of the part of the apparatus already stimulated, the white paper does not excite the same sensation in it as in the remainder of the retina. It may be supposed that the white-black substance undergoes active katabolic change as the result of the excessive stimulus, and that this is succeeded by anabolism when the intensity of the stimulus is reduced.

The effect of *simultaneous contrast* may be shown by placing a disc, or cross, of grey paper on a coloured sheet, and covering the whole with tissue-paper. The grey will appear green on a red background, red on a green, blue on a yellow, and yellow on a blue, the grey patch in each case assuming the colour antagonistic to that of the background. This phenomenon is explained by Hering as being due to *retinal induction*, that is, when one of the three photo-chemical substances undergoes dissimilation or assimilation in one part of the retina, this is accompanied by the converse change in the same substance in the adjacent part of the retina.

Successive contrast is seen if one gazes at a coloured disc for half a minute or a minute, and then transfers the gaze to a white sheet. The antagonistic colour will be seen on the sheet: it is green if the original disc be red, blue if it be yellow, and so on, and it constitutes one form of negative after-image. On Hering's theory the after-image is due to anabolic changes following katabolic, or *vice versa*. On Young's theory both simultaneous and successive contrast are ascribed to changes in the cortex of the cerebral hemisphere.

THE MOVEMENTS OF THE EYEBALL

In a state of rest the two eyeballs lie in the orbital cavities with their optic axes projecting horizontally forwards and

parallel with each other. Conjugate movements of the two eyes take place, either upwards or downwards, or to the right or left; or certain of these movements may be combined, or may be accompanied by rotation of the eyeballs. Further, during accommodation there is convergence of the eyeballs.

These various movements take place about the three principal axes of each eyeball, the antero-posterior, vertical, and horizontal axes, and are effected by the six extra-ocular muscles of each eye. The cornea is moved upwards and inwards by the superior rectus, upwards and outwards by the inferior oblique, and directly upwards by the combined action of these two muscles. The inferior rectus turns the cornea downwards and inwards, the superior oblique turns it downwards and outwards, and these two muscles together turn it directly downwards; the internal rectus rotates the eyeball inwards, the external rectus turns it outwards. The cornea may be moved into intermediate positions by the combined action of two or more muscles acting together. When any one muscle contracts, there is reciprocal relaxation of its antagonist; thus contraction of the internal rectus is accompanied by relaxation of the external rectus of the same eye.

The external rectus is supplied by the sixth, the superior oblique by the fourth, and the remaining muscles, together with the levator palpebræ superioris, by the third cerebral nerve.

In man, vision is binocular, and the eyeballs always move together in such a way that the image of the object looked at falls on the fovea of each eye. If the object is a distant one, the visual axes are parallel; if the object is a near one, there is convergence of the visual axes. In either case objects which are not in the direct line of vision fall on "corresponding points" of the two retinæ, and each pair of images gives rise to a single sensation. If the mechanism for combined movements fails for any reason, the images of external objects are not formed on corresponding points, and double vision, or *diplopia*, results, the image in each eye exciting a separate sensation from that in the other.

THE FIELD OF VISION

When an object is looked at, its image is formed on the fovea, and it is seen distinctly. This is known as "direct vision." At the same time, surrounding objects are focussed on the retina outside the fovea, and are seen less distinctly. This is known as "indirect vision." The extent of the outer world included in

both direct and indirect vision constitutes the *visual field*, and is measured by means of an instrument called the perimeter. A simple form of this consists of a graduated arc which can be moved into any meridian, and which is provided with a white spot at its axis. The subject closes one eye, and with the other gazes steadily at the white spot. A white or coloured object is then moved from the extreme end of the arc until it comes into the field of vision, when its position is recorded on a chart. This is repeated for other meridians, and then the recorded points are connected on the chart by lines, thus giving a map of the field of vision. The field for a white object is larger than that for a coloured object, and, of the primary colours, blue and yellow have the largest field and green the smallest, while red is intermediate (fig. 66).

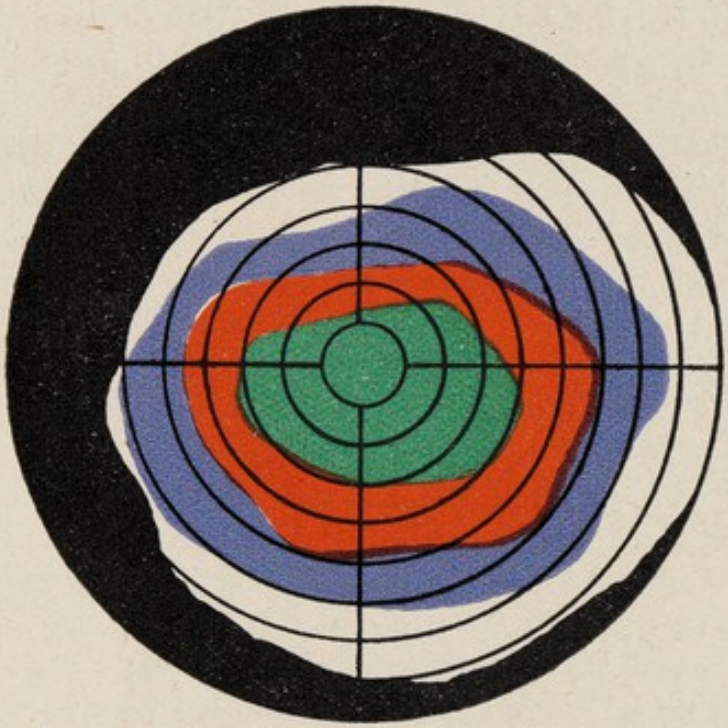


FIG. 66.—Perimetric chart for right eye, showing fields for white, blue (and yellow), red, and green. (After Howell.)

The field for white extends to 90° on the temporal side, about 80° downwards, 65° to the nasal side, and 50° upwards. The field on the nasal side is obstructed by the bridge of the nose, but the area of the retina on which the obstructed rays would fall is insensitive. When both eyes are in use, the fields of vision overlap, so that the combined field extends to 65° on either side of the central point, that is, the point which is focussed on the fovea.

VISUAL JUDGMENTS

The flat picture formed on the retina gives rise to sensations of light, colour, and shade. These sensations are conveyed to the association-areas of the brain, where the interpretation of the picture takes place, this process constituting visual judgment. If, for the sake of simplicity, the image of a single object be considered, judgments are formed as to its position in space its distance from the eye, its size, form, and solidity. These

judgments are based partly on the visual sensation, partly on previous experience derived not only from vision but also from the other senses. A new-born infant is unable to interpret its visual sensations, but it gradually learns to correlate these with tactile and other impressions, until finally the visual sensation alone conveys impressions which, at first, were dependent on other senses as well as that of sight.

An object can be localised as the result of experience that an image on a given part of the retina corresponds with a definite position in space. The image on the retina is inverted, but the object is seen in the upright position because the interpretation of the image is again the result of experience. The retina, in fact, acquires "local sign."

Experience always enters largely into judgments of size and distance, and the latter are closely related to each other. If the size of an object is known, its distance is estimated by the visual angle which it subtends ; in other words, by the size of its image on the retina. On the contrary, if the distance of an unfamiliar object is known, its size can be judged in the same way. Other factors, however, enter into judgments of distance. If the object is close at hand, the degree of convergence of the eyes and of accommodation required to see it distinctly are of assistance. The importance of convergence in this respect can be shown by holding a pencil vertically about 40 cm. from the face, and attempting to touch it from one side with another pencil, first with one eye closed, and then with both eyes open. If the object is distant, its outline is more or less indistinct, owing to the fact that the atmosphere is never perfectly transparent, and the degree of blurring varies with the distance. The difficulty of estimating the size of an object in a fog is a common experience. The estimation of the size and distance of an unfamiliar object at an unknown distance is assisted by comparison with other objects which are more familiar, and of which the relation in space to the unfamiliar object can be determined.

The judgment of solidity is dependent mainly on binocular vision. A solid object, not too far away from the eyes, gives rise to a slightly different image in each eye, and the fusion of these images in consciousness results in the idea of solidity. The same fact is made use of in connection with the stereoscope. Two pictures taken from slightly different points of view are fused by means of prisms, and in this way give the impression of depth, which cannot be obtained from a single flat picture.

Binocular vision is thus of the greatest importance in assisting the formation of judgments of the solidity of objects, and still more in estimating accurately the position of those which are

close at hand. It follows, therefore, that whereas the permanent loss of an eye involves a certain diminution of the field of vision, it also involves the much greater disadvantage of increasing the difficulty of forming the visual judgments on which depend the performance of accurate mechanical work.

OPTICAL ILLUSIONS

It follows from what has been said as to the interpretation of visual sensations that the judgments based upon these are exceedingly fallible, and that this is so is a matter of everyday knowledge. Judgments based upon experience are biassed by that experience, as is well shown by the accompanying illustration (fig. 67), in which parallel lines appear to be alternately convergent and divergent because of the short, oblique, cross lines.

FIG. 67.—Zöllner's lines. (Starling's *Principles of Physiology.*)

SECTION IV

THE SENSE OF HEARING

The ear consists of three parts, the outer, middle, and inner ear. The outer ear consists of the pinna and the external auditory (acoustic) meatus. The pinna is functionless in man, but in some of the lower animals it serves to collect the sound-waves and conduct them to the meatus, along which they are transmitted to the membrana tympani. The meatus is about 2·5 cm. in length, and is directed inwards and forwards. It is slightly curved in its course, the convexity of the curve being upwards ; in consequence of the curve it is difficult for foreign bodies to reach the membrana tympani, which stretches across the inner end of the meatus.

THE MIDDLE EAR

The middle ear, or tympanic cavity, consists of a chamber in the temporal bone containing a chain of ossicles by which the sound-waves are transmitted to the internal ear (fig. 68). The cavity is bounded laterally by the membrana tympani, its medial, superior, inferior, and posterior walls are bony, and anteriorly it

exhibits two openings, that of the Eustachian tube (auditory tube) below, and the canal for the tensor tympani muscle above.

The membrana tympani, which separates the external from the middle ear, lies obliquely, and is shaped like a shallow funnel with the concavity outwards, the central depression being called the umbo. The membrane is semi-transparent and is composed of three layers, an outer cutaneous layer continuous with the skin lining the meatus, an inner mucous layer formed of the

FIG. 68.—Scheme of ear. (After Landois.)

mucous membrane lining the tympanic cavity, and a middle fibrous layer composed of radial and circular fibres.

Two openings are present in the medial wall of the tympanic cavity, both closed by membrane in the fresh condition. One, the fenestra ovalis (fenestra vestibuli), is oval in shape; the other, the fenestra rotunda (fenestra cochleæ), is circular, and lies below and behind the fenestra ovalis.

The ossicles of the middle ear are three in number, the malleus, incus, and stapes. The *malleus*, or hammer-bone, consists of a head and two processes, the longer of which, the handle, is attached to the tympanic membrane, its tip reaching to the umbo, while the shorter process, the processus gracilis, projects anteriorly. The posterior surface of the head of the malleus articulates with the body of the incus by a saddle-shaped joint of such a nature

that, when the head of the malleus moves outwards, a cog-like process upon it is locked in a corresponding depression on the incus. If, however, the head of the malleus moves inwards, the joint surfaces separate, and in this way traction on the membrane closing the fenestra ovalis is avoided, and the internal ear is safeguarded. The *incus*, or anvil-bone, consists of a body and two processes (crura). The body articulates with the malleus, and the longer of the two processes articulates with the stapes. The *stapes*, or stirrup-bone, articulates by its head with the long process of the incus, and its base is attached to the membrane which closes the fenestra ovalis. The head of the malleus is attached by an anterior, a superior, and a lateral ligament to the wall of the tympanic cavity, and the short process of the incus is attached by a ligament to the posterior wall of the cavity. As the result of these attachments the malleus and incus can be rotated only around an axis which passes through the processus gracilis of the malleus and the short process of the incus. This movement of rotation takes place when the handle of the malleus moves inwards with the membrana tympani, the head of the malleus and body of the incus moving outwards, and the long process of the incus moving inwards and exerting pressure through the stapes on the membrane in the fenestra ovalis. The movements of the ossicles are controlled to some extent by two muscles, the *tensor tympani*, which is inserted near the root of the handle of the malleus, and the *stapedius*, which is inserted into the neck of the stapes.

The Eustachian tube connects the cavity of the tympanum with that of the pharynx. It is generally closed, but it is opened each time swallowing occurs. When it opens, the pressure of the air in the middle ear is adjusted to that of the atmosphere, and in this way the tympanic structures are protected from the injurious effects of too small or too great a pressure on the membrana tympani.

THE INTERNAL EAR

The internal ear consists of a series of cavities in the temporal bone, forming the osseous labyrinth, within which is a corresponding series of membranous structures, the membranous labyrinth. The osseous labyrinth contains a clear fluid, the perilymph; the membranous labyrinth is filled with a similar fluid, the endolymph.

The anterior portion of the labyrinth, or cochlea, contains the end-organs of hearing; the posterior part is concerned with the sense of position, and will be described later.

The Cochlea.—The cochlea consists of a tube coiled in a spiral fashion round a central bony modiolus, and making altogether two and a half turns round the latter (fig. 69). A spiral bony ridge projects from the modiolus into the tube, and is known as the osseous spiral lamina ; attached to this is a membrane, the basilar membrane, which extends to the outer wall of the tube, where it meets a fibrous projection, the spiral ligament. A

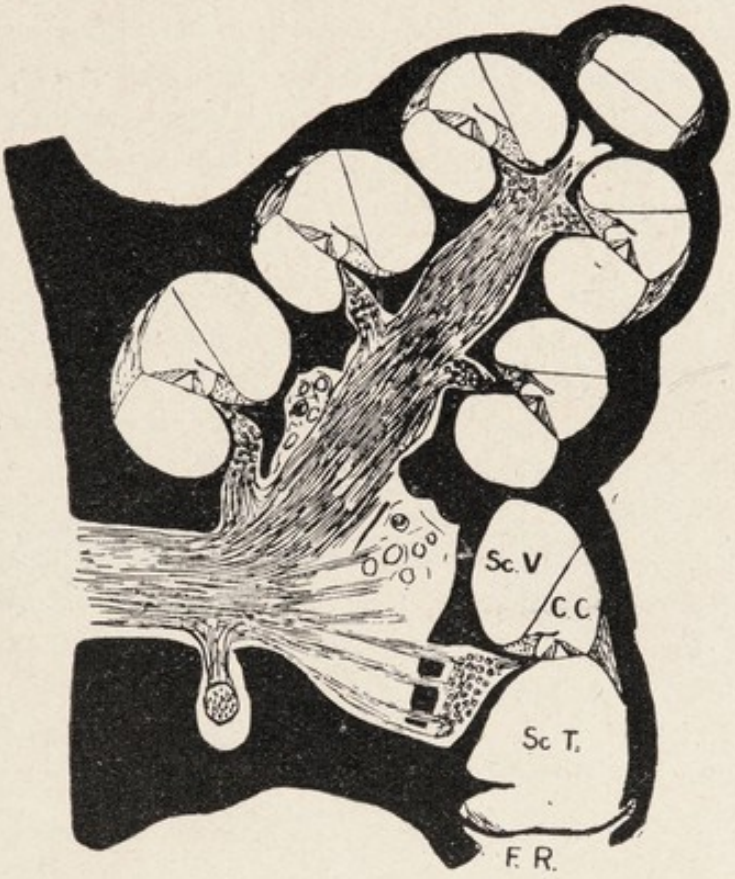


FIG. 69.—Vertical section of the cochlea of the guinea-pig.

Sc.V., scala vestibuli; C.C., canal of the cochlea or scala media; S.T., scala tympani; F.R., membrane in fenestra rotunda

relatively thick layer of connective tissue, the *limbus laminæ spiralis*, rests on the osseous spiral lamina, and ends abruptly near the basilar membrane by an overhanging border. A delicate membrane, the membrane of Reissner, is attached to the upper surface of the limbus and to the wall of the tube in such a way as to cut off a portion, triangular in section, known as the canal of the cochlea (ductus cochlearis). The bony tube is thus divided by the membrane of Reissner and the osseous spiral lamina with the basilar membrane into three divisions, the *scala vestibuli* above Reissner's membrane, the *canal of the cochlea* already described, and the *scala tympani* (fig. 69). The scala vestibuli and scala tympani form part of the bony labyrinth, and communicate at

the apex of the cochlea by the helicotrema. The scala vestibuli is closed at its lower end by the membrane in the fenestra ovalis, the scala tympani by the membrane in the fenestra rotunda. The scala vestibuli and scala tympani contain perilymph. The canal of the cochlea forms part of the membranous labyrinth and contains endolymph. It communicates with the saccule of the posterior part of the membranous labyrinth by a fine tube, the *canalis reuniens* (fig. 72).

The Organ of Corti.—The end-organ for hearing lies in the canal of the cochlea, and is called the organ of Corti. It consists of a specialised epithelium resting on the basilar membrane (fig. 70). On section the epithelium is seen to be arranged in

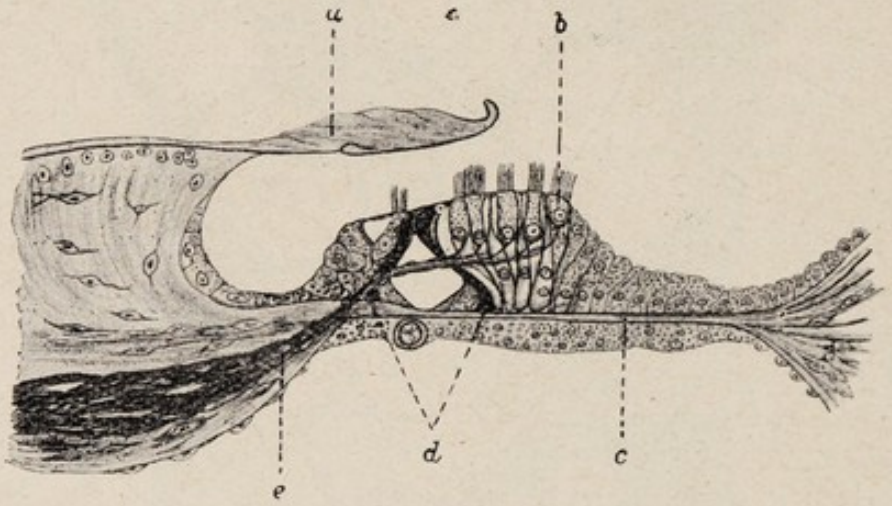


FIG. 70.—Structure of organ of Corti (diagrammatic).

a, membrana tectoria; *b*, hair-cell; *c*, basilar membrane; *d*, rods of Corti; *e*, cochlear nerve-fibres and (on the left) spiral ganglion.

relation with two rows of rod-like cells, the rods of Corti, which are inclined towards each other in such a way as to form a tunnel. The basal ends of the rods are expanded, and in the angle which each forms with the basilar membrane is a small nucleated mass of protoplasm. The free end of each outer rod is shaped like the head of a swan, the back of it fitting into the end of the inner rod, which resembles the proximal end of the ulna. It is estimated that there are about 6000 inner, and about 4000 outer, rods. The heads of the outer rods are continued outwards as phalangeal processes, which unite with corresponding processes on the outer supporting cells to form the *reticular membrane*.

On either side of the rods of Corti are hair-cells, a single row on the inner side, four or five rows on the outer side, the free ends of the outer cells occupying the apertures in the reticular membrane. Each hair-cell has a group of hair-like processes projecting from its free end. The hair-cells are held in position by

supporting cells, the cells of Deiters. Beyond the hair-cells the supporting cells become shorter, and the epithelium is continuous with the flattened cells lining the canal of the cochlea.

A thick membrane, the *membrana tectoria*, extends from the limbus laminæ spiralis so as to rest upon the organ of Corti.

The fibres of the cochlear nerve occupy the centre of the modiolus and are distributed along the spiral lamina (fig. 69). They are the central processes of the bipolar cells of the spiral ganglion, which lies in the spiral lamina. The peripheral processes of these cells emerge from the spiral lamina to be distributed as fibrils around the hair-cells of the organ of Corti.

THE MECHANISM OF HEARING

When sound-waves fall upon the tympanic membrane they cause the latter to vibrate, much in the same way as the head of a drum vibrates when hit by a drumstick. The membrane has no periodicity of its own, partly because of its peculiarities of structure, and partly because its vibrations are damped by the attached handle of the malleus. With each inward movement of the membrane the handle of the malleus and the long process of the incus also move inwards, the latter carrying the stapes with it. The malleus and incus together form a lever, the fulcrum of which is the axis of movement described above, the handle of the malleus being the power arm, and the long process of the incus forming the load arm. The length of the handle of the malleus is to that of the long process of the incus as 3 to 2, and it therefore follows that the movement of the tympanic membrane is diminished in amplitude in the proportion of 3 to 2, while at the same time it is increased in force by one half, or in the proportion of 2 to 3. Further, as the membrana tympani is twenty times the size of the membrane in the fenestra ovalis on which the vibrations are directed, it follows that the pressure of a sound-wave on the membrana tympani is increased to thirty times in its passage across the middle ear ($3/2 \times 20 = 30$).

The vibrations of the membrana tympani, transmitted by the chain of ossicles to the fenestra ovalis, set up corresponding waves of pressure in the perilymph ; these travel up the scala vestibuli and down the scala tympani. The wave in the perilymph is communicated through the membrane of Reissner and basilar membrane to the endolymph of the canal of the cochlea, and thus the stimulus is conveyed to the organ of Corti. The increase of pressure in the scala tympani is passed on to the membrane which closes the fenestra rotunda, causing it to bulge towards the middle ear.

The adequate stimulus for the organ of Corti is the wave set up in the endolymph as the result of sound-waves in the air. Sound-waves consist in an alternate condensation and rarefaction of the gases of the atmosphere, and they travel through the air at a rate of about 350 metres a second. They give rise to two kinds of sensation, one that of noise, when the sound-waves follow each other irregularly, the other that of a musical note, when the waves follow one another with a certain rhythm.

Musical sounds vary in pitch, in intensity, and in timbre or quality. (1) *Pitch* depends on the frequency of the vibrations constituting the note, and the more frequent the vibrations, the higher the pitch. The highest note which can be appreciated by the human auditory apparatus has a frequency of about 40,000 vibrations per second, but some animals can detect sounds of higher pitch than this. The lowest note used in music, that of the sixty-four foot organ pipe, has a frequency of sixteen vibrations per second, and gives an impression rather of vibration than of sound.

(2) *Intensity* or *loudness* depends on the amplitude of the vibrations giving rise to the note. This can be shown by recording the vibrations of a tuning fork on a moving drum, when it is seen that the more extensive the movement of the fork, the louder is the note produced by it.

(3) *Quality* or *timbre* is due to the form of the wave. In the case of the tuning fork the wave is simple, and the note is a pure one uncombined with any secondary vibrations. The notes produced by musical instruments owe their distinctive quality to the production of overtones, which combine with the fundamental note and produce a compound wave. A violin string, for example, not only vibrates as a whole, giving the fundamental note, but also vibrates in segments, producing the overtones which are due to the vibration of halves, thirds, fourths, and still smaller segments of the whole string. The particular quality of the tones produced by any instrument depends upon the number and degree of prominence of the particular overtones.

When two notes are sounded together, the result may be, on the one hand, consonance or harmony, or, on the other hand, dissonance or discord. Discord is due to the fact that the two notes have nearly the same vibratory period, with the result that, at certain intervals, the summit of one wave occurs at the same instant as the trough of the other, so that the two neutralise each other, causing a momentary silence. Later, the summits of two waves will correspond, and the degree of sound will be momentarily increased. The rapidly alternating increase and diminution in volume of the sound-wave constitute what is called a *beat*, and

if these beats number thirty-three or more in a second, they give rise to the jarring sensation known as discord. When two notes, sounded together, give a sensation of harmony, there are no such beats, the two waves being combined to form a compound wave of regular rhythm.

The auditory mechanism is capable not only of appreciating sounds, but also of distinguishing differences of pitch, and even, in the case of trained musicians, of analysing a combination of notes, sounded together, into its constituents. Various theories have been held as to the part played by the different structures in the cochlea, and by the cerebral cortex itself, in the discrimination of pitch, but it will only be necessary here to state the known facts and to mention two views based upon these facts.

(1) It is a well-known physical fact that a string which vibrates with the rhythm of, say, middle C will be thrown into vibration if that note is sounded near it ; this is called *resonance*. Similarly, if a vibrating tuning fork be held over the mouth of a tall glass jar and water be slowly poured into the jar, when the water is at a certain depth the sound of the tuning fork will be intensified by the resonance of the column of air in the jar.

(2) From the distribution of the cochlear nerve-fibres around the hair-cells, it may be assumed that the latter are the end-organs for hearing.

(3) The rods of Corti are not present in the cochlea of birds, and are therefore not an essential part of the auditory mechanism.

(4) The basilar membrane is composed of about 24,000 radial fibres, and it increases in width from the base to the apex of the cochlea, the shortest fibres being 0·041 mm. and the longest 0·495 mm. in length.

(5) Experimental destruction of the base of the cochlea in dogs made the animals deaf to high notes, whereas destruction of the apex resulted in deafness to low notes. Similar results have followed disease in man.

These facts suggest that different parts of the basilar membrane resonate to notes of different pitch, the longer fibres responding to low notes and the shorter fibres to high notes. The vibrations of the basilar membrane set up waves in the endolymph, by which the hair-cells are stimulated, after-vibrations being damped by the tectorial membrane. On this theory, first suggested by Helmholtz, the analysis of sound takes place in the cochlea, each note causing definite fibres of the basilar membrane to resonate, and thus acting as a stimulus to the hair-cells opposite that part of the membrane. If this hypothesis is correct, a note of any particular pitch will always excite an impulse in the same nerve-fibres.

A more recent theory is that of Wrightson, according to whom the basilar membrane consists of two parts, an inner elastic portion, the arcuate zone, underlying the arch of Corti, and an outer inelastic, and " to some extent rigid," portion, extending from the outer rods of Corti to the spiral ligament, and called the pectinate zone. The arcuate zone moves like a hinge on the fixed point of the fibrous continuation of the osseous spiral lamina, and the pectinate zone moves in a similar way on the spiral ligament. The membrana tectoria is attached at its outer margin to the supporting cells of the organ of Corti, and is pressed against the hairs of the hair-cells.

Changes of pressure in the perilymph cause an up and down movement of each zone, the arcuate zone stretching slightly, and carrying with it the arch of Corti. The apex of Corti's arch is thus tilted inwards with an upward movement, and outwards with a downward movement, of the arcuate zone ; and the upper ends of the hair-cells, fixed by the reticular membrane, move with it. Movement of the free ends of the hairs of the hair-cells being prevented by the resistance of the membrana tectoria, the hairs themselves are bent outwards with the upward movement, and inwards with the downward movement. The higher the pitch of the note giving rise to the movement, the more rapid will be the latter. The greater the amplitude of the movement, the greater will be the bending of the hairs. Every complexity of the sound-waves is registered by such movements. The final analysis takes place, not in the cochlea as in Helmholtz's theory, but in the cerebral cortex.

The auditory impulses reach the cerebral cortex of the temporal lobe by the auditory tract (p. 102), arriving first at the audito-sensory area, and being transferred to the audito-psychic area. The further conveyance of the impulses to the association-areas enables judgments to be arrived at as to the nature of the sounds, as, for example, the rumbling of thunder or the meaning of spoken language.

In some of the lower animals the judgment of the direction from which a sound proceeds is aided by movement of the external ears. In man the projection of sound is more difficult, especially if its source is in line with the mesial plane of the body. Some assistance is obtained by moving the head and noting to which ear the sound is more distinct in each position. As a rule, man relies largely on the co-operation of sight to localise the direction of a sound, and a blind-folded person has great difficulty in forming a judgment as to the source of a brief sound produced in line with the mesial plane of his body.

THE VOICE AND SPEECH

Voice is produced in the larynx; modified in character by the resonating chambers formed by the upper respiratory passages, the mouth, the accessory sinuses of the nose, and the chest; and converted into speech by contraction of the muscles of the palatal region, the tongue, and the lips, and of those which move the lower jaw.

The larynx is a chamber placed at the proximal end of the trachea. Its cavity is narrowed at one part to a slit, the *rima glottidis*, by lateral folds of the lining membrane, called the *vocal cords* (vocal folds) (fig. 71). The rima glottidis can be altered in width by muscular contractions. When it is nearly closed, and strong expiratory air-currents are produced, the vocal cords are thrown into vibration, and a musical note, the voice, is produced.

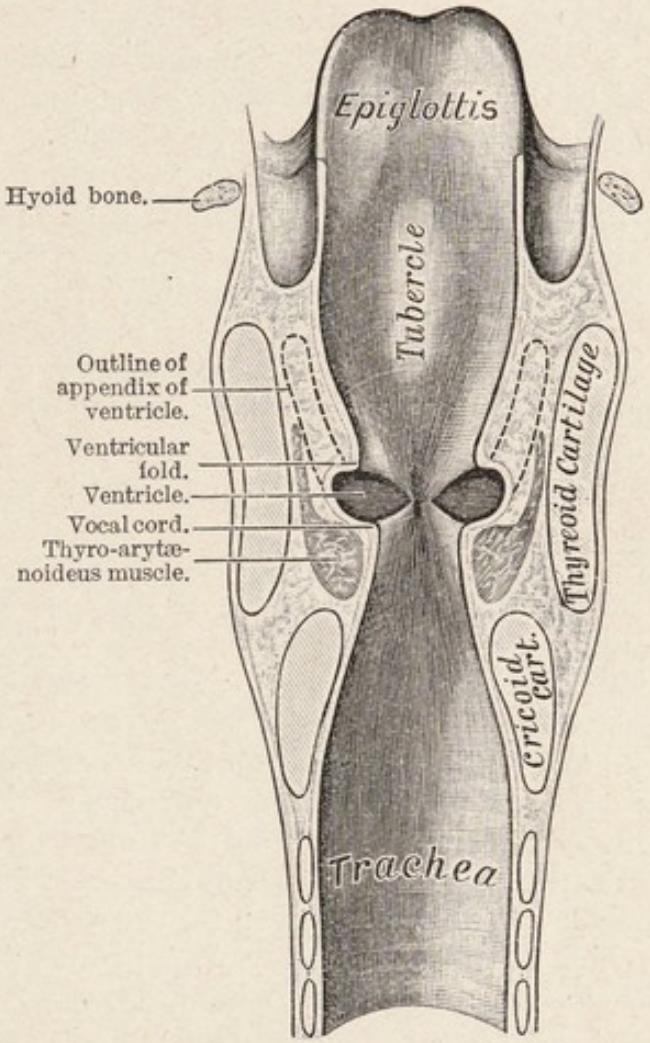


FIG. 71.—Coronal section of larynx and upper part of trachea. (Gray's *Anatomy*.)

Structurally, the larynx consists of a number of cartilages, articulating with each other by joints. It also possesses muscles, the contractions of which determine movements of the cartilages on each other, and variations in width of the rima glottidis. The cavity is lined by a mucous membrane, continuous with that of the trachea below and of the pharynx above.

The principal *cartilages* are the cricoid, thyroid, two arytenoids, and the epiglottis. The *cricoid* cartilage is placed next to the trachea, and is shaped like a signet ring, with the broad part situated posteriorly. The *thyroid* cartilage consists of two lateral wings, united in front at an acute angle. The posterior inferior angle of each wing articulates with a facet on the cricoid cartilage, so that the latter can rotate to

a limited extent on the thyroid. Each *arytenoid* cartilage is tetrahedral in shape, one surface articulating with the upper part of the signet of the cricoid, in such a way that the arytenoid can be rotated, or moved laterally or medially. A second surface of the arytenoid looks towards the median plane, and the others look outward and forward, and outward and backward respectively. The *epiglottis* is a leaf-shaped structure, and is placed vertically, the stalk of the leaf being attached to the receding angle of the thyroid cartilage, and the broad part projecting upwards.

The cricoid and thyroid consist of hyaline cartilage; the arytenoids of hyaline cartilage at their bases, and elastic cartilage at their apices; and the epiglottis of elastic cartilage.

The epithelium of the mucous membrane lining the larynx is ciliated, except over the vocal cords and on the anterior surface and upper half of the posterior surface of the epiglottis, in which situations it is of the stratified squamous type.

The *vocal cords* run from the arytenoid cartilages to the inner angle of the thyroid. Above them are two less prominent folds of the lining membrane, called the *false vocal cords* (ventricular folds). The opening of the larynx above is bounded by the ary-epiglottidean folds, running from the apices of the arytenoid cartilages to the sides of the epiglottis.

The intrinsic muscles of the larynx are (1) the *arytenoid*; this muscle connects the postero-external surfaces of the arytenoid cartilages, and by its contraction approximates these cartilages; (2) the right and left *crico-thyroid* muscles; these cause the cricoid to rotate on the thyroid cartilage, and thus increase the tension of the vocal cords; (3) the right and left *lateral crico-arytenoid* muscles; these bring about rotation of the arytenoid cartilages so that the vocal cords are approximated; (4) the right and left *posterior crico-arytenoid* muscles, which are antagonistic to the lateral crico-arytenoids, and by their contraction, widen the rima glottidis; (5) the *thyro-arytenoid* muscles, also bilateral, which lie in the respective vocal cords, and, by their contraction, relax these structures, thus being antagonistic to the crico-thyroid muscles; and (6) the *ary-epiglottidean* muscles, right and left, which, by their contraction, bring about constriction of the upper aperture of the larynx.

All these muscles, with the exception of the crico-thyroid, are supplied by the inferior laryngeal branch of the vagus nerve; the crico-thyroid is supplied by the external laryngeal branch of the vagus.

The rima glottidis consists of two parts, (1) that lying between the arytenoid cartilages, which takes no part in voice production, and is called the respiratory glottis, and (2) the anterior portion, lying between the vocal cords, which is known as the vocal glottis. The latter has a respiratory as well as a vocal function.

Voice-Production.—The changes which occur in the larynx during voice-production may be observed with the aid of the

laryngoscope. This instrument consists of a mirror which can be held in position in the pharynx so as to give a reflected image of the interior of the larynx to the eye of the observer. In such an image the vocal cords appear white, the false vocal cords pink in colour.

When a note is produced the vocal cords are brought close together, and an expiratory current of air causes them to vibrate. The current of air must have a certain pressure, and this is produced by contraction of the muscles of the thorax and abdomen which are concerned in forced expiration.

The note produced may vary in loudness, in pitch, and in quality or timbre. The degree of *loudness* varies with the force of the expiratory current. The *pitch* is determined partly by the length and partly by the tension of the vocal cords. In children the pitch is relatively high, because the cords are short. At the time of puberty the larynx increases considerably in size, more so in the male than in the female, and as a result a boy's voice " breaks," that is, becomes much lower in pitch. The possible variation in pitch in any individual is, on an average, about two octaves. This is mainly due to variations in the tension of the vocal cords brought about by the reciprocal action of the crico-thyroid and thyro-arytenoid muscles. The pitch is also affected by the length of the vocal cords free to vibrate, this being determined by the movements of the arytenoid cartilages. Further, the force of the expiratory current influences the pitch, the stronger the blast of air the higher being the note produced.

The *quality* of the note is due to the resonance produced in the various resonating chambers, the air in the chest vibrating with the lower notes, and that in the mouth and pharynx and in the accessory sinuses of the nose, with the higher pitched notes. Hence the terms " chest " notes and " head " notes used in connection with singing.

Speech.—The sounds which constitute speech are due to modifications of the simple laryngeal note, and are brought about by alterations in the shape of the mouth and in the adjustment of the lips and teeth. The vowel-sounds are continuous vibrations, whereas the formation of consonants depends on the interruption of vibrations.

For the production of the broad " a " vowel-sound, the mouth cavity is widely open ; for the " i " (ee) sound, the space between tongue and palate is much reduced ; for " u " (oo), the posterior part of the tongue is raised against the palate.

Consonants are classified as dental, guttural, or labial, according to the position at which the interruption of the

laryngeal note takes place. Thus " t " and " d " are dentals, " p " and " b " are labials, and " g " and " k " are gutturals.

In whispering there is no phonation; the glottis is open, and the words produced are the result of the modification of the air-current by the speech mechanism.

The movements which occur in the larynx in connection with swallowing and breathing will be referred to in the description of deglutition and respiration.

SECTION V

PROPRIOCEPTIVE SENSES

Our knowledge of the position of the body is derived partly from tactile and visual impulses, and partly from impulses

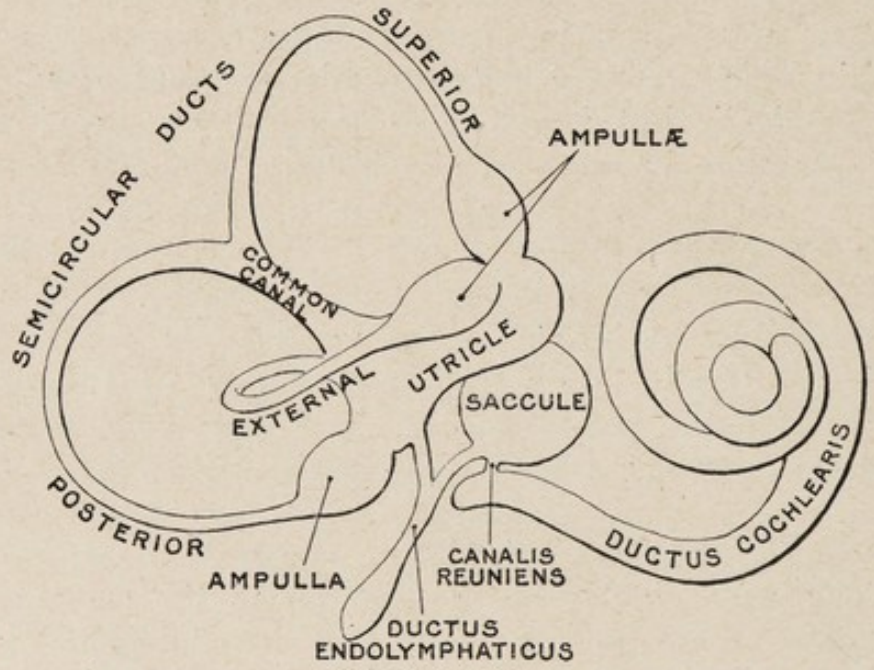


FIG. 72.—The membranous labyrinth. (Enlarged.)
Gray's *Anatomy*.

reaching the central nervous system from the posterior part of the labyrinth and from the skeletal muscles and the joints; the impulses arising in the muscles, joints, and labyrinth are called proprioceptive impulses.

The Labyrinth.—The part of the bony labyrinth behind the cochlea consists of a cavity called the vestibule, into which the scala vestibuli opens in front and three semicircular canals open behind. Within the bony semicircular canals lie the three membranous semicircular canals (ducts). The latter open into the membranous utricle, which, together with the saccule, occupies the vestibule, the utricle and saccule being connected by the saccus (ductus) endolymphaticus (fig. 72). The semicircular canals

are arranged in three planes at right angles to one another. The external canal lies in the horizontal plane; the superior vertical canal and the posterior vertical canal lie in vertical planes at right angles to one another, each forming an angle of 45° with the median plane, as shown in fig. 73.

The canals open into the utricle by five orifices, one of which is common to the medial end of the superior, and the upper end of the posterior, canal; each canal has a dilatation or ampulla at one end.

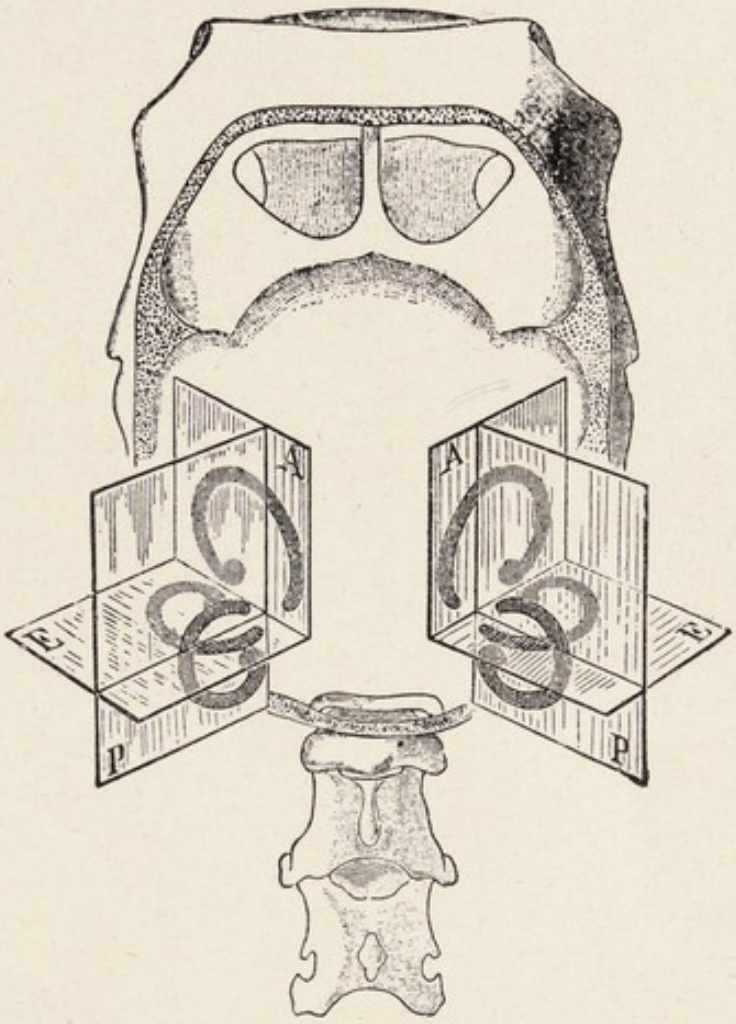


FIG. 73.—Figure showing the situation of the three semicircular canals in the skull of the pigeon. (Starling's *Principles of Physiology*.)

A, plane of anterior or superior semicircular canal; P, plane of posterior canal; and E, that of horizontal canal.

Note that the anterior canal of one side, and the posterior canal of the other side, are in the same plane.

The utricle, saccule, and membranous semicircular canals are lined by flattened epithelium resting on connective tissue; in each ampulla the connective tissue is thickened at one point to form a projection, which is covered with columnar epithelium supporting a number of cells provided with hairs, and which is called the *crista acustica* (*septum transversum*). Similar thickenings occur in the utricle and saccule, these being called *maculæ acusticæ;* they have the same structure as the cristæ, with the addition of small concretions of lime, called otoliths, scattered among the processes of the hair-cells. The fibres of the vestibular nerve are distributed to the cristæ and maculæ acusticæ, and end in fibrils round the hair-cells. The vestibular nerves join the cochlear nerve to form the eighth cerebral nerve. The vestibular fibres enter the pons and divide into ascending and descending branches, which end in the chief vestibular nucleus, collateral

fibres passing to the nucleus of Deiters and the nucleus of Bechterew. From these cell-stations other fibres are distributed: (1) by the restiform body to the masses of grey matter in the interior of the cerebellum, and (2) by the posterior longitudinal bundle to the nuclei of the third, fourth, and sixth cerebral nerves, and to the grey matter of the spinal cord.

The bony labyrinth contains perilymph, and the membranous cavities contain endolymph; the membranous structures are attached to the bony labyrinth by fibrous strands.

The functions of the semicircular canals have been ascertained chiefly by experiments on pigeons, in which they are easily accessible. If the horizontal canals are destroyed, the head oscillates from side to side in a horizontal plane; after section of the posterior, or the superior, vertical canals, the head and body are thrown into constant movement in a vertical plane, so that the animal tends to turn somersaults.

After destruction of all the canals, the animal is in constant violent movement, but can neither stand, walk, nor fly. In course of time partial recovery takes place, but the symptoms return when the eyes are bandaged, showing that the partial recovery is due to compensatory utilisation of the visual sensations.

It is clear from these observations that the canals are essential for the co-ordination of muscular movements and for the maintenance of equilibrium. Each movement of the head sets up a stimulus in one or other of the canals, giving rise to impulses which pass along the vestibular nerve to the cerebellum; these impulses serve to co-ordinate and restrain the movement. In the absence of these guiding impulses the movements become completely uncontrolled and the sense of the position of the head is lost. The existence of three pairs of canals, in three different planes, makes it possible for impulses to be aroused in whatever plane the head is moved.

These impulses originate in the *movements* of the endolymph, which take place when the head is moved, and cause the pressure on the hair-cells of the cristæ to be increased or diminished. This was shown by Ewald, who connected a small tube with the exterior of one membranous canal in such a way that he was able to blow suddenly on the canal so as to cause the endolymph to flow towards the ampulla. Every time this was done the animal moved its head and eyes in the plane of the stimulated canal and in the direction of the current. If, for example, the endolymph was made to flow along the right horizontal canal towards the ampulla, the animal turned its head towards the left. In the normal animal an abrupt movement of the head

from right to left will, owing to the lag in the movement of the endolymph as compared with that of the head, cause the fluid in the right utricle to exert pressure on the hair-cells in the ampulla of the horizontal semicircular canal. At the same time the pressure on the hair-cells in the ampulla of the left horizontal canal will be diminished. Similar changes of pressure will be produced in the superior and posterior canals by movements of the head in other planes. These changes in pressure give rise to impulses which travel to the brain and bring about co-ordination of movement.

The afferent impulses arising in the semicircular canals maintain equilibrium and muscular co-ordination, even after removal of the cerebral hemispheres. In normal circumstances, however, they also affect consciousness, and we are aware of the movements of the head. Interference with these impulses in man by disease of the canals brings about sensations of giddiness and disturbance of equilibrium (Menière's disease).

It has already been pointed out (p. 76) that muscular tone is reflex in origin, and dependent on afferent impulses; these reach the motor neurons in the spinal cord from (1) the posterior nerve roots, (2) the cortex of the cerebral hemispheres, (3) the cerebellar cortex, and (4) the labyrinth. Every muscular movement involves variations in muscular tone, some muscles becoming taut, and others relaxed; and the changes of tone are necessary for the smooth contraction of the muscles involved and for the proper co-ordination of the resulting movement. The semicircular canals are particularly concerned with the variations in tone of different muscles according to the position of the head and body in space. In the rabbit, for example, when the head is raised the tone of the muscles of the fore-limbs is increased, the effect being abolished by destruction of the semicircular canals. These reflex variations of muscular tone, which are known as *postural reflexes*, play a part in the muscular adjustment of the animal to changes of position and assist in the maintenance of equilibrium.

The *maculæ acusticæ* are subject to constant stimulation by the otoliths. The part of the macula upon which the otoliths exert pressure varies according to the position of the head, and the stimulation of the hair-cells by the pressure of the otoliths is also variable. The impulses to which these stimuli give rise serve to give information as to the position of the head when at rest, or in progressive, as distinct from rotary, movement. Confirmation of this is found in experiments on the otocyst of palæmon, a crustacean. When iron filings are substituted for the sand normally present in the otocyst, and a magnet is used

to affect the direction of pressure of the filings, the movements of the creature are such as would be expected if the cause of the pressure were gravity.

Muscular Sense.—Even when the eyes are closed we are conscious of the position of the body and limbs when at rest, and of movement of the limbs, whether this be active or passive. This consciousness constitutes muscular sense, and is brought about by afferent impulses constantly passing from special structures in the muscles, joints, and ligaments. About one-third of the fibres in a nerve to a muscle are afferent in function, and do not degenerate on section of the anterior roots. The

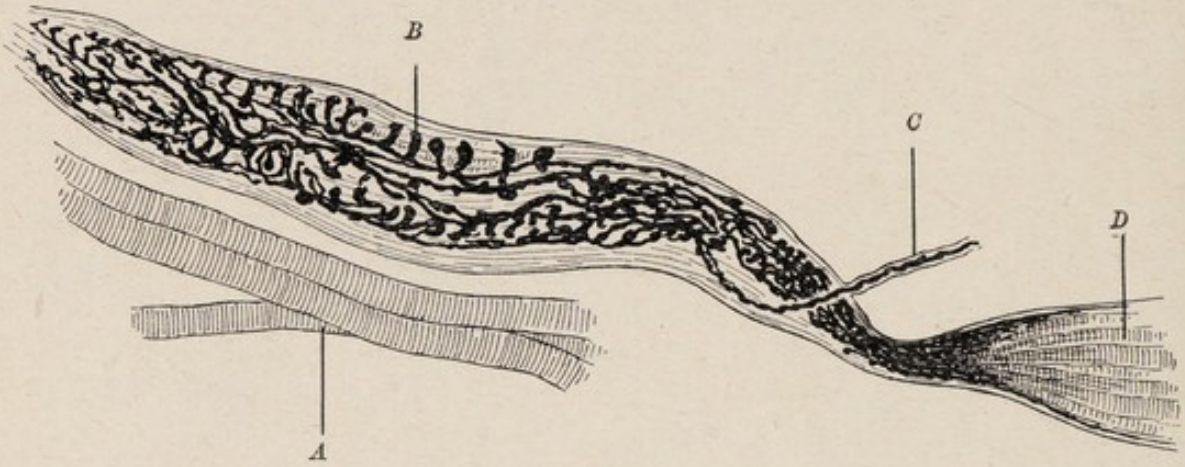


FIG. 74.—A neuromuscular spindle from a cat's muscle. (From a specimen lent by G. Winfield.)

A, ordinary muscular fibres; *B*, arborisation of nerve-fibres; *C*, medullated nerve ending in spindle; *D*, fine muscular fibres.

afferent fibres terminate in the muscles in *neuromuscular spindles* lying between the ordinary muscle-fibres. The spindles consist of fine muscular fibres surrounded by a connective tissue sheath (fig. 74). A nerve-fibre loses its myelin sheath, pierces the covering of the spindle, and divides into bundles of fibrils which make several spiral turns round the muscle-fibres, and then end by arborisation. Other nerve-endings are found in tendon, and are formed by the arborisation of a nerve-fibre around a bundle of tendon-fibres.

Sensation of passive movements is due chiefly to impulses arising in the joints, that of active movements to impulses arising in the muscles, the movement acting as a stimulus to the muscle-spindles, or to the nerve-endings in the tendons. It is through this sense that we are able to form an estimate of weight.

The impulses giving rise to muscular sense also take part in the co-ordination of muscular movement, as has already been

described (p. 88), and their absence may lead to disturbances of equilibrium.

The maintenance of equilibrium is dependent, therefore, on afferent impulses from the labyrinth, from the muscles, and from the eyes and the skin; when the sensations resulting from the impulses from these different sources are discordant, we experience a feeling of giddiness, and at the same time equilibrium is disturbed.

CHAPTER VI

THE BLOOD

All the active cells and tissues are in intimate relationship with capillary vessels, through which blood is continually flowing. Both tissue-element and outer wall of capillary are bathed with a fluid called lymph, and a constant interchange of material takes place through the lymph between the tissues and the blood. On the one hand, nutritive substances and oxygen pass from the blood to the tissues to furnish a source of energy and to repair loss of substance, and, on the other hand, carbonic acid and other waste materials pass from the tissues to the blood. An exchange of water and salts also takes place by diffusion through the capillary wall. In some organs certain substances, called hormones, are supplied to the blood, and are carried in it to the cells or muscle-fibres which they are destined to influence. Further, as the blood circulates, now through muscles and glands in which heat is produced, now through other structures in which heat is lost, it serves to equalise the temperature of the different parts of the body.

Freshly shed blood is a red, viscid, opaque fluid with a specific gravity of 1059. The specific gravity may be ascertained with a single drop of blood by making a mixture of chloroform and benzol, and finding the proportions of the two fluids in which a drop of blood remains suspended without tending either to sink or to rise. The specific gravity of the mixture, ascertained by means of a hydrometer, is that of the blood itself.

When human blood is examined under the microscope, it is seen to consist of two kinds of corpuscles floating in a pale yellow fluid, the blood-plasma. The corpuscles which are most numerous are the red blood-corpuscles, or erythrocytes. The other variety of corpuscle, the white blood-corpuscle, or leucocyte, is present in the proportion of one leucocyte to every 500 to 700 red cells. In man the corpuscles form from two-fifths to half of the total bulk of the blood.

The *red corpuscles*, when seen singly, are yellow in colour,

but when massed together they give blood its red appearance. They are circular, biconcave, non-nucleated discs, each having a diameter of 7·5 thousandths of a millimetre (7·5 μ). In all mammals, except the camel tribe, the shape of the red corpuscle is the same as that of the human erythrocyte; in camels the corpuscles are oval and biconcave.

The *white blood-corpuscle* is a colourless, nucleated cell, and several varieties occur in human blood. The most abundant type, forming about 70 per cent. of the total number of leucocytes, is the *polymorphonuclear*, so called because its nucleus, which consists of lobes connected by fine strands, is variable in shape. This cell is rather larger than the erythrocyte, being about 10 μ in diameter. It possesses the power of amœboid movement, and, because of its function of ingesting bacteria and foreign particles, is said to be "phagocytic." Its protoplasm contains numerous fine granules which stain with neutral dyes, and are described as *neutrophile*. A somewhat similar corpuscle, in which, however, the nucleus is usually kidney-shaped, contains large granules which stain deeply with acid dyes, such as eosin. These cells are called *eosinophile*; they form from 1 to 5 per cent. of the total number of leucocytes. A *basiphile* variety, in which the granules stain with such basic dyes as methylene blue, is found only occasionally in normal blood. *Small and large lymphocytes* form about 25 per cent. of the total number of leucocytes, the small variety being the more numerous. Lymphocytes are distinguished by containing a large spherical nucleus surrounded by hyaline protoplasm, which does not contain granules.

Other bodies, called *blood-platelets*, are found in recently shed blood, but these cannot be seen when precautions are taken to prevent the blood coming in contact with foreign substances; and it is doubtful whether they are a formed constituent of normal blood. Blood-platelets are colourless bodies, one-third to one-half the size of red corpuscles, and each contains a central group of granules resembling a nucleus.

The blood of a healthy man contains about 5,000,000 red corpuscles in each cubic millimetre, that of a woman about 4,500,000. The corpuscles are counted by means of a hæmocytometer. This consists of a glass cell of known depth, the floor of which is ruled in squares of known size. The blood is diluted 100 times in a special pipette with a slightly hypotonic solution of sodium sulphate, which prevents coagulation, and the cell is filled with the mixture. The corpuscles settle on the squares and can be counted under the microscope. The volume corresponding with each square and the dilution of the blood

being known, the number of corpuscles per cubic millimetre of blood can be calculated. The number is diminished by hæmorrhage and in certain diseases, and is increased by living at high altitudes.

The white corpuscles number from 7000 to 10,000 in each cubic millimetre of blood. They can be counted by means of the hæmocytometer, the blood being diluted 100 times with a saline solution similar to that used for red corpuscles, but containing a little methylene blue to stain the leucocytes.

THE RED BLOOD-CORPUSCLES

Each red corpuscle is soft, and alters its shape readily so that it can pass through even the narrowest capillary vessels. It is also elastic, and readily regains its shape when the compressing influence is removed. Two views are held as to the intimate structure of the erythrocyte. According to one, the corpuscle consists of a sponge-like framework (stroma) containing hæmoglobin, the blood-pigment, loosely combined with the stroma. Sharpey Schafer's view, on the other hand, is that the corpuscle consists of an envelope containing the hæmoglobin in solution in its interior. Whichever view be adopted, it is clear, from the behaviour of the corpuscle in the presence of reagents, that its superficial layer behaves to some extent as a semi-permeable membrane, readily allowing the passage of water, but not of salts. Thus, if red blood-cells are placed in 0·9 per cent. sodium chloride solution, which is isotonic with mammalian blood-plasma, they are unaltered in appearance. But, if they are placed in a fluid the salt content of which is markedly below that of blood-plasma, water passes into the corpuscle by osmosis and distends it, so that ultimately the membrane ruptures and the hæmoglobin is discharged. On the contrary, if the surrounding fluid is hypertonic, for example 2 per cent. NaCl, water passes out of the corpuscle, which in consequence becomes shrunken and crenated.

The envelope of the corpuscle is dissolved by weak alkalies or by ether, and this makes it probable that it is of a fatty nature. Bile-salts (which are solvents of fats), amyl alcohol, soaps, higher fatty acids, and saponin or sapotoxin also destroy the red corpuscles, setting free the hæmoglobin. The same result can be attained physically by alternately freezing and thawing blood. The setting free of the hæmoglobin by any of these means is called *hæmolysis*.

Certain physiological substances also bring about hæmolysis and have been termed *hæmolysins*. Snake-venom, and, in many

cases, the serum from an animal of another species act in this way. Moreover, the serum of an animal A, which is not naturally hæmolytic for the blood of another animal B, may be made hæmolytic for the blood of that animal, if A has been inoculated with red cells from the species B some days before the experiment is made. Thus rabbit's red corpuscles are not affected by the serum of a guinea-pig. If, however, rabbit's blood has been previously injected into a guinea-pig, the serum from the latter will dissolve rabbit's red corpuscles.

Serum which is either naturally or artificially hæmolytic loses its power to dissolve red corpuscles if it is heated to 55° C. But this heated and therefore inactive serum can have its hæmolytic power restored by the addition of serum from a normal animal. The hæmolytic power of any serum, therefore, depends upon the presence of two substances, one which is present in normal serum and is destroyed at a temperature of 55° C., and is usually called *complement*; and a second which is stable at 55° C., and may be produced in an animal by injection of the corpuscles of another animal.

Hæmoglobin may thus be set free from the erythrocytes, and pass into solution in the surrounding fluid, in three ways :—

(1) By a physical process, as by dilution with water or by alternate freezing and thawing.
(2) By chemical means, for example, the solution of the lipoid stroma of the corpuscles by bile-salts, amyl alcohol, soaps, or other reagents.
(3) By physiological agents, called hæmolysins, the exact mode of action of which is not known.

As a result of hæmolysis by any of these methods the blood is said to be 'laked.' The hæmoglobin is in solution, and the blood, previously opaque on account of the reflection of light from the erythrocytes, becomes transparent.

THE CHEMICAL COMPOSITION OF RED BLOOD-CORPUSCLES

The red blood-corpuscles may be obtained in sufficient quantity for analysis by centrifugalising blood and washing the deposit with 0·9 per cent. NaCl. They are found to consist of 63·3 per cent. of water and 36·7 per cent. of solids. Hæmoglobin forms 95 per cent. of the dry solids, the remainder being made up of nucleoprotein, lecithin, cholesterol, fatty acid, and inorganic salts, the most abundant of the latter being potassium phosphate. The stroma is, therefore, as has already been pointed out, largely of a lipoid nature.

Hæmoglobin is a compound of *globin* with an iron-containing substance, *hæmatin*; globin is a protein having the properties of a histone (p. 11). The molecule of hæmoglobin is a very large one, and its formula is given by one authority as $C_{758}H_{1203}N_{195}S_3FeO_{218}$. Although it is a colloid, hæmoglobin crystallises fairly readily. The crystals vary in shape in different animals, but in all cases they belong to the rhombic system. In man they are rhombic prisms, in guinea-pigs they form tetrahedra (fig. 75). Hæmoglobin is purple in colour, is soluble in water, and its solutions, when examined with the spectroscope, show a broad absorption-band in the green between Frauenhofer's lines D and E (fig. 76, sp. 2).

FIG. 75.—Hæmoglobin crystals, magnified. (From Quain's *Anatomy*.)
1, from human blood; 2, from the guinea-pig; 3, squirrel; 4, hamster.

The most important property of hæmoglobin is its affinity for oxygen, each molecule having the power of combining with two atoms of oxygen to form oxyhæmoglobin. The combination is a loose one, for the attached oxygen (dissociable oxygen) is given up if the solution containing the compound be exposed to a vacuum, or if a reducing agent, such as ammonium sulphide, be added to it, HbO_2 (oxyhæmoglobin) again becoming Hb (hæmoglobin). In the living body the same reduction takes place as the blood circulates through the capillaries of the tissues; as the blood flows through the lungs, hæmoglobin takes up oxygen and is converted into oxyhæmoglobin. In virtue of its power to combine with and give up oxygen, hæmoglobin acts as a carrier of oxygen from the lungs to the tissues. Oxyhæmoglobin has a characteristic scarlet colour, and its spectrum exhibits two absorption bands in the green, between the D and E lines (fig. 76, sp. 1).

The oxygen-carrying power of hæmoglobin depends upon hæmatin, the prosthetic group of the molecule, and the value of hæmatin in this respect is determined by the presence of iron. The actual amount of iron in the blood is small. Hæmatin forms about 4 per cent. of the hæmoglobin molecule, and iron accounts for about 11 per cent. of the hæmatin, or about 0·05 per cent. of blood itself. Iron has on this account been described as

the gold currency of the body, and it is carefully preserved. Red corpuscles are continually being destroyed in the liver, and the broken-down material is excreted to a large extent in the bile. Hæmatin appears in the bile in an iron-free form as bilirubin, the primary bile-pigment, the iron being retained by the liver-cells. The iron is eventually used in the formation of new erythrocytes, this process taking place in the red marrow.

Hæmoglobin can also combine with gases other than oxygen,

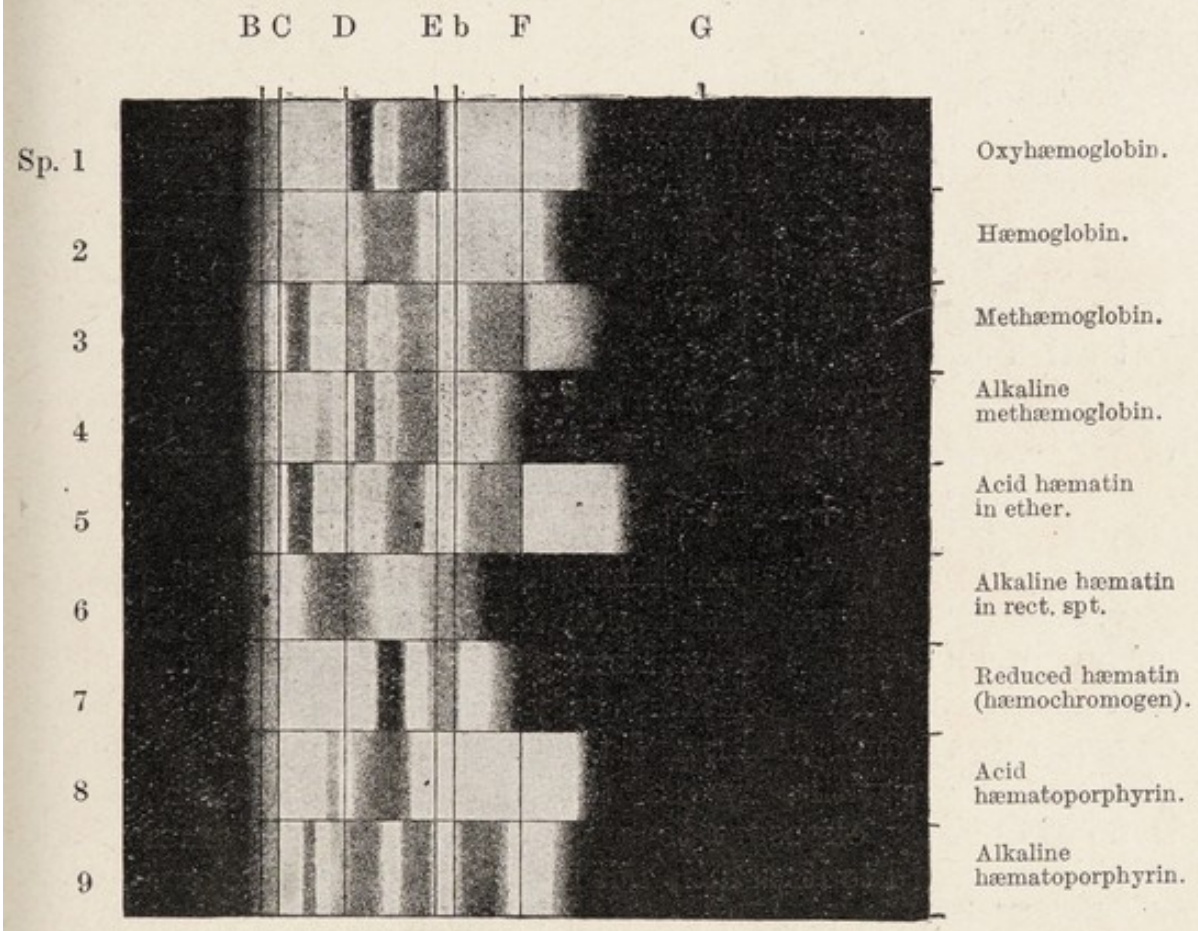


FIG. 76.—Spectra of hæmoglobin and its derivatives. (From MacMunn's *Spectrum Analysis.*)

and if exposed to air containing carbon monoxide it combines with this gas to form a stable compound *carboxyhæmoglobin* (HbCO). The affinity of hæmoglobin for carbon monoxide is so much greater than for oxygen that, if blood is exposed to air containing 0·07 per cent. carbon monoxide (and 21 per cent. oxygen), half of its hæmoglobin enters into combination with carbon monoxide. A very small proportion of carbon monoxide in the air breathed will thus greatly diminish the oxygen-carrying power of hæmoglobin upon which the life of the animal depends. Carboxyhæmoglobin differs slightly in colour from oxyhæmoglobin, strong solutions having a more florid appearance, and weak solutions retaining a pink colour, whereas the same dilution of oxyhæmoglobin has a yellow tinge. Solutions of carboxy-

hæmoglobin, when examined spectroscopically, exhibit two bands in the green slightly nearer to the violet end than those presented by oxyhæmoglobin. Carboxyhæmoglobin is unaffected by the addition of ammonium sulphide; but, if the solution containing it is exposed to a vacuum, carbon monoxide is evolved and reduced hæmoglobin is formed.

Hæmoglobin forms a still more stable compound with nitric oxide, HbNO, but this is purely a laboratory product, and is only of theoretical interest.

When a solution of oxyhæmoglobin is treated with ferricyanide of potassium, a volume of oxygen is given off corresponding with the dissociable oxygen of the oxyhæmoglobin molecule, and the solution becomes brown, its spectrum showing a characteristic band in the red in addition to other bands (fig. 76, sp. 3). The brown substance is called *methæmoglobin*. When oxyhæmoglobin is treated with hydrazine hydrate, there is given off a volume of nitrogen corresponding with the volume of dissociable oxygen present in oxyhæmoglobin, as is indicated by the equation

$$HbO_2 + N_2H_4.H_2O = N_2 + 3H_2O + Hb.$$

On the contrary, when methæmoglobin is treated in the same way, it never yields more than half the amount of nitrogen given off by an equal weight of oxyhæmoglobin. It may be concluded that methæmoglobin contains only half as much dissociable oxygen as oxyhæmoglobin, and that each molecule of methæmoglobin combines with only one atom of oxygen. Methæmoglobin is unaffected by exposure to a vacuum, but when ammonium sulphide is added to its solution, it is first converted into oxyhæmoglobin and is then rapidly reduced to hæmoglobin; shaking the solution with air then brings about the formation of oxyhæmoglobin. The formation of methæmoglobin, therefore, does not involve any disruption of the hæmoglobin molecule.

Decomposition Products of Hæmoglobin.—If a solution of hæmoglobin (or oxyhæmoglobin) is warmed with an acid or an alkali, the globin is converted into metaprotein, and *hæmatin* is set free. In the pure condition, hæmatin is a dark brown or black amorphous substance, insoluble in water, soluble in acids or alkalies. In acid solution its spectrum shows, besides other absorption-bands, a characteristic band in the red (fig. 76, sp. 5), nearer the red end of the spectrum than that given by methæmoglobin. The spectrum of the alkaline solution exhibits a rather faint band just to the red side of the D line (fig. 76, sp. 6). On the addition of ammonium sulphide, alkali-hæmatin is converted into reduced alkali-hæmatin or *hæmochromogen*, the spectrum

of which shows two absorption-bands in the green, some distance to the violet side of the D line, the band nearer D being the more distinct of the two (fig. 76, sp. 7). As these bands can be seen in extremely dilute solutions, the formation of hæmochromogen constitutes a delicate spectroscopic test for blood-pigment.

As has already been said, hæmatin contains the iron of the hæmoglobin molecule, and it has had the formula $C_{34}H_{34}N_4FeO_5$ assigned to it. It forms a compound with hydrochloric acid, hydrochloride of hæmatin or *hæmin*, which is easily obtained by heating blood with glacial acetic acid in the presence of sodium chloride. Hæmin occurs in dark brown rhombic crystals (fig. 77), and its formation is utilised as a medico-legal test for blood. In the reduced condition, hæmatin will recombine with globin to form hæmoglobin, or a substance indistinguishable from hæmoglobin, provided the hæmatin has not been precipitated.

Fig. 77.—Hæmin crystals, magnified. (Preyer.) From Quain's *Anatomy*.

If hæmatin (or hæmoglobin) be treated with a strong mineral acid, iron-free hæmatin or *hæmatoporphyrin*, $C_{34}H_{38}N_4O_6$, is formed. Acid solutions of this substance show a spectrum with two absorption-bands, one on either side of the D line, that to the red side being the narrower (fig. 76, sp. 8). The spectrum of alkaline solutions (fig. 76, sp. 9) is somewhat similar to that of methæmoglobin. Hæmatoporphyrin occurs occasionally in the urine in sulphonal poisoning, its spectrum in such cases being of the alkaline type. Two similar substances are found in the body, *hæmatoidin* in old blood-clots, and *bilirubin*, the primary bile-pigment; they are formed from hæmoglobin and are said to be identical, each containing one atom less of oxygen than does hæmatoporphyrin. The proof that the capacity of hæmoglobin to combine with oxygen depends upon the presence of iron in its molecule is furnished by the fact that hæmochromogen, which contains iron, can take up and give off oxygen, whereas hæmatoporphyrin, which contains no iron, is unable to do so.

THE ESTIMATION OF HÆMOGLOBIN

The estimation of the amount of hæmoglobin contained in a sample of blood is usually carried out by a colorimetric method.

The apparatus used is called a *hæmoglobinometer* (fig. 78) and consists of two tubes, one of which is sealed and contains a standard dilution of ox-blood, the hæmoglobin of which has been converted into carboxyhæmoglobin; the reason for this is that carboxyhæmoglobin is more stable than oxyhæmoglobin, and therefore the colour of the standard solution is more permanent. A little distilled water is placed in the second tube, which is graduated; 20 c.mm. of blood are measured in a special pipette, and then discharged into the graduated tube. The

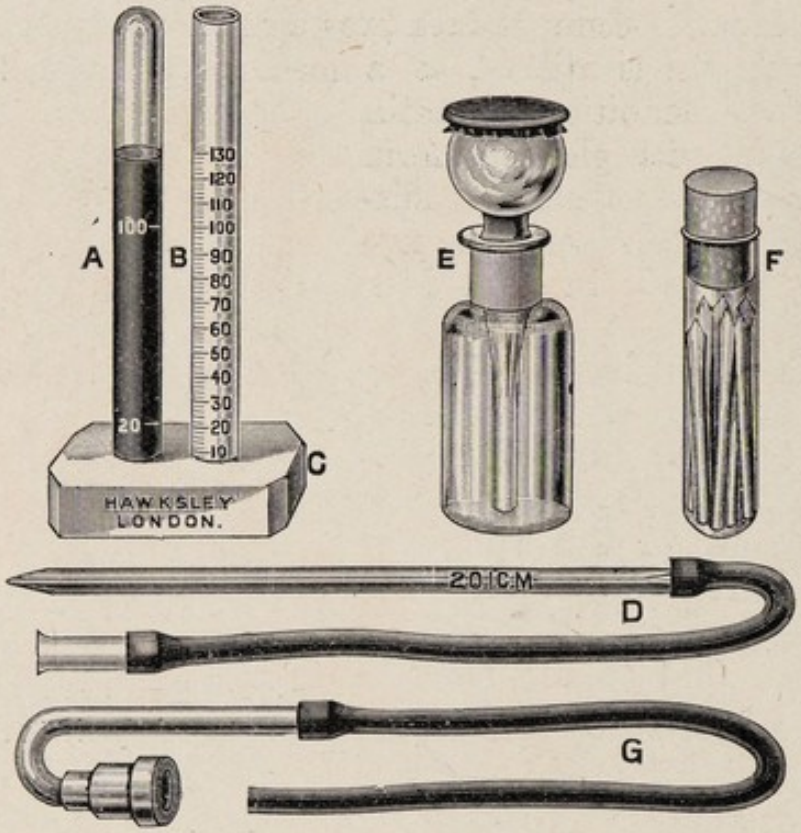


FIG. 78.—Hæmoglobinometer. (From Messrs. Hawksley.)
A, standard tube; B, graduated tube; C, stand; D, measuring pipette; E, distilled water bottle; F, needles; G, gas tube.

blood, laked by the water, is exposed to coal-gas, and in this way the hæmoglobin is converted into carboxyhæmoglobin. It is then diluted with distilled water till the tints of the two tubes are alike, and the level of the fluid in the graduated tube is read. If the latter is at the figure 100, the amount of hæmoglobin is said to be normal or 100 per cent. If it is over 100, the blood is unusually rich in hæmoglobin; if the percentage is below 100, the blood is deficient in hæmoglobin. The figure 100 per cent. is purely conventional, the amount of hæmoglobin actually present in blood being normally about 14 per cent.

If the number of red corpuscles in the blood is ascertained at the same time, the value of the hæmoglobin content of each

corpuscle can be stated. Thus, if the number of corpuscles is the normal five millions per cubic millimetre and the hæmoglobinometer gives a reading of 50 per cent., each corpuscle contains only half the normal amount of hæmoglobin.

THE ORIGIN AND FATE OF RED BLOOD-CORPUSCLES

(1) *In early embryonic life* red blood-corpuscles are formed in areas, known as "blood-islands," lying in the *area vasculosa*

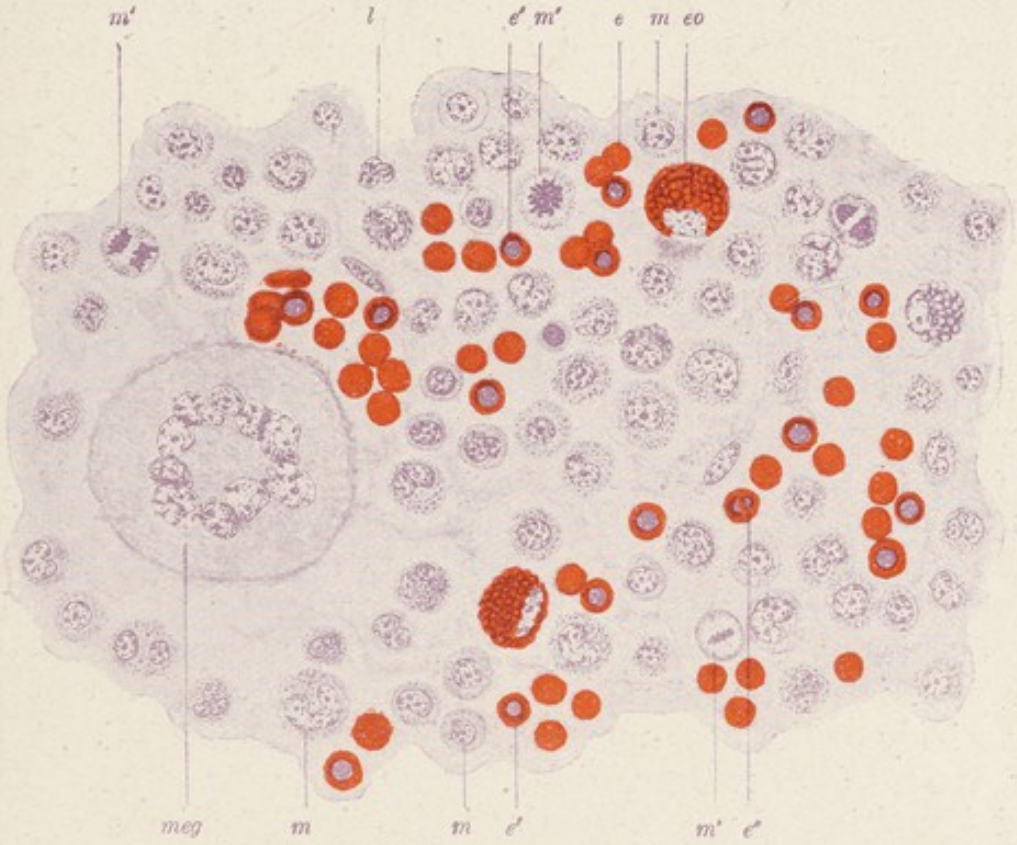


FIG. 79.—Red marrow of young rabbit. Magnified 450 diameters. (From Sharpey Schafer's *Essentials of Histology.*)

e, erythrocytes; *e'*, erythroblasts; *e''*, a coloured cell undergoing mitotic division; *l*, a polymorphonuclear leucocyte; *m*, ordinary myelocytes; *m'*, myelocytes undergoing mitotic division; *eo*, an eosinophile myelocyte; *meg*, a giant-cell or megakaryocyte.

of the blastoderm. The blood-islands lie between the mesoderm and the entoderm, and are said to be derived from the latter. They consist of branched cells which unite to form a syncytium. The nucleus of each cell divides and subdivides, each new nucleus becoming surrounded by protoplasm containing hæmoglobin. At the same time a fluid, the plasma, appears between the nucleated fragments. The coloured cells thus formed are known as *erythroblasts*, and are the red corpuscles of the embryo. They multiply by mitotic division. *In later embryonic life* similar nucleated coloured cells, or erythroblasts, are found undergoing division in the sinus-like blood-vessels of the liver, and also in the pulp of the spleen.

Non-nucleated erythrocytes, like those developed in post-natal life, are formed in the embryo in connective tissue. The connective tissue cells become coloured by the formation of hæmoglobin, and the coloured protoplasm is subdivided into a number of discs, or erythrocytes, which lie free in the hollowed interior of the cell. Adjacent cells have meanwhile become united to form a syncytium, and the hollows become continuous along the connecting branches, so that a system of blood-vessels is formed.

(2) *In post-natal life* nucleated red corpuscles or erythroblasts are found in the red marrow of bone (fig. 79). These are constantly undergoing mitotic division; the cells thus formed lose their nuclei by atrophy or extrusion, and pass into the blood-capillaries, which in the marrow probably have incomplete walls. Nucleated red corpuscles may pass into the blood-stream after birth in certain diseases in which a rapid destruction of blood-corpuscles is taking place.

The duration of the existence of a single red corpuscle is not known, but there is evidence that large numbers of these cells are destroyed daily to form the pigment of the bile. Fragments of broken-down erythrocytes are also of constant occurrence in the cells of the spleen. Moreover, the pigment of hair and that of the coloured parts of the skin is believed to be derived from hæmoglobin. Blood-corpuscles are also lost by accidental hæmorrhage, in disease, and, in the female, by menstruation. The deficiency brought about in all these ways, normal or abnormal, is as a rule rapidly and completely made good by the activity of the bone-marrow, which, in post-natal life, is the only source of the red corpuscles. When an unusually large and rapid formation of red corpuscles is required, for instance after severe hæmorrhage, the red marrow increases in amount, and replaces the yellow marrow to some extent.

THE WHITE BLOOD-CORPUSCLES

The distinguishing feature of the polymorphonuclear leucocytes is their power of amœboid movement, a power which is shared by the eosinophile cells, and to a much less extent by the lymphocytes. The leucocytes are able to make their way through the capillary walls between the epithelial cells, and wander out into the tissue-fluids of the body. They are especially susceptible to certain chemical stimuli (*chemiotaxis*), and are found to concentrate in large numbers round various chemical substances placed in their neighbourhood. For example, they appear in force where pathogenic bacteria are active, and serve a useful purpose in surrounding and destroying these germs, thus con-

stituting an important protective mechanism for the body (fig. 80). When the leucocytes fail to overcome and ingest the bacteria, they may themselves be destroyed by the bacterial toxins. The same function of the removal of useless or harmful material is shown in other ways. For example, the removal of the tail of the tadpole is effected by leucocytes, and in the mammalian body dead cells and organic foreign substances, such as buried catgut ligatures, are ingested by the same cells. On account of this property of "eating up" bacteria and dead matter, polymorphonuclear leucocytes are included under the term *phagocytes*.

The leucocytes consist largely of proteins, namely cell-albumin, cell-globulin, and nucleo-protein; they also contain a little glycogen, some neutral fats, lecithin, and cholesterol. The inorganic salts which are most abundant in their composition are, as in the case of the red corpuscles, chlorides and phosphates of potassium.

Fig. 80—Phagocytosis. Three polymorphonuclear leucocytes, stained to show ingested bacteria. × 1500.

In the embryo, leucocytes are derived from cells which resemble the erythroblasts but are colourless. In post-natal life the polynuclear and eosinophile cells, as also the basiphile cells, when they occur, are derived from the special cells of red bone-marrow called *myelocytes*; the lymphocytes are derived from lymphatic glands and lymphoid tissue generally. The nuclear changes which accompany cell-division can be seen in definite areas, known as germ-centres, in the lymphoid tissue of the lymphatic glands and elsewhere.

The condition called *leucocytosis*, or increase of the number of leucocytes in the blood, occurs normally during the digestion of a protein meal. It also takes place in many infective diseases, being accompanied by overgrowth of the red marrow, in which the polymorphonuclear cells are formed. The increase in the number of polymorphonuclear leucocytes in the blood is part of the process by which the body resists and overcomes infection by micro-organisms.

THE BLOOD-PLASMA

When blood is shed it rapidly becomes viscid, and in a few minutes sets to form a clot. It is therefore necessary to use means to retard or prevent clotting in order to obtain plasma for

examination and analysis. The various methods which are used for this purpose will be described in connection with coagulation.

Plasma is a pale yellow fluid, and has a specific gravity of about 1030, this being considerably lower than that of blood as a whole. The red corpuscles have a specific gravity of about 1090, and therefore sink if blood which is prevented from coagulating is allowed to stand.

On analysis, plasma is found to contain a large number of substances, some of which, particularly fibrinogen, appear to be essential constituents of the plasma itself, some are food-stuffs being conveyed to the tissues, some are waste products being carried to excretory organs, and others are hormones, enzymes, and bodies of like nature. A list of the principal constituents is given in the following table :—

The Composition of Blood-Plasma

Water, 91 to 93 per cent.

Proteins—serum-albumin, serum-globulin, fibrinogen—6 to 8 per cent.

Glucose, 0·1 to 0·15 per cent.

Neutral fats, lecithin, and cholesterol.

Urea (0·02 to 0·05 per cent.), amino-acids, urates.

Inorganic salts — chlorides, sulphates, phosphates, and bicarbonates of sodium, potassium, calcium, magnesium, and iron. The most abundant salts are chloride and bicarbonate of sodium, in contradistinction to the red cells and the tissues, in which the chief salts are mono- and di-potassium phosphate and potassium chloride.

Pigment and aromatic substances.

Gases in solution—oxygen, carbonic acid, and nitrogen.

The Proteins of Plasma.—If an equal volume of a saturated solution of sodium chloride is added to plasma, and the mixture is allowed to stand, a sticky white precipitate separates out, consisting of *fibrinogen.* This substance is a globulin, and the precipitate may be dissolved in weak salt solution. Fibrinogen exists in much smaller quantity than the other proteins, forming about 0·3 per cent. of the plasma. If plasma is allowed to clot, a comparatively insoluble, stringy substance, called *fibrin,* is formed, and, if this is removed, the fluid which remains is plasma minus fibrinogen, and is called *serum.*

When serum is treated with an equal volume of a saturated solution of ammonium sulphate, a precipitate of *serum-globulin* is obtained. This precipitate is found to be a mixture of two substances, one of which, euglobulin, is a true globulin, while

the other, pseudo-globulin, resembles albumin in being soluble in distilled water. If serum from which serum-globulin has been removed is saturated with ammonium sulphate, a precipitate of *serum-albumin* is obtained. The filtrate from this contains no other protein. Fibrinogen coagulates at about 56° C., serum-globulin at 75°, and serum-albumin at a slightly higher temperature.

Although albumin and globulin can be separated from serum by chemical methods, there is reason to believe that in the serum itself these two substances are combined to form one—*serum-protein.*

The Osmotic Pressure of Blood-Plasma.—It has already been pointed out that the osmotic pressure of the plasma is the same as that of the corpuscles, so that it is also the same as that of the blood as a whole. It has been found by experiment that the proteins of plasma have a slight osmotic pressure, but the osmotic pressure of plasma is chiefly due to the inorganic salts. One method of ascertaining the osmotic pressure of a fluid is to determine its freezing-point (p. 17) ; in the case of blood this is found to be 0·56° C. below the freezing-point of water.

If the osmotic pressure of the blood becomes higher than that of the tissues, water will pass from the tissues into the blood in the capillaries, and salts will diffuse from the blood into the tissues. If the osmotic pressure of the blood becomes lower than that of the tissues, the reverse processes will occur, water passing from blood to tissues and salts from tissues to blood. This interchange is an important factor in the maintenance of the balance between the intake and output of water and salts.

PROTECTIVE AND OTHER SUBSTANCES IN THE PLASMA

A large number of substances, when introduced under the skin or directly into the circulation (but not when given by the mouth), give rise to the formation by the tissues, and the setting free in the blood-stream, of products which tend to destroy or to precipitate the substance introduced, or to neutralise its action. The products thus formed are called *antibodies*, those which excite their formation being called *antigens*. Antigens are colloidal, and many proteins, including harmless bodies such as egg-white and caseinogen, can act as antigens. Crystalloid substances of small molecular weight, such as sugar, seem unable to give rise to antibodies.

If a little human blood-serum is injected into a rabbit on several occasions at intervals of a week, the blood-serum of the

rabbit acquires the power, when tested *in vitro*, of precipitating the proteins of human serum, but not those of the serum of other animals. The substance thus formed in the rabbit's blood is called a *precipitin*. If the rabbit is injected with sheep's serum, the precipitin formed will precipitate sheep's serum *in vitro*, but not that of any other animal. The precipitin acts, therefore, only on the serum of an animal of the same species as that from which blood is taken for injection into the rabbit; and the reaction is said to be *specific*. Since this reaction is not only one of the most delicate known tests for the presence of blood, but also makes it possible to ascertain the species of animal from which the blood was derived, it has been used in medico-legal cases to ascertain whether blood, for example on clothes or weapons, is of human origin or not.

Again, the poisons (toxins) formed by bacteria give rise, when introduced into the body, to antibodies which neutralise the toxin. If, for example, a minute amount of diphtheria-toxin is injected at intervals into an animal, the latter forms *antitoxin* in considerable amount. This antitoxin is able to neutralise diphtheria-toxin, and such an animal will now survive the injection of a dose of toxin many times larger than that which would previously have killed it; and it is said to be *immune* to that toxin. In this example the toxin and antitoxin combine directly with one another. In other cases, however, the antibody which is formed does not itself destroy the antigen, but forms a link between the antigen and a substance present in normal serum and known as *complement*; the complement, thus linked on to the antigen, is able to destroy it. Antigens of this kind include bacteria, red blood-corpuscles and tissue-cells, and the antibodies are called *lysins*. The formation of *hæmolysin* (p. 176) is an example of this process.

The capacity to form antibodies, which can destroy or neutralise bacteria and their toxins, is one of the fundamental means by which human beings are enabled to resist, or to recover from, diseases of bacterial origin.

Anaphylaxis.—If a small dose of an antigen, such as egg-white, is injected into an animal, and, after an interval of sixteen days or more, a second, even smaller, dose is given, the animal becomes extremely ill, and may die in a few minutes. In guinea-pigs, which are particularly sensitive, there is a marked fall of blood-pressure, extreme constriction of the bronchioles, and convulsions. This hypersensitiveness of an animal to a second dose of an antigen is known as *anaphylaxis*.

THE REACTION OF THE BLOOD

Every aqueous solution contains free hydrogen (H) ions and hydroxyl (OH) ions, and its reaction depends upon the proportion of these two ions to one another. In a perfectly neutral solution the two kinds of ion are present in equal amount, whereas, if the hydrogen ions are in excess, the solution is acid, and if the OH ions are the more numerous, it is alkaline. In any aqueous solution, whatever its reaction may be, the product of the H and OH ions is a constant figure, and the reaction of the solution can therefore be ascertained if the number or, as it is usually expressed, the concentration, of either H or OH ions is measured. It is customary to determine the number of H ions, and the reaction of a fluid is measured by the concentration of H ions present in it, this being indicated by the formula C_H.

The reaction of the blood depends upon the relative amount of carbonic acid and of sodium bicarbonate present in solution in the blood-plasma. When in solution, both carbonic acid (H_2CO_3) and sodium bicarbonate undergo ionic dissociation to a slight extent, the former yielding H ions and the latter OH ions in excess ; and the relative amount of carbonic acid (H_2CO_3) and of sodium bicarbonate normally present in the plasma is such that its concentration in H ions is almost the same as that of pure water, being just on the alkaline side of absolute neutrality. This ratio can be altered by adding more carbonic acid to the blood and keeping the amount of sodium bicarbonate constant, or by keeping the amount of carbonic acid constant and adding to the blood a fixed acid (*e.g.* lactic acid) which reacts with sodium bicarbonate. In either case, the concentration of H ions increases, and the reaction of the blood tends to become acid. The reaction of the circulating blood is extremely constant, but, under certain conditions, these processes take place in the normal animal, and the reaction of the blood alters slightly, thereby giving rise to marked physiological effects in the body. Any considerable change in the reaction of the circulating blood is incompatible with life.

But a considerable amount of a fixed acid can be added to blood without producing more than a trivial change in its reaction. The reason is that the acid reacts with sodium bicarbonate to form a neutral salt, setting free carbonic acid (H_2CO_3) which undergoes so little ionic dissociation that the H ion concentration of the blood increases very slightly. Hence the presence of sodium bicarbonate in the plasma helps to prevent the reaction of the blood from altering to such an extent as to become injurious to

the organism; and this substance is often called the "alkali reserve" of the blood.

The proteins in the plasma also assist in keeping the reaction of the blood constant since they too can combine with acids (or alkalies) to form compounds which undergo scarcely any ionic dissociation.

THE COAGULATION OF THE BLOOD

When blood is shed, it begins to set into a jelly-like clot within three to ten minutes. The clot gradually contracts, expressing a yellow fluid, the serum, as it does so; and within ten to forty-eight hours the process results in a shrunken, firm clot floating in the expressed serum. If coagulation has taken place slowly, so that the corpuscles have had time to settle, the upper part of the clot will be paler than the deeper part, because the lighter leucocytes do not sink so quickly as the heavier red cells.

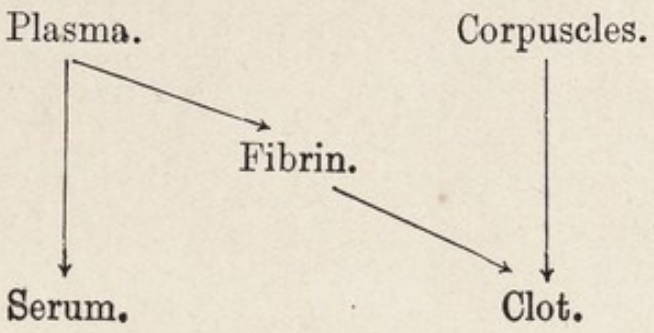
If a drop of blood be placed on a slide and covered with a cover-slip, the process of clotting may be observed microscopically. It is found that the red corpuscles become aggregated into rouleaux, and that between the aggregations delicate threads of fibrin make their appearance. Clotting thus consists in the formation of a meshwork of threads of fibrin, entangling the corpuscles; and the subsequent shrinking of the clot is due to the contraction of the newly formed fibres.

Fibrin may be obtained in quantity by whipping a large volume of freshly shed blood with a bundle of twigs, to which it adheres as it is formed. Blood treated in this way will not clot subsequently, and is spoken of as *defibrinated blood*. The fibrin, when freed from blood-pigment by washing, is a white, stringy substance, easily stretched and possessing considerable elasticity. It is insoluble in water and in dilute salt solutions, but dissolves slowly in 5 per cent. sodium chloride. It swells up and slowly dissolves in 0·2 or 0·4 per cent. hydrochloric acid, with the formation of acid metaprotein.

If the clotting of blood be delayed or prevented by one of the methods described later (p. 194), and the blood be centrifuged, the corpuscles will settle to the bottom of the vessel, and the supernatant plasma can be poured off. If fibrinogen is precipitated from the plasma by the method described on p. 186 and then dissolved in weak salt solution, the solution usually clots, fibrin being formed.

The essential change in the coagulation of blood is therefore the conversion of fibrinogen into fibrin. The former substance is

no longer present in defibrinated blood or in serum. The process of clotting may be represented diagrammatically in this way :



When fibrinogen is freed from other substances by repeated precipitation, a solution of the pure substance is found to have lost the property of spontaneous coagulation. If, however, some blood-serum is added to such a pure solution, clotting will occur. It is clear, therefore, that at least two substances are necessary for the formation of fibrin, and that one of these is contained in blood-serum. If twenty volumes of alcohol are added to one volume of serum, a precipitate of serum-proteins is formed, and becomes insoluble in water if allowed to remain under alcohol for some days or weeks. If this precipitate be then dried and extracted with water, the solution so obtained will, if added to a solution of fibrinogen, cause the latter to clot. The watery extract contains a substance of unknown composition, which has been called *thrombin*.

We therefore find that the formation of fibrin is due to the interaction of fibrinogen and thrombin ; and, further, it has been shown that a combination of the two bodies takes place, because, if excess of fibrinogen be present, the amount of fibrin formed is proportional to the amount of thrombin added to it. The latter fact is opposed to the theory formerly held that thrombin belongs to the group of ferments. Moreover, fibrin can be partly broken down by treating it for some time with 8 per cent. sodium chloride solution, thrombin being set free.

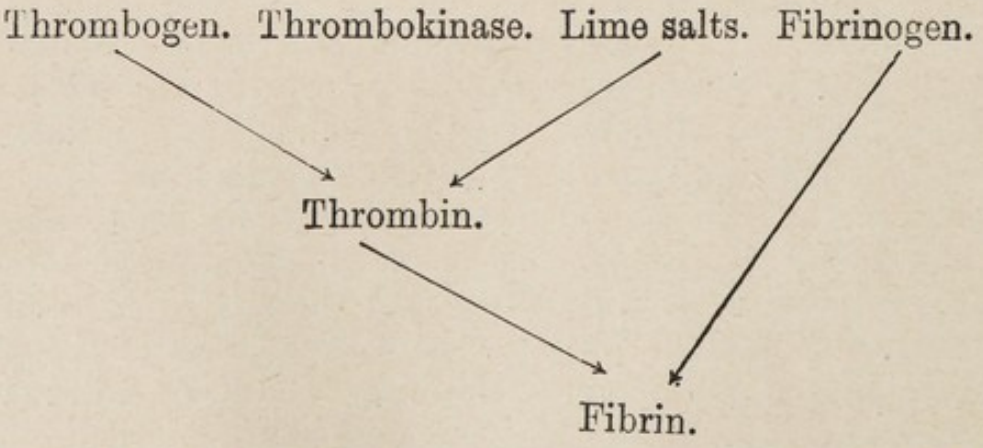
Thrombin itself is not contained in the blood-stream of the living animal. If blood is drawn directly from a blood-vessel into alcohol, it contains no thrombin, so that the latter body must be produced after the blood is shed. It has, in fact, been shown that it is derived from a precursor, which has been called *thrombogen*, by the combination of the latter substance with calcium salts. If freshly shed blood is mixed with potassium oxalate solution in such quantity that the mixture contains 0·1 per cent. of potassium oxalate, the calcium salts of the plasma are precipitated as calcium oxalate, and the blood will not clot. The subsequent addition of calcium chloride is followed by

coagulation. If, however, a solution of thrombin to which potassium oxalate has been added, is mixed with "oxalated" blood, clotting will take place, although no calcium is present. The presence of calcium is essential, therefore, to the formation of thrombin, but the thrombin, when once formed, will cause blood to clot, even when calcium salts are absent.

The formation of thrombin from thrombogen and calcium salts is brought about, or at least facilitated, by an activating substance called *thrombokinase*, which is derived in mammals mainly from the blood-platelets. If "oxalate plasma" from a mammal is allowed to stand for two or three days on ice, a precipitate of platelets collects at the bottom of the vessel. The plasma still contains thrombogen, but will no longer coagulate on the addition of lime salts. It will clot, however, if some of the precipitated platelets, or an extract of an animal tissue, be added to it along with the lime salts, the extra factor, obtained from the platelets or tissue, being thrombokinase. Again, the blood of birds contains no platelets, and will not clot if it is drawn directly from a blood-vessel without contact with the tissues. If, however, it is allowed to flow over the adjacent tissues in its passage from the vessel, or if a little tissue-extract is added to it, it will coagulate readily. Thrombokinase is therefore present in nearly all the tissues of the body as well as in the platelets, and this wide distribution facilitates the protective clotting of the blood which takes place on wounded surfaces. The leucocytes have also been supposed to discharge thrombokinase when blood is shed.

The facts described above in connection with the subject of the coagulation of the blood are generally accepted, but the exact interpretation of them put forward by different authors, as well as the nomenclature applied to the different substances concerned, varies somewhat.

The factors concerned in coagulation may be diagrammatically summarised as in the following table :—



Thrombogen, lime salts, and fibrinogen exist normally in blood.

When blood is shed, thrombokinase, derived from blood-platelets or from the tissues, brings about the combination of thrombogen and lime salts to form thrombin; thrombin then combines quantitatively with fibrinogen to form fibrin.

The Nature of Thrombin.—For many years thrombin was believed to belong to the group of ferments, but it has been shown (1) that it is not destroyed by boiling, and (2) that the amount of fibrin formed is in proportion to the amount of thrombin present. (1) Thrombin in watery solution is not affected by boiling, but thrombin contained in serum is inactivated by boiling. The inactivated substance in the latter case, however, is reactivated by the addition of alkali. The destruction of a ferment, on the contrary, at or somewhat below a temperature of 100° C. is one of its most characteristic features. (2) It is characteristic of a ferment that, if the products of its activity be removed, it will in time act upon all the substrate which is present. Thrombin, however, is used up in the formation of fibrin, so that if there is an excess of fibrinogen the surplus remains unchanged, unless fresh thrombin is added.

Blood does not clot in the vessels, and this must be due to one of two things: either an essential factor for coagulation is not present, or clotting is prevented by some agent which inhibits the process. With regard to the former possibility, fibrinogen exists in normal blood, calcium salts are undoubtedly present, and thrombogen must be a constituent of the blood in some form. If it be accepted that platelets are only formed when blood comes into contact with foreign matter, it would appear that the immediate precursor of thrombokinase is not in existence in the circulating blood. This has already been shown to be the case in birds, the blood of which contains no platelets. There is, therefore, good ground for believing that the circulating blood contains little or no thrombokinase. As regards the second possibility, evidence has been brought forward by some observers to show that a substance, *anticoagulin* or *antithrombin*, is a normal constituent of blood, and that it is formed in the liver. It is stated, for example, that the injection of thrombokinase or of thrombin into a blood-vessel results in the production of such an antibody, so that the blood becomes deficient in coagulating power, just as a precipitin is produced as the result of the injection of foreign protein. Hence it has been inferred that small quantities of thrombin are continually being produced in the blood, thrombokinase being also set free by the breaking down of white blood-corpuscles and of the tissues generally. The presence of thrombin leads to the formation of antithrombin in the liver, and in this way clotting in the blood-vessels is prevented.

Conditions which Accelerate Clotting.—The rate of coagulation is accelerated (1) by a certain degree of warmth, (2) by agitation of the blood, and (3) by increasing the extent of the foreign surface with which the blood is in contact. A practical application of the latter fact may be made by applying a sponge or cotton wool to a bleeding surface to aid in the arrest of hæmorrhage. It is probable that the foreign surface facilitates the formation and disintegration of platelets, with consequent increased production of thrombokinase.

Intravascular Clotting.—The rapid injection into the blood-stream of an animal of a quantity of a saline extract of a cellular organ, such as the thymus or a lymph-gland, leads to the coagulation of the blood throughout the whole vascular system. This result is generally ascribed to the presence of nucleo-protein in the extract. Small quantities of a similar extract, if slowly injected, have an opposite effect, rendering the blood incoagulable. The difference in the results, according to the quantity of extract injected, has not been satisfactorily explained. Intravascular clotting is also produced by the injection of thrombokinase or of the venom of certain snakes, but not by moderate quantities of thrombin.

Conditions which Retard or Prevent Clotting.—These may be classified as—

(1) Prevention of contact with a foreign surface.
(2) Removal of one or more of the substances concerned in the formation of fibrin.
(3) Interference with the interaction of the substances concerned in the formation of fibrin.
(4) The use of an anticoagulin, or the production of antithrombin by the injection of certain substances into the blood-stream before the blood is shed.

(1) Coagulation is delayed if blood is shed into a vessel the interior of which is smeared with grease of any kind. It is delayed for a longer time if the blood is kept in contact with the lining of a blood-vessel. If a large vein containing blood is ligatured in two places and the ligatured portion is excised, the blood in the vein, which is then known as a "living test-tube," may remain fluid for days.

(2) (*a*) Lime salts are precipitated by the addition of potassium oxalate or of sodium fluoride to blood. (*b*) Sodium fluoride precipitates not only calcium but also thrombogen, so that fluoride blood will not clot on the subsequent addition of lime salts. (*c*) Sodium citrate may also be used to prevent coagulation. It forms with calcium a double salt, calcium sodium citrate, which is soluble, and in which the calcium is combined with the acidic

radical and does not become a free ion. Calcium will not combine with thrombogen unless it is in the ionised condition. (*d*) If one volume of a saturated solution of magnesium sulphate be added to three volumes of blood, and the mixture be allowed to stand for twenty-four hours, the thrombokinase and thrombogen are precipitated and clotting will not take place on dilution. For the first few hours after the addition of the sulphate the clotting is merely retarded by the excess of salt, and the blood will clot if it is diluted.

(3) (*a*) Coagulation may be prevented by cooling freshly shed blood to 0° C. (*b*) The addition to the blood of an equal volume of saturated solution of sodium sulphate will prevent or delay clotting, but coagulation will take place when the mixture is diluted, showing that the action of the salt is purely mechanical. (*c*) Plasma is said to lose the power of coagulation when it is deprived of its lipoid constituents.

(4) Hirudin, a substance obtained by extracting the glands in the head of the leech, is an anticoagulin, and will prevent clotting either if added to shed blood or if previously injected into a blood-vessel. The injection of peptone will render blood incoagulable, and such blood, when added to blood shed in the ordinary way, will prevent coagulation of the latter ; but peptone itself has no retarding effect on coagulation when added to shed blood. From experiments such as these it is clear that peptone has no direct action in preventing coagulation, but that it leads to the production of an antithrombin, which is discharged into the circulating blood. This is apparently formed in the liver, since blood, containing peptone, which is perfused through the liver only becomes incoagulable.

Coagulation-Time.—The time taken for coagulation of a sample of blood may be conveniently estimated by means of Dale and Laidlaw's *coagulometer*. This consists of a short capillary tube containing a leaden shot. The finger is pricked and blood is run into the tube, which is then immersed in water at a selected temperature, the ends of the tube being closed. The tube is moved so as to keep the shot rolling until the latter stops dead with the tube vertical. The time between the appearance of blood on the finger and the stopping of the shot is the coagulation-time. It varies from one and a half minutes at 40° C. to about eight minutes at 19° C. for normal blood. After a severe hæmorrhage the coagulation-time of the blood is shortened.

THE TOTAL QUANTITY OF BLOOD IN THE BODY

The amount of blood in the body of an animal may be ascertained in the following way. A small sample of the animal's blood

is first taken, diluted 100 times with distilled water, and kept as a standard of comparison. The animal is then bled, and the blood-vessels are washed out with saline solution. Finally the animal is minced, and the tissues are extracted with distilled water to remove any remaining blood. The blood, saline washings, and watery extract are mixed, and a sample of the mixture is diluted till it is of the same tint as the standard sample. The amount of dilution being known, the total amount of blood can be calculated. Two experiments of this kind have been performed on the bodies of guillotined criminals, and from these it was found that the blood in man forms one-thirteenth of the weight of the body.

Haldane has devised a method for ascertaining the quantity of blood in the living subject. This method is based upon the affinity of hæmogloblin for carbon monoxide. A small quantity of blood is withdrawn, and its oxygen capacity, that is, the amount of oxygen with which it will combine, is estimated. The subject is then allowed to breathe air containing a known amount of carbon monoxide, say 120 c.c., which is absorbed by the blood. A certain proportion of the hæmogloblin of the blood combines with the carbon monoxide, forming carboxyhæmogloblin. A small quantity of blood is again withdrawn, and the proportion of its hæmoglobin which is combined with carbon monoxide is estimated by a colorimetric method. If one-sixth of the hæmogloblin is combined with carbon monoxide, and 100 c.c. of blood were shown to be capable of combining with 18 c.c. of oxygen, then, since carbon monoxide replaces an equal volume of oxygen, 100 c.c. of blood have taken up 3 c.c. of CO. The total volume of blood must thus be $100 \times \frac{120}{3} = 4000$ c.c. By this method the total blood has been calculated to be approximately one-seventeenth of the weight of the body.

Another method of measuring the volume of the blood has recently been introduced and is applicable to man. It consists essentially in injecting into the circulation a known amount of a dye, the one usually employed being *vital red*. After waiting three minutes to allow the dye to become uniformly distributed in the plasma, a sample of blood is withdrawn from a vein and centrifuged. The plasma is coloured red by the dye, and its depth of colour is matched against that of a known dilution of the dye in saline solution. Another sample of the individual's blood is centrifuged in a graduated tube in order to ascertain the relative amount of plasma and corpuscles in the blood. From these data the volume of the blood can be determined. If, for example, 1 c.c. of a 1 per cent. solution of the dye is injected, and the plasma, when subsequently withdrawn, matches in colour a 0·001 per cent.

solution of the dye, the dye injected into the blood has been diluted 1000 times by the plasma ; hence the volume of the plasma is 1000 c.c., and, if the plasma is found to form 50 per cent. of the blood, the total volume of the blood is 2 litres.

Results obtained by this method indicate that the blood forms approximately one-thirteenth of the body-weight, being on an average $5\frac{1}{2}$ to 6 kilograms. In health the volume is very constant, although it is said to be increased during pregnancy and also in individuals living at high altitudes.

CHAPTER VII

THE VASCULAR MECHANISM

SECTION I

The life of the muscles, of the nervous system, and of every tissue of the body, depends upon their receiving an adequate supply of food and oxygen; and one of the most important functions of the blood is to convey oxygen and nutritive material to the tissues, and to carry away carbon dioxide and waste products which are formed by the tissues. In order that this function may be carried out, the heart and blood-vessels furnish the mechanism by which a constant circulation of the blood throughout the body is maintained; and, by means of the central nervous system, the activities of this mechanism can be varied in response to the ever-changing needs, either of the body as a whole, or of its different parts.

The heart acts as a pump, and drives the blood along the arteries, through the capillaries and veins, and back to the heart. The actual interchange of nutritive material and waste products between the blood and tissues takes place solely through the walls of the capillaries, and the entire circulatory mechanism is adapted to maintain the conditions favourable to this interchange.

THE HEART AND BLOOD-VESSELS

The heart is a hollow muscular organ lying in the thorax between the lungs, and slightly to the left of the middle line of the body. It is conical in shape, the apex being directed downwards and to the left, and is divided by a septum into right and left halves, which do not communicate directly with each other. Each half consists of two chambers, an upper thin-walled auricle (atrium) and a lower thick-walled ventricle. Into the right auricle open the superior vena cava, bringing blood from the head and upper limbs, the inferior vena cava, conveying blood from the rest of the body, and the coronary sinus conveying blood

from the muscular substance of the heart itself. The right auricle opens into the right ventricle by an orifice guarded by a valve known as the tricuspid valve; this consists of three triangular cusps, arising from the fibrous junction between the auricle and ventricle and hanging down into the ventricle. The cusps consist of connective and elastic tissue, and are so arranged as to permit the flow of blood from auricle to ventricle, but not in the reverse direction. From each cusp a number of tendinous threads, *chordæ tendineæ*, pass to be attached to projections of the ventricular wall, known as the papillary muscles.

The right ventricle possesses two openings: (1) the auriculo-ventricular just described, and (2) the opening into the pulmonary artery, which conveys blood from the heart to the lungs. The latter opening is provided with a valve having three semilunar cusps composed of strong fibrous and elastic tissue. In the centre of the free border of each cusp is a small fibrous nodule, the corpus Arantii, which serves to strengthen the valve. When the valve is closed, the free borders of the cusps come into contact with each other and are pressed together, thereby preventing the return of blood from the pulmonary artery to the ventricle.

The general arrangement of the left side of the heart is very similar to that of the right side. Two pulmonary veins from each lung open into the left auricle. The auriculo-ventricular valve possesses only two cusps; it somewhat resembles a bishop's mitre, and is known as the mitral valve. The cusps, like those of the right auriculo-ventricular valve, are connected by tendinous cords with the papillary muscles and with the wall of the left ventricle. Opening out of the left ventricle is the aorta, which is provided with a valve having three semilunar cusps similar in structure to those of the pulmonary artery.

The cavities of the heart are lined by a smooth membrane, the *endocardium*, composed of delicate connective and elastic tissue covered by flattened endothelial cells.

The substance of the heart, *myocardium*, consists of muscular tissue bound together by connective tissue and supplied with blood from the coronary arteries. The muscle is arranged in sheets composed of fibres, which are built up of short cylindrical segments or cells; each cell has an oval nucleus and shows an indistinct longitudinal and transverse striation. The fibres are branched, the branches of adjacent fibres uniting with one another, so that the heart-muscle forms a continuous network of cells, known as a *syncytium*.

The wall of the auricles is composed of (*a*) superficial fibres common to both auricles, and (*b*) deep fibres, both looped and annular, proper to each auricle; the annular fibres form muscular

rings around the openings of the great veins. The auricles are joined to the ventricles by strong fibrous rings, which encircle the auriculo-ventricular orifices, and by a band of modified muscular tissue, known as the *auriculo-ventricular bundle*, the importance of which will be considered later.

The muscular fibres of the ventricles are arranged in a very complex manner. A superficial stratum runs in a spiral direction from the fibrous rings, which unite the auricles and ventricles, to the apex of the heart ; here the fibres form a whorl and then ascend in the inter-ventricular septum and on the inner surfaces of the ventricles, to end in the papillary muscles. Between the layers thus formed are deeper, transverse fibres, most of which are arranged in an S-shaped manner, springing from the papillary muscles of one ventricle and ending in the papillary muscles of the other ventricle ; they are united by muscular strands with the layers of the superficial stratum. The muscle is so arranged that, when contraction occurs, the cavities of the ventricles become smaller.

The wall of the left ventricle, which drives the blood through the greater part of the body, is approximately three times as thick as that of the right ventricle, which drives the blood only through the lungs ; the thin-walled auricles merely discharge their contents into the relaxed ventricles. The capacity of the two ventricles is approximately the same, amounting in each case to a maximum of 140 to 200 c.c. in man, and it is rather greater than that of the auricles.

The pericardium is a fibrous sac enclosing the heart, attached below to the diaphragm and lined by flattened cells ; where the great vessels pass through it the epithelial layer is reflected and covers the surface of the heart (*epicardium*). The inner wall of the sac is smooth and is moistened by a little lymph (pericardial fluid), so that the movements of the heart are carried out with hardly any friction. The pericardium also serves to prevent over-distension of the heart when it is being filled by the inflow of blood from the veins.

The Blood-Vessels.—*The arteries*, which convey blood from the heart to the capillaries, are thick-walled tubes made up of muscular and elastic tissue. A medium-sized artery shows three coats—outer, middle, and inner. The outer coat is composed of fibrous tissue. The middle coat consists of smooth muscle-fibres arranged circularly, and of yellow elastic fibres. The inner coat consists of flattened endothelial cells united edge to edge by a cement-substance, some loose connective tissue, and a thick elastic lamina next the middle coat. The middle coat of the large arteries, such as the aorta, contains a large proportion of elastic

tissue and a correspondingly small amount of muscle, whereas that of the small arteries (arterioles) is purely muscular.

The *capillaries* form a dense network round and among the tissue-elements in almost every part of the body, and consist of a single layer of flattened cells united by cement-substance. Their calibre varies slightly, but the average diameter is little wider than that of a red corpuscle.

The *veins* possess three coats, but their walls are thin, contain much less muscular and elastic tissue than the arteries, and are strengthened by the presence of a considerable amount of fibrous tissue, especially in the outer coat. Many veins have valves, consisting of fibrous tissue covered on each surface by endothelial cells, and so arranged that they allow blood to flow towards the heart, but prevent any flow in the opposite direction.

The arteries remain patent when divided, and a high internal pressure is required to distend their thick muscular and elastic walls, whereas the thin-walled veins collapse when opened and become distended under a very low internal pressure.

THE COURSE OF THE CIRCULATION

The heart beats rhythmically and gives on an average seventy to seventy-two beats a minute. The beat consists of the contraction of the auricles, followed almost immediately by that of the ventricles, and is succeeded by a pause, during which the whole heart is completely relaxed. The contraction of the auricles and ventricles is spoken of as auricular or ventricular *systole*, the period of relaxation being called *diastole*. At each beat the ventricles expel blood into the aorta and pulmonary artery, from which it is distributed by the former to the body as a whole, and by the latter to the lungs.

The blood entering the aorta from the left ventricle is conveyed by the arteries arising from it to the capillaries of the various organs of the body, with the exception of the lungs. From these organs it is returned by veins, which unite with each other, eventually forming the venæ cavæ; these open into the right auricle. The blood passes from the right auricle into the right ventricle, from which it is forced into the pulmonary artery; it then flows along the subdivisions of this artery through the pulmonary capillaries into the pulmonary veins (two from each lung), and thence into the left auricle. From the left auricle the blood enters the left ventricle and is again sent out into the aorta (fig. 81).

In the abdomen, the blood passes through a double set of capillaries. The veins from the digestive tract and spleen unite

to form a single large vein, the portal vein, which on reaching the liver again breaks up into capillaries; these open into the hepatic veins, which join the inferior vena cava. This arrangement is called the *portal circulation.*

The complete circulation consists, therefore, of two parts, the one from the right side of the heart through the lungs and back to the left side of the heart, known as the *pulmonary* or *lesser* circulation, and the other from the left side of the heart throughout the rest of the body and back to the right auricle, forming the *systemic* or *greater* circulation. As the blood traverses the lungs it takes up oxygen, becoming scarlet in colour (arterial blood). Arterial blood is found in the pulmonary veins, in the left side of the heart, and in the systemic arteries. During its passage through the capillaries in the various tissues the blood loses much of its oxygen, receives carbonic acid, and becomes darker in colour (venous blood). The venous blood is carried along the systemic veins to the right side of the heart and into the pulmonary artery to take up a further supply of oxygen from the lungs.

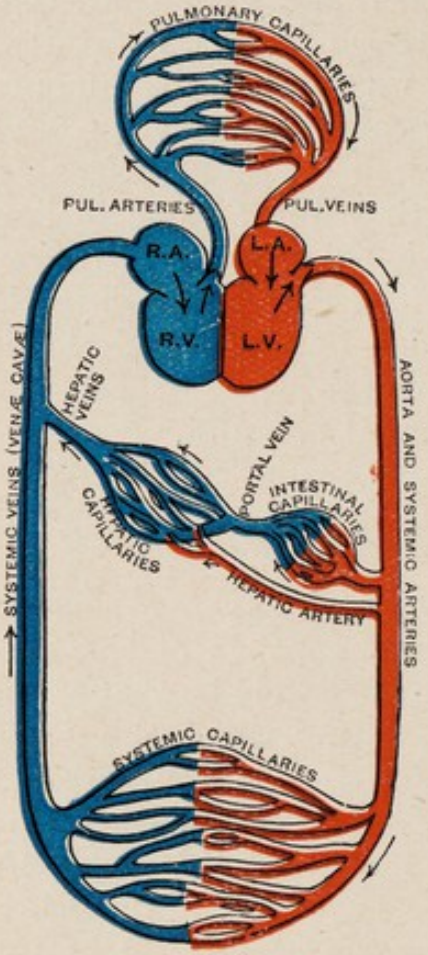


FIG. 81.—Diagram showing the course of the circulation.

Red represents arterial blood; blue represents venous blood. R.V. right ventricle. L.V., left ventricle.

THE BLOOD-PRESSURE

When an artery is cut across, the blood spurts out from its central end (the end nearest the heart) with considerable force and for some distance; and, evidently, the blood contained in the arteries is exerting a high pressure upon the wall of the vessels. When a vein is divided, the blood escapes from its peripheral end in a slow, steady stream.

The arterial blood-pressure can be measured by allowing the blood to flow into a vertical glass tube tied into the central end of a divided artery. The blood will be seen to attain a height of three or four feet or more, and to show oscillations corresponding with each heart-beat. The pressure inside the artery is then equal to that exerted by the column of blood. The method is un-

satisfactory, partly because the clotting of the blood in the tube soon brings the experiment to an end, partly because, in a small animal, the loss of blood from the body may interfere with the circulatory mechanism. It is customary, therefore, to place in the artery a small cannula, filled with a half-saturated solution of sodium sulphate to delay clotting, and to connect the cannula with one limb of a U-shaped tube (manometer) containing mercury. The height in millimetres of a column of mercury which just counterbalances the pressure of the blood in the arteries, and prevents the blood from escaping into the cannula, is taken

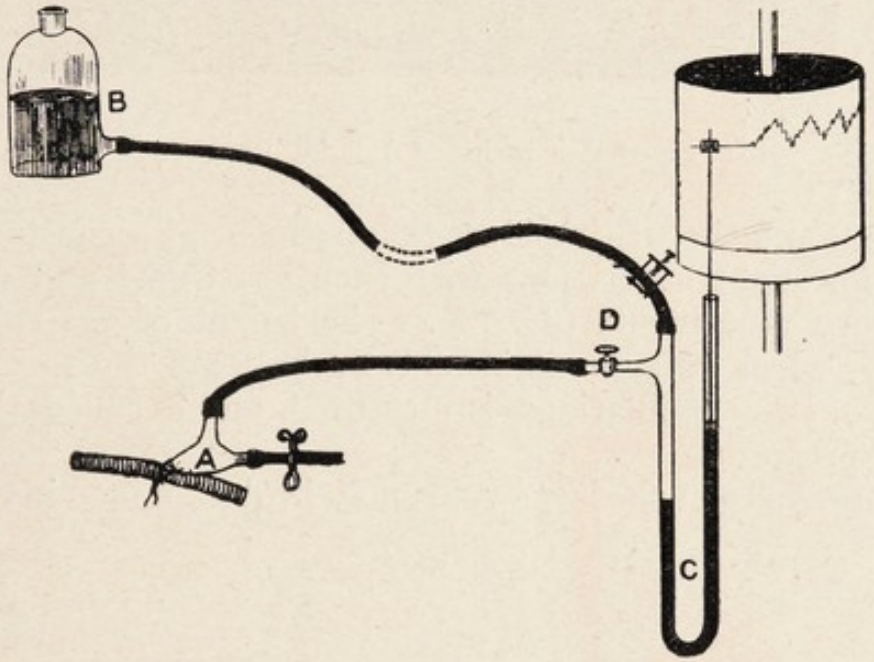


FIG. 82.—Apparatus for taking a blood-pressure tracing.
A, cannula inserted in an artery; B, pressure-bottle; C, mercurial manometer.

as a measure of that pressure; and the arterial pressure is said to be so many (*e.g.* 100) mm. Hg. A writing point attached to a float resting on the mercury in the other limb of the manometer can be used to record the pressure on a moving, smoked surface (kymograph).

The following method is used (fig. 82). An artery (such as the carotid or femoral) is exposed in an anæsthetised animal, and the flow of blood is shut off by a clip. The artery is ligatured about 2 or 3 cm. beyond the clip, opened between the clip and the ligature, and a cannula containing a half-saturated solution of sodium sulphate is tied into it. This cannula is connected by thick rubber tubing with a bottle containing a half-saturated solution of sodium sulphate, and with one limb of the manometer. By raising the bottle the cannula and connecting tubing can be filled with sodium sulphate solution under such pressure that the column of mercury in the limb to which the float is attached

rises from 100 to 150 mm. higher than the column in the limb connected with the artery. The connection between the pressure-bottle and the manometer is then shut off by a screw-clamp, and the clip is removed from the artery. The column of mercury rises or falls slightly until its pressure counterbalances that of

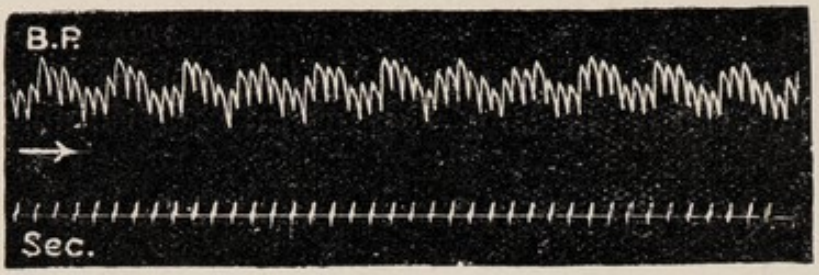


FIG. 83.—Tracing of Arterial Pressure.

the blood, and the writing lever then remains at a constant level, except for slight oscillations with each heart-beat and with the respiratory movements (fig. 83). The height of the column of mercury, when its summit is midway between the top and the bottom of these oscillations, is measured, and is called the *mean* arterial pressure.

The pressure in the large veins may be determined in a similar

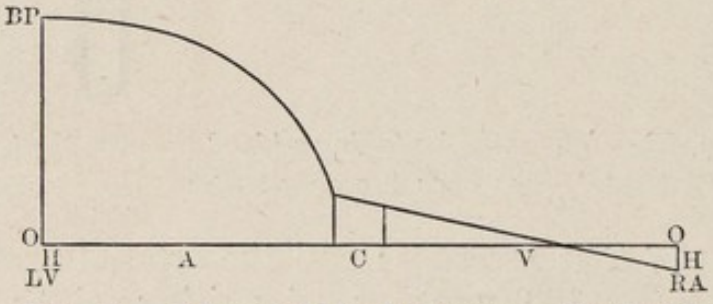


FIG. 84.—Scheme of blood-pressure. (Starling's *Principles of Physiology.*)

LV, left ventricle; A, arteries; C, capillaries; V, veins; RA, right auricle; OO, line of no pressure; BP, blood-pressure; H, heart.

manner, except that, as the pressure is low, the whole manometer is usually filled with sodium sulphate solution.

Observations made in this way show that, whereas in a systemic artery the mean blood-pressure may vary from 100 to 140 mm. Hg, and alters slightly with each heart-beat and respiratory movement, the venous pressure amounts only to a very few mm. Hg, and is not affected by the heart-beat. It is found that the arterial pressure is highest in the aorta, rather less in the medium-sized arteries, and that there is an abrupt fall of pressure in the arterioles; in the capillaries the pressure is low,

and finally there is a further fall of pressure in the veins until, in the large veins near the heart, it may actually be negative, that is, less than the atmospheric pressure. These differences of pressure are diagrammatically represented in fig. 84. The pressure in the pulmonary artery varies from 20 to 25 mm. Hg, and on the average is about one-sixth of that in the aorta or its main branches.

We may now consider the factors which are concerned in this distribution of pressure, and in the conversion of the jerky flow of blood in the arteries into a continuous flow in the capillaries and veins.

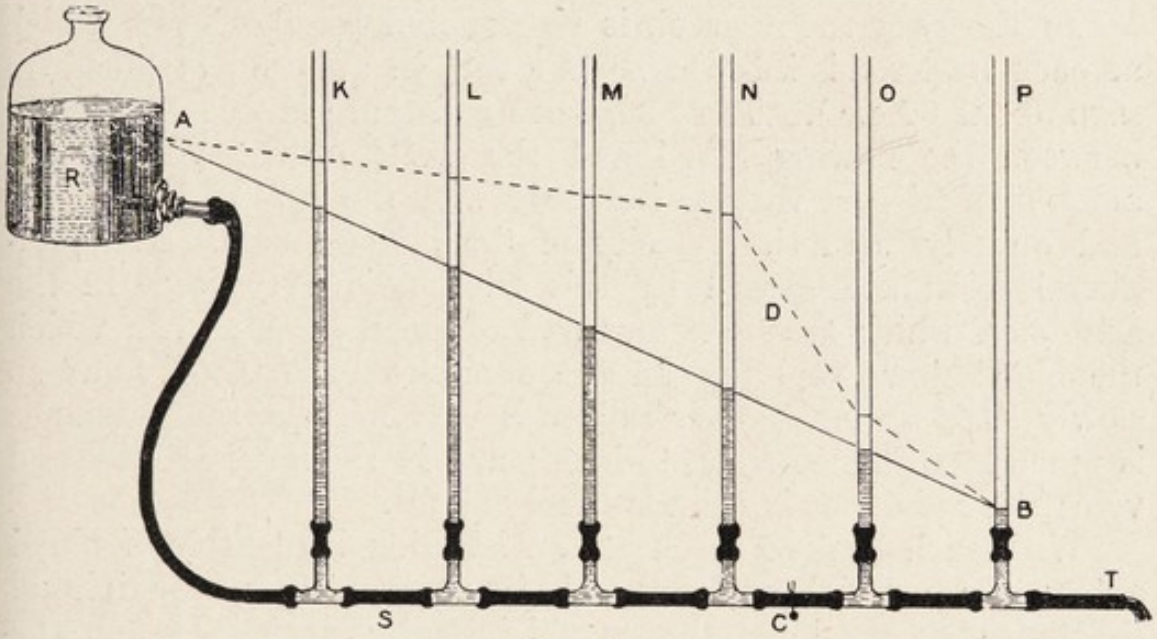


FIG. 85.

They are (1) the beat of the heart, (2) the elasticity of the arteries, and (3) the peripheral resistance.

The action of these factors is a purely mechanical one, and can be reproduced in an artificial scheme such as is shown in fig. 85. A reservoir R containing a coloured fluid is attached to a horizontal rubber tube ST open at its other end, and a number of vertical glass tubes open at the top are connected with this tube at equal distances from one another. As the fluid flows from the reservoir, it rises in the vertical tubes to a height corresponding with the pressure at that point, and the line AB joining the top of the columns of fluid in the tubes shows that there is a uniform fall of pressure along the rubber tube. The pressure falls because of the friction between the fluid and the wall of the tube; owing to the friction, there is some resistance to the flow of fluid along the tube and the hydrostatic pressure is gradually used up in overcoming this resistance. If a screw-clip is placed on the rubber

tube at C and gradually tightened, thereby introducing a greater resistance to the flow of fluid along the tube, the pressure rises on the proximal side, and falls on the distal side, of the clip, the pressure gradient along the tube being indicated by the dotted line, A, D, B.

When the flow of fluid from the reservoir is made intermittent by alternately compressing and releasing the connection between it and the tube at short intervals, the fluid in the vertical tubes K, L, M, and N, between the reservoir and the resistance at C, shows corresponding oscillations in height, whereas in the tubes O and P, beyond C, these oscillations are absent, and fluid flows from the end of the rubber tube in a steady stream.

In the body the reservoir is represented by the heart, which at each beat sends into the aorta a certain quantity of blood (in man about 60 c.c.). The peripheral resistance is due to friction between the flowing blood and the walls of the vessels, the amount of friction varying inversely with the bore of the vessels and directly with the velocity of the blood-stream. The peripheral resistance caused by this friction is very large in the arterioles, which are numerous and of small bore, and in which the blood flows rapidly. In the capillaries the blood flows so slowly that, although their calibre is very minute, the resistance is much less than in the arterioles ; and in the large arteries and veins the resistance is comparatively slight.

With each beat of the heart an additional quantity of blood enters the arterial system, and, if there were no peripheral resistance, an equal quantity would *instantly* escape through the arterioles into the capillaries. But the resistance offered by the arterioles is so great that, when the blood is forced during systole into the already distended arterial system, there is not an immediate escape of a corresponding amount from the arteries into the capillaries. The force exerted by the heart at each beat is used, partly in driving the blood through the arteries into the capillaries during the beat, and partly, indeed chiefly, in distending the arteries so that they can accommodate the additional blood sent into them, while the pressure within them rises. The energy expended by the heart during systole is thus, to a large extent, momentarily stored in the arteries as potential energy ; and during diastole this energy again becomes kinetic, the arteries shrinking by virtue of their elasticity and thereby forcing blood in a steady stream through the arterioles into the capillaries, with a consequent fall in the arterial pressure. The result is that an intermittent supply of blood to the aorta is converted into a continuous flow in the capillaries and veins.

When the amount of blood entering the arterial system during

systole is equal to that leaving it, partly during systole and partly during diastole, the mean arterial pressure remains steady. Any increase or decrease in the amount of blood entering the aorta at each beat will tend to raise or lower the arterial pressure. Similarly dilatation of the arterioles will allow more blood to leave the arteries with each beat, the arteries will therefore be less distended with blood, and the pressure on their walls (arterial pressure) will diminish. Conversely, constriction of the arterioles will diminish the outflow from the arteries, and will lead to a rise of arterial pressure.

Although the driving force of the heart-pump is sufficient to propel the blood round the body and back to the heart, its action is normally assisted (1) by the respiratory movements, which will be considered later (p. 276), and (2) by skeletal muscular movements. Every muscular movement tends to squeeze blood along the veins towards the heart, any reflux being prevented by the valves with which these veins are provided.

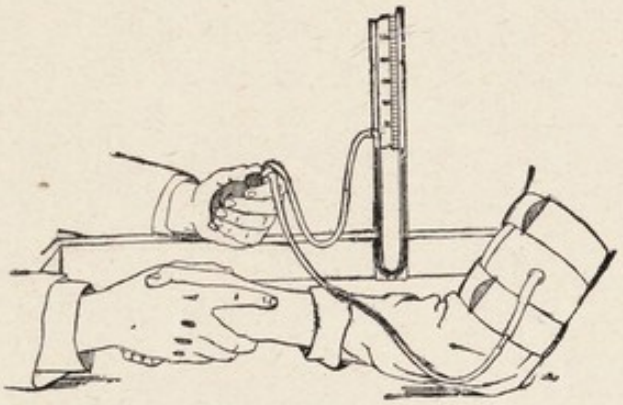


Fig. 86.—Riva-Rocci sphygmomanometer. (From Messrs. Hawksley.)

BLOOD-PRESSURE IN MAN

Arterial Pressure.—The highest blood-pressure occurring during the cardiac systole is called the *systolic* pressure; the pressure at the end of diastole is the *diastolic* pressure, the difference between the two being called the *pulse*-pressure. The systolic pressure is measured by means of a Riva-Rocci sphygmomanometer. This consists (fig. 86) of a leather band about four inches wide, inside which is a rubber bag communicating with a mercurial manometer and connected with a small pressure-bulb. Attached to the bulb is a screw by which the bag can be put into communication with, or shut off from, the external air.

The band and the bag are fastened round the upper arm. The observer feels the radial pulse with the fingers of one hand, while with the other he squeezes the bulb and distends the bag with air. The leather band does not stretch, and the pressure of the rubber-bag, as it distends, is exerted entirely on the arm, and compresses the blood-vessels; at the same time the pressure rises in the manometer. The bulb is squeezed until the pressure in the bag is just sufficient to obliterate the brachial artery and

the radial pulse disappears. When this occurs, the pressure in the bag is equal to that in the manometer, and is noted. The screw attached to the bulb is then gently turned, the air slowly escapes, and the pressure falls; when the radial pulse is just perceptible, the pressure in the manometer is again observed. The mean between the two readings is the *systolic arterial pressure*. This represents the pressure on the outer wall of the artery which exactly balances the greatest pressure within the artery during systole, and at which the lumen of the artery is just obliterated.

If air is allowed gradually to escape from the bag after the systolic pressure has been determined it will be observed that at a certain point the oscillations of the mercury and the radial pulse show a maximal excursion with each beat of the heart. This is

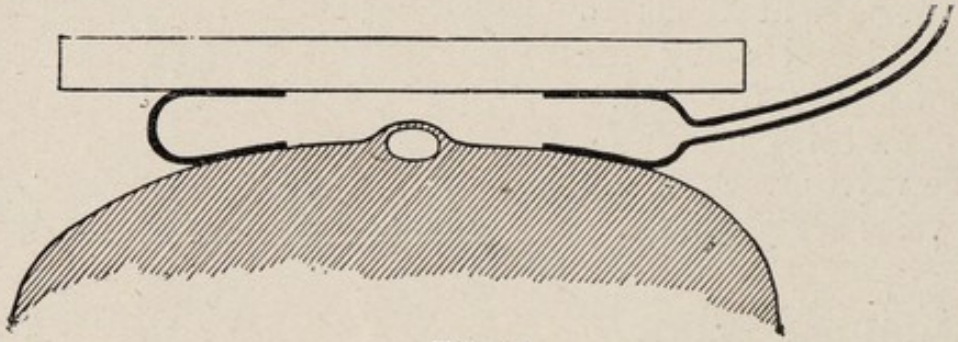


FIG. 87.

(From Starling's *Principles of Physiology*.)

due to the fact that the systolic pressure is sufficient to distend the vessel, whereas between the beats of the heart the artery is collapsed. The pressure in the bag at this point represents the *diastolic* pressure, and the lowest level of the manometer *between* the beats gives a record of the diastolic pressure. By measuring the diastolic and systolic pressures, the *pulse-pressure*, which is the difference between them, can be determined. The systolic pressure in the healthy adult varies in the large arteries, such as the brachial, from 100 to 110 mm. Hg; it becomes higher with increasing age, and at fifty, even in health, is about 140 to 150 mm. Hg. It is temporarily raised during muscular or mental work, and falls again during rest.

A modification of this method of measuring arterial blood-pressure in man is the *auditory method*, in which the flow of blood along the artery peripherally to the rubber bag is ascertained, not by feeling the radial pulse, but by listening through a stethoscope to the sounds produced in the brachial artery at the bend of the elbow. When a full stream of blood is flowing along the vessel, a continuous rushing sound is heard. When the pressure

exerted by the rubber-bag is equal to the diastolic pressure, the sound is altered to a series of sharp reports synchronous with the heart-beats. As the pressure in the bag rises still higher, these reports become fainter, and they finally cease to be heard when the pressure in the bag (and manometer) is just above the true systolic pressure.

Venous Pressure is measured in the following manner :—A flat rubber bag, having a hole through the centre of each flat surface (fig. 87), is placed over a peripheral vein and covered by a glass plate, the junctions being made air-tight with glycerol ; a tube leads from the bag to a manometer and to a pressure-bulb. Air is blown into the bag, the glass plate being firmly held in position ; when the pressure reaches a certain height the vein collapses, and the reading of the manometer represents the venous pressure. The same method, a smaller bag being used, may be employed to determine *capillary pressure*, the collapse of the capillaries being indicated by blanching of the skin. The capillary pressure is from 15 to 40 mm. Hg. The venous pressure varies from 8 to 10 mm. Hg in the smaller veins ; in the large veins near the heart it is only 1 or 2 mm. Hg, and may be negative.

VELOCITY OF THE BLOOD-FLOW

The rate at which fluid flows along a tube, the bore of which is constant, depends solely upon the amount of fluid entering the tube in a given time. The same principle holds good in the body, and, provided the calibre of the blood-vessels remains unchanged, the *actual* velocity of the blood-stream as a whole is determined by the amount of blood expelled from the heart into the aorta in a given time, that is to say, it depends upon the driving force of the heart-pump. If the heart ceases to beat, the circulation comes to a standstill ; if the heart is beating feebly, very little blood enters the aorta, and the blood flows slowly round the body. If, however, the heart is beating forcibly and frequently, the velocity of the blood-flow may be considerable. These differences are of importance, since the rate at which oxygen is carried from the lungs to the various tissues of the body is determined by the rapidity of the circulation.

The *relative* velocity of the blood-flow in the arteries, capillaries, and veins is determined solely by the total width of the channels through which the blood is flowing. Since the same quantity of blood has to pass in a given time through each cross-section of the bed of the vascular system, it is obvious that the smaller the cross-section the greater must be the velocity of the blood-flow. For the same reason water flows rapidly in a river where the

channel is narrow, and slowly where the channel widens out into large pools.

When an artery divides, each branch is smaller than the parent artery, but the total cross-section of the two branches is larger than that of the parent artery. The total cross-section of the vessels thus increases with each branching, and in the capillaries it has been estimated to be about 800 times as great as that of the aorta. The sectional area of the veins gradually decreases as they unite to form larger vessels, and that of the large veins entering the heart is approximately twice as great as that of the aorta. It has been found that whereas the average velocity of the blood in the large arteries is about 400 to 500 mm. a second, it varies from $\frac{1}{2}$ to 1 mm. a second in the capillaries, and is from 200 to 250 mm. a second in the large veins.

In a small organ, such as the kidney or submaxillary gland, the velocity of the flow of blood is also modified by *local* changes in the arterioles. Dilatation of the arterioles lessens the resistance to the flow of blood through the organ without affecting the general arterial blood-pressure, and, since the resistance to the blood-flow is lessened in that organ as compared with other organs in the body, the blood flows through that section of the circulatory system with increased velocity and in larger amount. This result, which furnishes an apparent exception to the general statement made above, occurs only when the organ is so small that alterations in the calibre of its arterioles do not appreciably affect the general blood-pressure.

Methods of Measuring the Velocity of the Blood-Flow—(1) **Ludwig's Stromuhr.**—This consists of two glass vessels A and B connected at the top (fig. 88). On A is a mark *c*, the capacity of the vessel between the mark *c* and the opening *a'* being exactly known. These vessels are fixed at their lower ends into a metal disc H, placed upon a similar disc N, and capable of being rotated upon the latter through two right angles. The openings *a'* and *b'* in the upper disc fit exactly over those (*a* and *b*) in the lower disc; from these openings in the lower disc arise two tubes F and G. The experiment is carried out as follows:—A clip is placed on an artery; the artery is then divided distally to the clip and one end of it is connected with tube F, the other with tube G. The vessel A, which communicates with the proximal end of the artery, is filled with olive oil up to the mark *c*, and the remainder of the apparatus is filled with defibrinated blood or saline solution. The blood is then allowed to flow from the artery through F into A, thus driving the oil over into B and sending the defibrinated blood into the peripheral end of the artery. As soon as the blood leaving the artery reaches

the mark *c*, the disc H is rapidly turned through two right angles, and the blood flowing from the artery now drives the oil back into A. When the oil again occupies its original position, the disc is once more rotated through two right angles. This process is repeated as often as necessary, the experiment being carried on for any desired period ; clotting of the blood can be prevented by the previous injection of hirudin into the animal. The diameter of the artery is then measured. From these data the

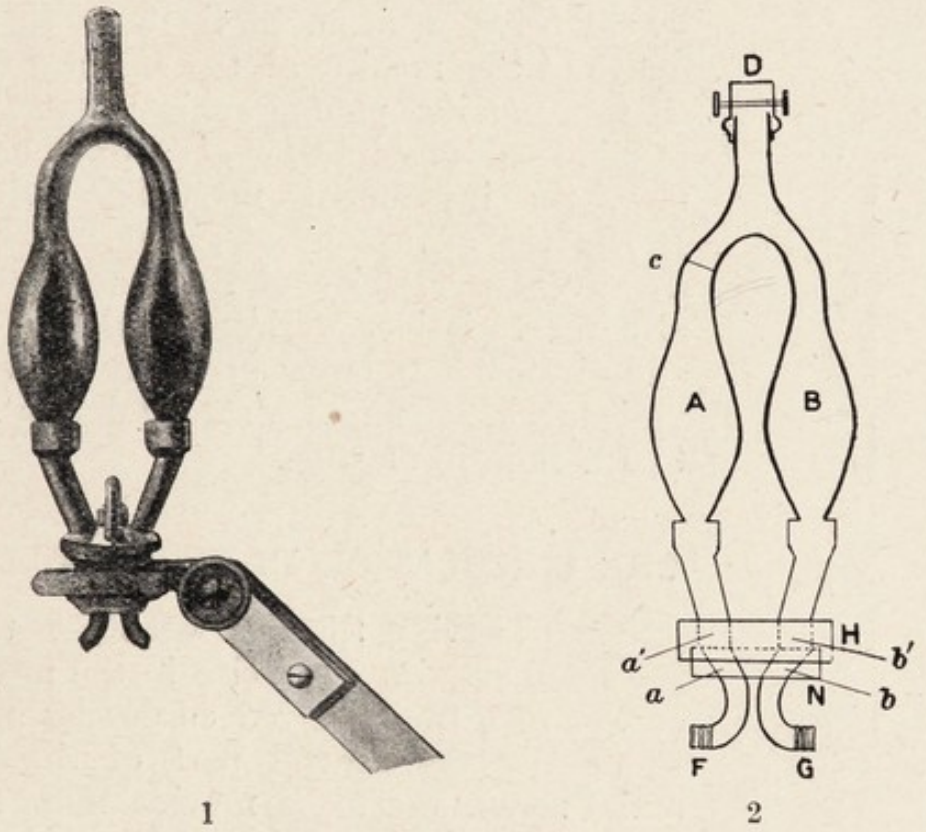


FIG. 88.—1, Ludwig's stromuhr ; 2, Diagrammatic representation.

velocity of the blood-flow can be calculated by means of the formula

$$\text{Velocity} = \frac{\text{volume (passing through the stromuhr) per second}}{\text{sectional area of blood-vessel}}$$

If the capacity of the bulb up to the mark *c* is 5 c.c., and it was filled six times in a minute, then the amount of blood passing through the instrument would be 30 c.c. in one minute, or $\frac{1}{2}$ c.c. in one second. Supposing the diameter of the artery to be 2 mm., the sectional area is πr^2, and the rate of flow can be calculated as follows :—

$$\text{Velocity} = \frac{0{\cdot}5 \text{ c.c.}}{3{\cdot}1416 \times 1^2} = \frac{500 \text{ c.mm.}}{3{\cdot}1416} = 159 \text{ millimetres per second.}$$

Many other instruments have been devised, of which the

most useful is the photohæmatachometer of Cybulski. This consists of two vertical tubes united at the top, and opening below into a horizontal tube, as shown diagrammatically in fig. 89. The proximal end of an artery is attached to the instrument at A, the blood escaping at B into the distal end of the artery. The blood will rise higher in the tube C than in the tube D, the difference in height of the two columns being directly proportional to the velocity of the blood-flow in the artery. A graphic record is obtained by allowing a beam of light to throw an image of the menisci of the columns of fluid on to a moving photographic plate. To determine the absolute velocity of the blood-flow, the instrument must be calibrated. It has the advantage of giving, not merely the average velocity of the blood-flow, but also the variations during ventricular systole and diastole. In one experiment the velocity varied from 250 mm. per second during systole to 127 mm. in diastole.

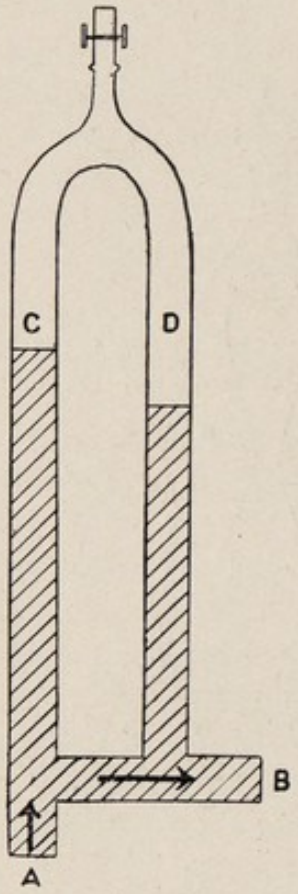


FIG. 89.—Diagram showing the principle of Cybulski's photohæmatachometer.

THE CIRCULATION IN THE CAPILLARIES

On observing the flow of blood through the small arteries and veins in the mesentery or web of a frog, the red corpuscles are seen to occupy the central part of the vessels (axial zone), and to be moving more rapidly than the peripheral layer of blood, in which are found most of the leucocytes. The formation of the axial zone is due to the fact that the specific gravity of the red cells is higher than that of the plasma. The lumen of the capillaries is so small that no axial zone is present. The velocity of the blood-flow in the capillaries can be directly observed with the aid of an eye-piece micrometer by noting the time taken by a red corpuscle to travel a given distance, and varies from 0·5 to 0·8 mm. per second; and, as the average length of a capillary is from 0·4 to 0·8 mm., any one corpuscle traverses the capillary in one second. During this time the interchange of oxygen and of carbonic acid, and of nutritive and waste material, between the blood and the tissues takes place through the capillary wall. The capillary pressure is intermediate between that in the arteries and veins, and is very easily influenced by a rise or fall in venous pressure.

If an irritant, *e.g.* dilute acetic acid, is applied for a moment or two to the surface of the frog's mesentery, the minute arterioles and the capillaries soon become dilated, and the blood flows more rapidly through them. Presently the leucocytes begin to adhere to the capillary walls, and some of them make their way through the interstices between the epithelial cells into the surrounding tissue, this being called *diapedesis*. At the same time, the capillary wall undergoes some alteration which allows much of the blood-plasma to pass through the walls of the capillaries into the lymph, and the blood remaining in the capillaries becomes more viscid. This increases the resistance to the flow of blood along the capillaries and the flow slackens and may cease, although the capillaries and arterioles are still dilated. Owing to the loss of plasma the capillaries ultimately become filled with a mass of red and white corpuscles. Sometimes the red corpuscles are also forced through the capillary walls. This series of events forms part of the process of *inflammation*, which is defined as the response of the tissues to an injury, provided the latter does not cause death at once. The injury may be mechanical or may be brought about by chemical substances, including bacterial products.

THE TIME OF THE CIRCULATION

One of the best methods for determining the circulation-time is to inject into one jugular vein a strong solution of methylene blue; the jugular vein on the opposite side is exposed and allowed to rest on a strip of white paper. The interval between the injection and the moment at which the blue colour becomes visible in the opposite vein is observed; it varies from 15 to 20 seconds.

Another method consists in sending a compensated electric current through a section of an artery, *e.g.* the left carotid, and through a galvanometer. A little concentrated salt solution is injected into the opposite carotid artery. When the salt is injected, it increases the conductivity of the blood, and as soon as the solution reaches the left carotid artery the electric current passes more easily through the artery, the compensation is upset, and the needle of the galvanometer is deflected.

The time thus measured represents, however, merely the time in which a blood-corpuscle can complete the shortest possible circuit in the circulatory system; and the average circulation-time of the blood as a whole is probably twice or thrice as long as that found by these methods.

SECTION II

THE PHENOMENA OF THE NORMAL HEART-BEAT

(1) **Changes in Form.**—Observation of the heart, exposed in an anæsthetised animal, shows that the beat begins with contraction of the great veins near the heart, and is followed immediately by the contraction of both auricles (atria), including their appendices. After a brief interval, known as the auriculo-ventricular interval, the ventricles contract synchronously, assuming the form of a short truncated cone. During their contraction the ventricles become shorter from above downwards, and, as the position of the apex remains almost unaltered, the auricles are pulled down towards the apex, and the aorta and pulmonary artery are stretched longitudinally. At the same time, the cross-section of the base of the ventricles alters, becoming more nearly circular and smaller. When the contraction of the ventricles ceases, the whole heart remains for a short time at rest.

(2) **The Sequence of Events within the Heart.**—During diastole the blood is flowing steadily into the right auricle from the great veins, and through the auricle into the right ventricle, into which the cusps of the open tricuspid valve are hanging. When the auricle contracts, it empties most of its contents into the ventricle, and thus completes the filling of the ventricle. Since the auricular contraction begins in the muscular rings forming the termination of the great veins, there is no reflux of blood along these veins. The ventricle, which is now full of blood, contracts almost immediately after the termination of the auricular systole, and the cusps of the tricuspid valve, which have already been carried towards each other by eddies set up behind them as the blood flowed from the auricle into the ventricle, are driven firmly into apposition by the pressure of the blood, their thin borders being tightly pressed together so that no blood can escape into the auricle. The contraction of the papillary muscles keeps the chordæ tendineæ taut, thereby preventing any inversion of the valve under the ventricular pressure.

The ventricle is now a closed cavity, and remains so until the pressure exerted by the contracting muscle upon the contained blood rises higher than that in the pulmonary artery. As soon as this happens, the semilunar valves open, and blood is driven into the pulmonary artery from the ventricle, which becomes nearly, but not quite, empty. When the systole of the ventricle ends, its walls relax, and the pressure in its cavity very rapidly falls below that in the pulmonary artery; as soon

as this occurs, the semilunar valves close, effectually preventing any reflux of blood into the ventricle. A fraction of a second later, the pressure in the ventricle becomes less than that in the right auricle, the auriculo-ventricular valve opens, and blood, which during the ventricular systole has been flowing into the auricle from the veins, again begins to enter the ventricle. The valves open or close with the slightest difference of pressure on either side. During ventricular systole the efficiency of the tricuspid valve is assisted by the diminution of the cross-section of the base of the heart. A similar series of changes takes place simultaneously in the left side of the heart (fig. 90).

The series of events just described constitutes a *cardiac cycle*,

FIG. 90.—Diagram to show the position of the mitral valve in ventricular systole (1), and in diastole (2).
A, auricle; V, ventricle.

and occupies on the average a period of 0·8 second. The cycle may be regarded as beginning with the auricular systole, which lasts 0·1 second and is followed by the ventricular systole, lasting approximately 0·3 second; during the remainder of the cycle, 0·4 second, the heart is completely relaxed. When the heart is beating slowly the duration of the cycle is lengthened, and when the heart is beating frequently it is shortened. These differences are due almost entirely to variations in the time occupied by the diastolic pause, the time taken up by the systole of the auricles and ventricles being remarkably constant.

(3) **Cardiac Impulse.**—If the hand be placed on the chest in man, an impulse will be felt corresponding with each heart-beat. It is most distinctly felt, and is often also visible, in the fifth intercostal space, about an inch below, and slightly internal to, the nipple. The impulse is due to a combination of two causes. In the first place, the left ventricle, which lies in contact with the chest-wall and is soft and flabby during diastole, becomes hard and tense with the onset of systole. The sudden hardening

of the ventricle gives a push to the soft tissues of the chest-wall with which it is in contact, thereby giving rise to the cardiac impulse. In the second place, the curved aortic arch tends to straighten out when the tension within it is raised by the entrance of blood from the heart. The same phenomenon may be readily observed in any curved elastic tube filled with fluid, into which more fluid is suddenly forced. The posterior end of the aortic arch rests against the vertebral column and ribs, and cannot alter its position; the anterior end, to which the heart is attached, is, therefore, pushed towards the chest-wall, carrying the heart with it.

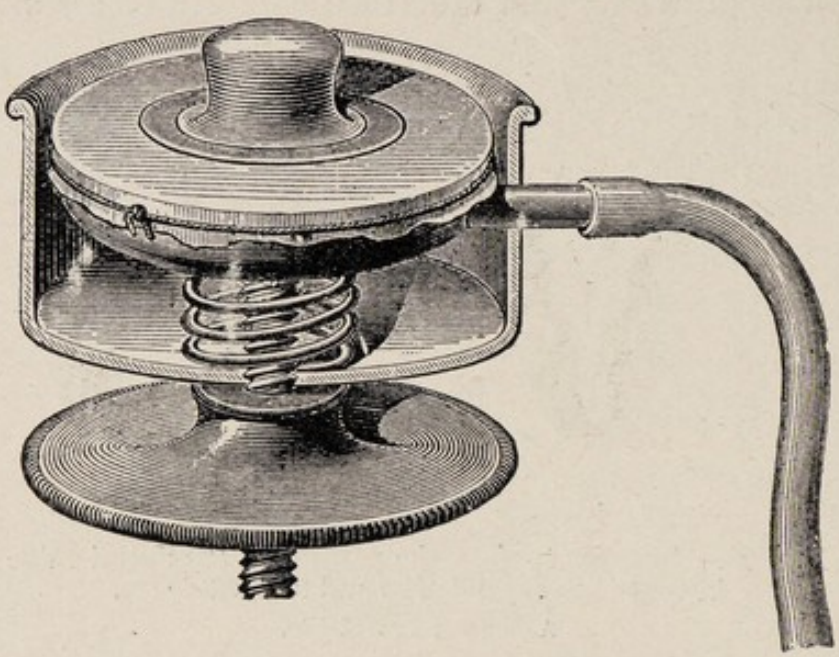


FIG. 91.—A cardiograph. (From Messrs. Baird & Tatlock.)

Although this impulse is often spoken of as the "apex-beat," the area of the left ventricle which is in contact with the chest-wall is some distance above the actual apex of the heart.

A graphic record of the cardiac impulse (cardiogram) is obtained by means of an instrument known as a *cardiograph*. One form of cardiograph (fig. 91) consists of a tambour, the membrane of which is provided with an ivory button which can be placed on the chest at the position of the cardiac impulse: the tambour is connected with a second tambour (fig. 94) provided with a recording lever. Another method of obtaining a cardiogram is to use a small metal cup, having at its base an opening by which it is connected with a tambour and recording lever; the cup is pressed on to the chest-wall in the region of the cardiac impulse. The general form of the tracings is shown in fig. 92, but it varies considerably with the pressure used and with the spot at which the instrument is applied to the chest.

(4) **The Heart-Sounds.**—If one listens through a stethoscope applied to the front of the chest, two sounds are heard with each

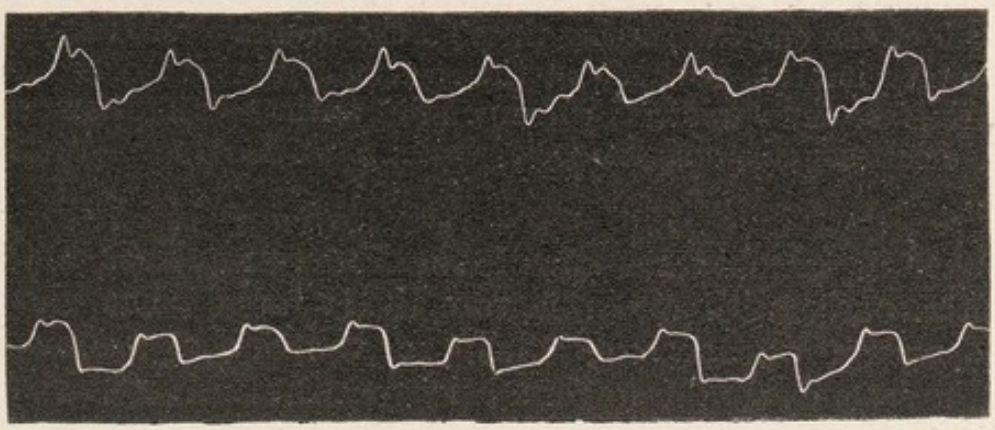


FIG. 92.—Two cardiograms obtained in man. To obtain the upper tracing the cardiograph was *lightly* pressed on the chest-wall. In the lower tracing the cardiograph was pushed *firmly* against the chest-wall. Upstroke = systole.

beat of the heart. They are often compared with the sounds lŭbb dŭp, the first being long and low-pitched, the second short and sharp.

The time relation between the heart-sounds and the other events

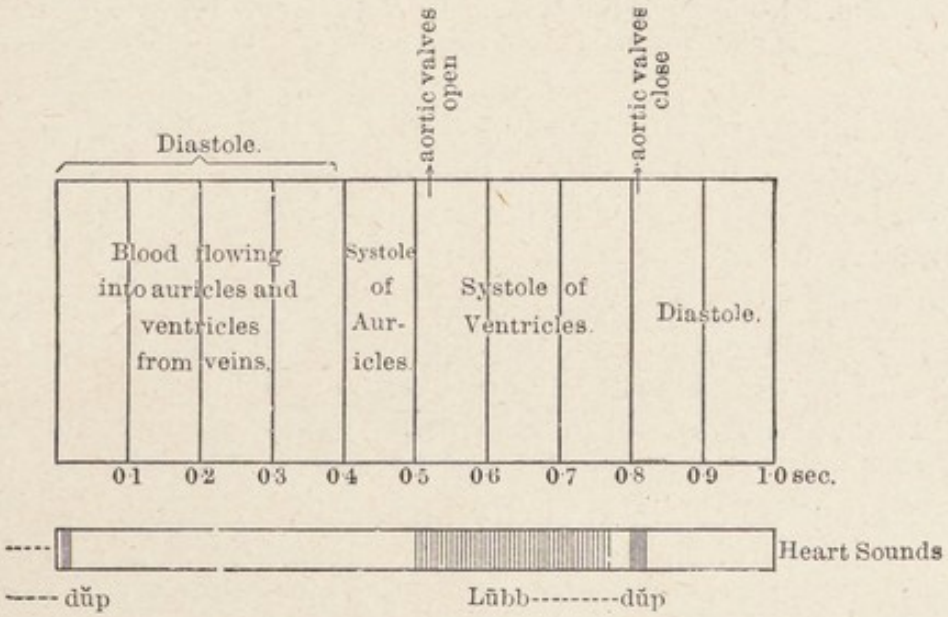


FIG. 93.—Diagram of events constituting a cardiac cycle. (Starling's *Principles of Physiology.*)

occurring during the cardiac cycle (fig. 93) has been determined in the following manner. A stethoscope is connected with an apparatus similar to the receiver of a telephone; the vibrations of the air in the stethoscope, set up by the heart-sounds, throw the membrane of the receiver into vibrations and so alter the contact between the silver and

carbon which form part of the receiver, and through which a current is passing. The current also passes through the primary circuit of an induction-coil, the secondary circuit being connected with a string galvanometer (p. 30). Each vibration of the membrane alters the strength of the current passing through the primary coil, and sets up momentary induced currents in the secondary circuit; deflections of the string are thus produced corresponding with the vibrations caused by the heart-sounds, and can be recorded on a moving photographic plate.

When a graphic record of the heart-sounds is obtained simultaneously with a cardiogram, it is found that the first sound occupies nearly the whole of ventricular systole, and that the second sound lasts for a brief space at the commencement of diastole.

The first sound is due to two causes, namely, (1) the vibrations set up by the closure of the tricuspid and mitral valves, and (2)

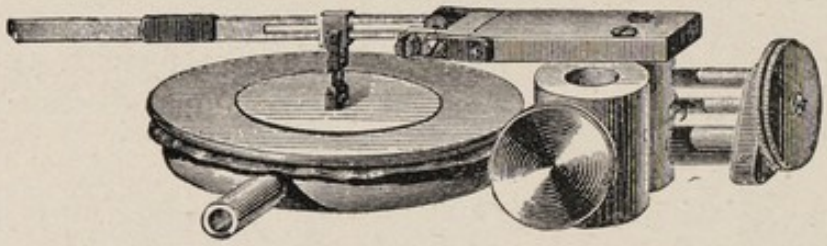


FIG. 94.—Marey's tambour. The writing point of the lever is not shown. (From Messrs. Baird & Tatlock.)

the contraction of the muscular wall of the ventricles. When the tricuspid or mitral valves become diseased so that they fail to close, the first sound is largely replaced by a "blowing" noise, known as a murmur or *bruit*. That the contraction of the heart-muscle contributes to the first sound is shown by the fact that, during the contraction of the bloodless, excised heart, a faint sound can be heard with the stethoscope, although in the empty heart the valves do not close during systole. The duration of the first sound almost to the end of systole furnishes additional evidence that its origin is partly muscular. The relative importance of the valvular and muscular factors is still a matter of discussion. The part of the first sound due to the muscular contraction is not peculiar to the heart, since a similar sound may be heard on listening to a contracting, voluntary muscle.

The second sound is due entirely to vibrations set up in the semilunar valves by their sudden closure at the end of systole, and is replaced by a murmur if these valves are diseased, or if, in an animal, they are hooked back and prevented from closing.

The first sound is most distinctly heard near the apex-beat;

the closure of the aortic valves is best heard in the second right intercostal space close to the sternum, and the closure of the pulmonary semilunar valves in the second left intercostal space.

(5) **Endocardiac Pressure.**—The pressure within the auricles and ventricles rises during systole and falls in diastole, and the variations in pressure are closely bound up with the other events taking place during the cardiac cycle. The changes in pressure occur so rapidly that a slowly moving fluid, such as mercury, fails to record them accurately, although a maximum and minimum mercury manometer may be employed to ascertain approximately the highest and lowest pressure occurring during a cardiac cycle. Such a manometer consists of the usual bent tube containing mercury, having interposed between it and the heart two tubes which can be used alternately. In one tube is a valve opening towards the manometer, and in the other a valve opening towards the heart. When the blood-stream passes along the former tube, the maximum pressure is registered; when it flows along the latter, the minimum is recorded.

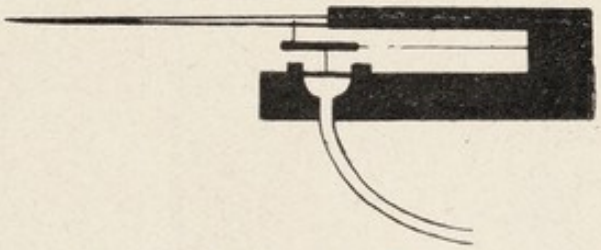


FIG. 95.—Hürthle's manometer. (Diagrammatic.)

In the early observations of Chauveau and Marey a cardiac sound, consisting of a long rigid tube having at its lower end a bulb of very thin rubber supported on a metal framework, was passed along the jugular vein into the right ventricle, or along the carotid artery into the left ventricle, of a horse. The upper end of the sound was attached to a Marey's tambour (fig. 94), which consists of a shallow metal cup having a small lateral opening and covered by a thin rubber membrane on which rests a light lever. The whole apparatus contains air, and any rise of pressure in the ventricle compresses the rubber bulb, thereby raising the membrane of the manometer and the lever: the movements of the lever are recorded graphically on a kymograph.

The method is unsatisfactory, first, becuase it is only appliable to large animals, and, secondly, because, owing to the compressibility of the air contained in the apparatus and to the oscillations of the elastic membrane of the tambour, waves are produced upon the tracing which sometimes render it inaccurate.

These drawbacks are considerably diminished in Hürthle's method, the essential features of which are (1) the use of a very small manometer with a thick rubber membrane (fig. 95), (2) the ubstitution for the sound of a tube opening directly into the

ventricle, and (3) the filling of the whole apparatus, including the manometer, with fluid (half-saturated sodium sulphate solution).

A still better manometer has been devised by Piper, in which instrumental errors are almost completely excluded (fig. 96). It consists of a metal cannula A, 6 cm. in length, containing a trocar B, by the aid of which the cannula can be thrust through the wall of the auricle or ventricle into the cavity of the heart. It is filled with saline solution containing hirudin, and even the smallest air-bubble must be excluded. The cannula expands at C to form a small chamber, one wall of which is covered by a thick, stretched rubber membrane D; to the outer surface of this membrane a tiny plane mirror E is attached.

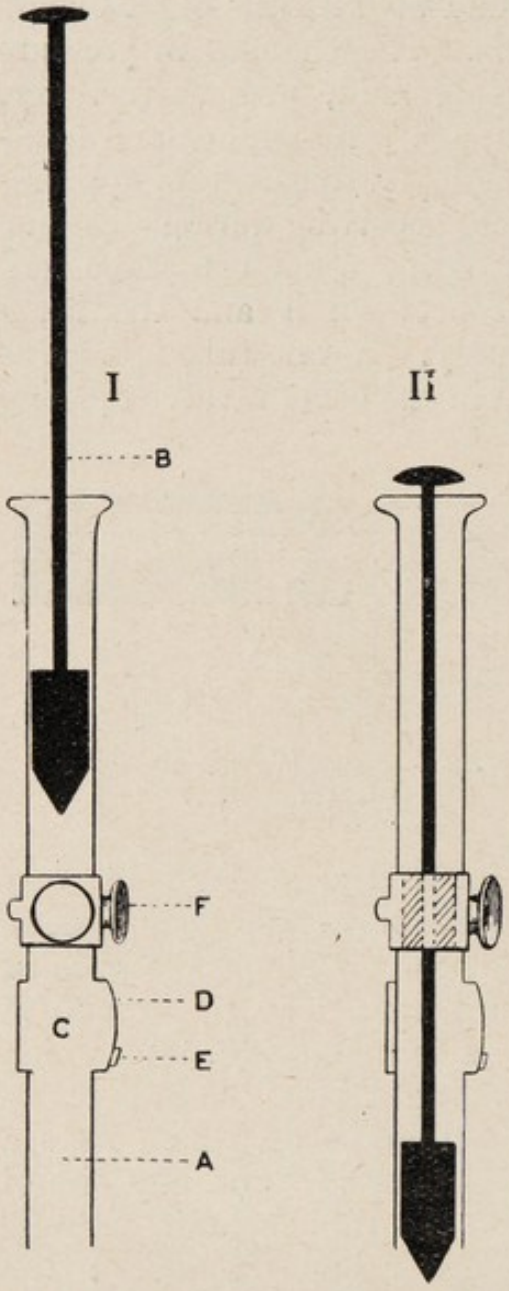


FIG. 96.—Piper's manometer. Explanation in the text.

When the cannula has been pushed into the heart and tied in position, the trocar is withdrawn and the tap F is closed so as to prevent the escape of blood; the cannula is then fixed with a clamp. As the endocardiac pressure varies, the membrane bulges or shrinks slightly and the position of the mirror alters; these movements are recorded, and greatly magnified, by throwing on to the mirror a beam of light, which is reflected on to a kymograph covered with photographic paper and excluded from other sources of light.

The advantages of this method are two-fold. In the first place the movements of the membrane are directly proportional to the variations in pressure, and, by the elimination of a lever, are recorded without inertia. In the second place, when the membrane is thrown into vibrations, these are so frequent (250 per second) that they cannot possibly be mistaken for oscillations produced by changes in the endocardiac pressure, and are so rapidly damped that they practically

do not occur when the endocardiac pressure is being recorded. A similar cannula may be passed into an artery so as to record changes in arterial pressure.

Fig. 97 represents a record, obtained by this method, of the changes of pressure in the left auricle and ventricle, and in the aorta, during a cardiac cycle. The middle curve, representing intra-ventricular pressure, shows at 1 a slight elevation (not always present) due to the auricular systole. This is followed almost immediately by the systole of the ventricle, which begins at 2 and occupies the period between 2 and 3; it usually lasts from 0·25 to 0·3 second. At first the curve rises very steeply; the

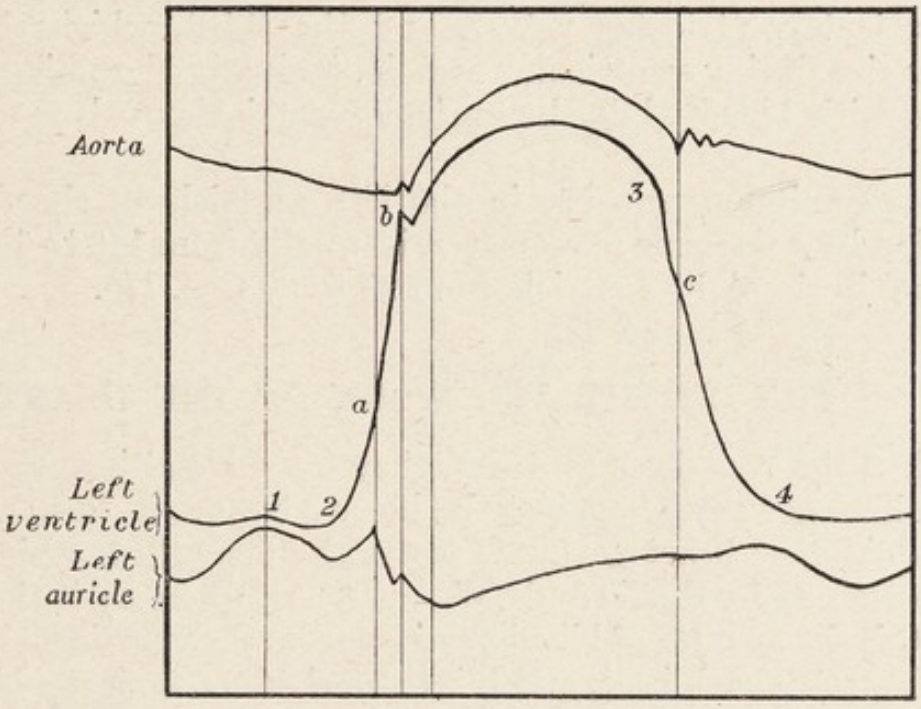


FIG. 97.—Simultaneous record of the changes of pressure in the aorta, left ventricle, and left auricle. (From Piper.)

auriculo-ventricular valves close at the point *a*, and from *a* to *b* the ventricle is a closed cavity. At *b* the intra-ventricular pressure becomes higher than that in the aorta, the semilunar valves open, and blood flows from the ventricle into the aorta during the whole period from *b* to 3, when the ventricle ceases to contract. The notch in the ascending part of the tracing immediately after the point *b* is due to the fact that, when the semilunar valves open, the escape of blood from the ventricle is momentarily impeded by the inertia of the column of blood in the aorta.

The portion of the tracing from *b* to 3 lasts about 0·18 second, and is generally known as the systolic plateau; it resembles a plateau, however, only when the arterial pressure is low, and its usual shape would be more accurately described as the systolic arch.

When the systole ends at 3, the intra-ventricular pressure rapidly falls; a short distance down the descending part of the tracing, namely, at the point *c*, the pressure in the ventricle falls below that in the aorta, and the semilunar valves close. Their closure does not alter the form of the intra-ventricular record, though it causes a series of small oscillations in the aortic pressure. At the point 4, the pressure in the ventricle falls below that in the auricle, the mitral valve opens, and blood flows into the relaxed ventricle.

Auricular Pressure.—A record of the changes of pressure in the auricle presents three main waves (fig. 97). The first corresponds with the auricular systole, the second with the sudden closure of the auriculo-ventricular valves, and the third, which shows a steady rise during ventricular systole, is due to the filling of the auricle with blood while the auriculo-ventricular valves are still shut.

The maximum pressure in the left ventricle of the dog, as recorded by a mercury manometer, is usually from 140 to 160 mm. Hg, and in the right ventricle from 25 to 30 mm. Hg.

THE OUTPUT AND WORK OF THE HEART

When the ventricles contract, they force blood into the aorta and pulmonary artery against the blood-pressure in these vessels. In so doing the heart performs work, the amount of which may be determined by the formula $W = Q \times R$, where W is the work done, Q is the amount of blood expelled from the ventricles (output of the heart) at each beat, and R is the resistance against which the heart is working; R is approximately represented by the mean arterial pressure.

The output of the heart may be measured indirectly by enclosing the heart in an apparatus (*cardiometer*) which fits closely round the base of the ventricles, and is connected with some form of tambour and recording lever. When the ventricles contract and expel blood into the arteries their volume diminishes, and, since the apparatus is air-tight, there is a corresponding fall of the recording lever.

One of the simplest forms of cardiometer is a glass vessel, resembling a large thistle funnel, the mouth of which is covered by a rubber membrane, with a hole in its centre. When the heart is placed in the cardiometer, the border of the membrane fits closely in the auriculo-ventricular groove, forming an air-tight junction. The cardiometer is attached to a piston recorder, which is more sensitive than an ordinary tambour and consists of a vulcanite piston fitting closely in a cylinder, the latter having an

opening at its lower end by which it can be connected with the cardiometer: a light counter-weighted lever is attached to the piston (fig. 98). The piston moves very easily, and its excursions are proportional to the changes in volume of the heart. In order to obtain a quantitative measurement of the output of the heart the instrument is calibrated.

Another and direct method of determining the output of the heart in an animal is the heart-lung preparation (fig. 99), devised by Knowlton and Starling. The common carotid artery, the descending aorta and the inferior vena cava are ligatured, and cannulæ containing a solution of hirudin in normal saline solution are placed in the innominate artery and the superior vena cava. The blood leaving the left ventricle through the innominate artery passes through a thin rubber tube A; this is enclosed in a glass tube, and can be compressed to any desired extent by means of a pump C

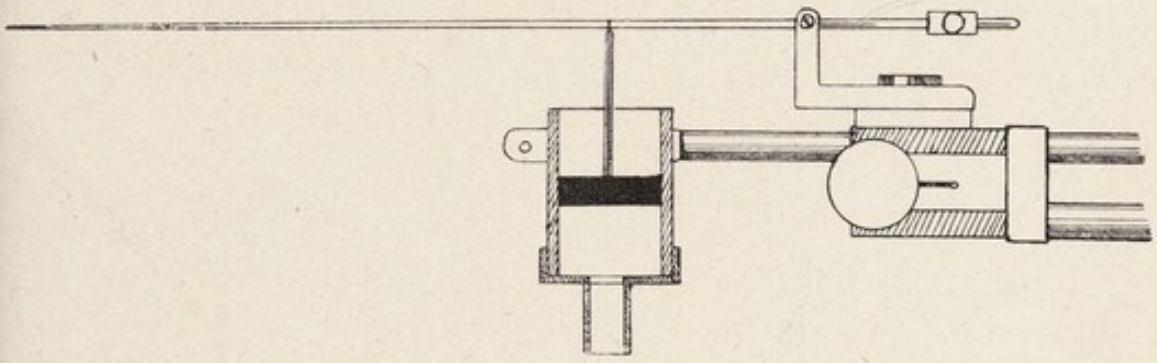


FIG. 98.—Piston recorder. (Diagrammatic.)

and pressure-bottle D, the resistance thus offered to the flow of blood through the tube replacing the resistance of the arterioles. The cannula in the artery is also attached to a mercurial manometer F, which records the arterial pressure. The small cylinder E contains air, forming an air-cushion, and to some extent replacing the elasticity of the arterial wall. After traversing the tube A, the blood enters a cylinder B in which it is warmed, and from which it passes into the superior vena cava, and then through the lungs to the left side of the heart. The circulation is thus confined to the heart and lungs, artificial respiration being maintained by a pump. The output of the left ventricle in a given time, *e.g.* five seconds, can be measured by clamping the tube G, opening the clip on H, and allowing the blood to flow into a graduated vessel instead of into the cylinder; and, if the rate of the heart is observed, its output at each beat can be calculated.

In man, the output of the heart has been indirectly determined in the following manner. The individual takes a deep breath of air containing a certain amount of nitrous oxide, which is very soluble in blood. After a few seconds he expires sufficiently

deeply to enable a sample of alveolar air to be collected in the manner described on p. 281. He then holds his breath for twenty to thirty seconds, and again expires deeply, a second sample of alveolar air being collected. The interval between the two expirations is called the experimental period; and during this period nitrous oxide is taken up in solution by the blood as it passes through the lungs, its solubility being such that 1 c.c. of

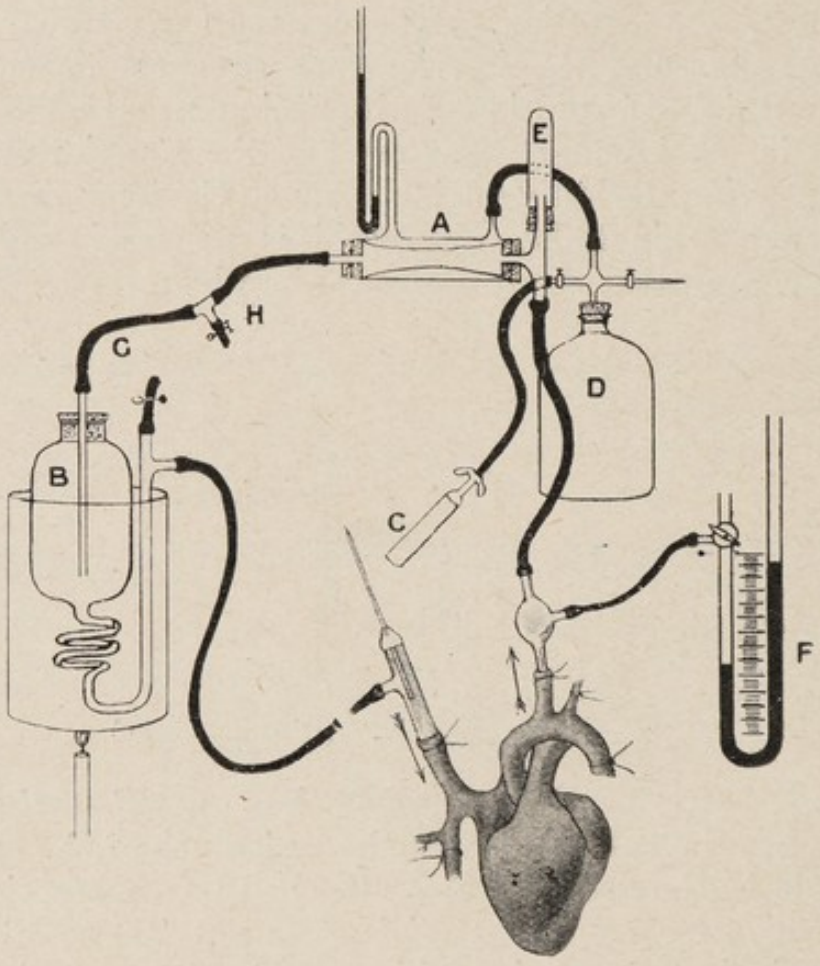


FIG. 99.—Arrangement of apparatus in the heart-lung preparation. (Knowlton and Starling.) Description in the text.

blood, if exposed to an atmosphere of pure nitrous oxide, will take up 0·43 c.c. of the gas. The total amount of air in the lungs at the beginning and end of the (experimental) period between the two expirations is determined by indirect means.

From these data the amount of blood passing through the lungs in a minute can be calculated. To take an example, the volume of air in the lungs at the beginning of the experimental period is 3·25 litres, and it contains, as shown by the analysis of the first sample, 12 per cent. nitrous oxide; the total quantity of nitrous oxide in the air of the lungs is $\frac{3250 \text{ c.c.} \times 12}{100} = 390$ c.c. At the

end of the period the total volume of air in the lungs is 3·0 litres, and the percentage of nitrous oxide in the second sample of expired air is found to be 10 per cent. Consequently the lungs contain 300 c.c. nitrous oxide. Thus 90 c.c. nitrous oxide have been taken up by the blood; and the average percentage of nitrous oxide in the air in the lungs is $\frac{12 \text{ per cent.} + 10 \text{ per cent.}}{2} = 11$ per cent.

With this percentage of nitrous oxide in the air of the lungs, each 1 c.c. of blood passing through them will take up $\frac{0{\cdot}43 \times 11}{100} = 0{\cdot}047$ c.c. nitrous oxide; and, in order to take up 90 c.c., 1·9 litres of blood must have passed through the lungs during the experimental period. If the experimental period lasted twenty-seven seconds, the flow of blood through the lungs per minute is 4·2 litres. This figure represents the output from the right ventricle during that period, and, if the pulse-rate is 70 per minute, the output per beat will be $\frac{4200 \text{ c.c.}}{70} = 60$ c.c. per beat. This figure may be taken as representing the average output of each ventricle in man, since in health the output of the two ventricles is the same.

The mean arterial pressure in man is about 90 to 100 mm. Hg. From these data the work done by the heart at each beat can be calculated. Thus Q × R = 60 grm. × 0·100 metre × 13·6 (specific gravity of mercury being 13·6 times that of blood) = 81·6 gram-metres. This figure represents the work done by the left ventricle. If the pressure in the pulmonary artery be taken as 20 mm. Hg, the work done by the right ventricle will be 60 grm. × 0·02 metre × 13·6 = approximately 16·4 gram-metres. The total work of the heart, therefore, is in this instance 98 gram-metres per beat.

The heart expels blood not only against the peripheral resistance, but with a certain velocity. The work (W) done in imparting this velocity to the blood is measured by the formula $W = \frac{QV^2}{2g}$, where Q = mass of blood expelled, V = its velocity during the systolic period, g = the force of gravity; it amounts to approximately 1 to 2 per cent. of the total work of the heart, and is negligible unless the output per beat is large.

We may now consider the conditions which determine the output and the work of the heart.

The Output of the Heart.—It has already been pointed out (p. 27) that, when a skeletal muscle contracts, the contractile stress developed in it is proportional to the initial length of its

muscle-fibres, *i.e.* its length just before it begins to contract, and that, if the muscle is stretched by means of a weight, it contracts more forcibly. The heart-muscle behaves in exactly the same

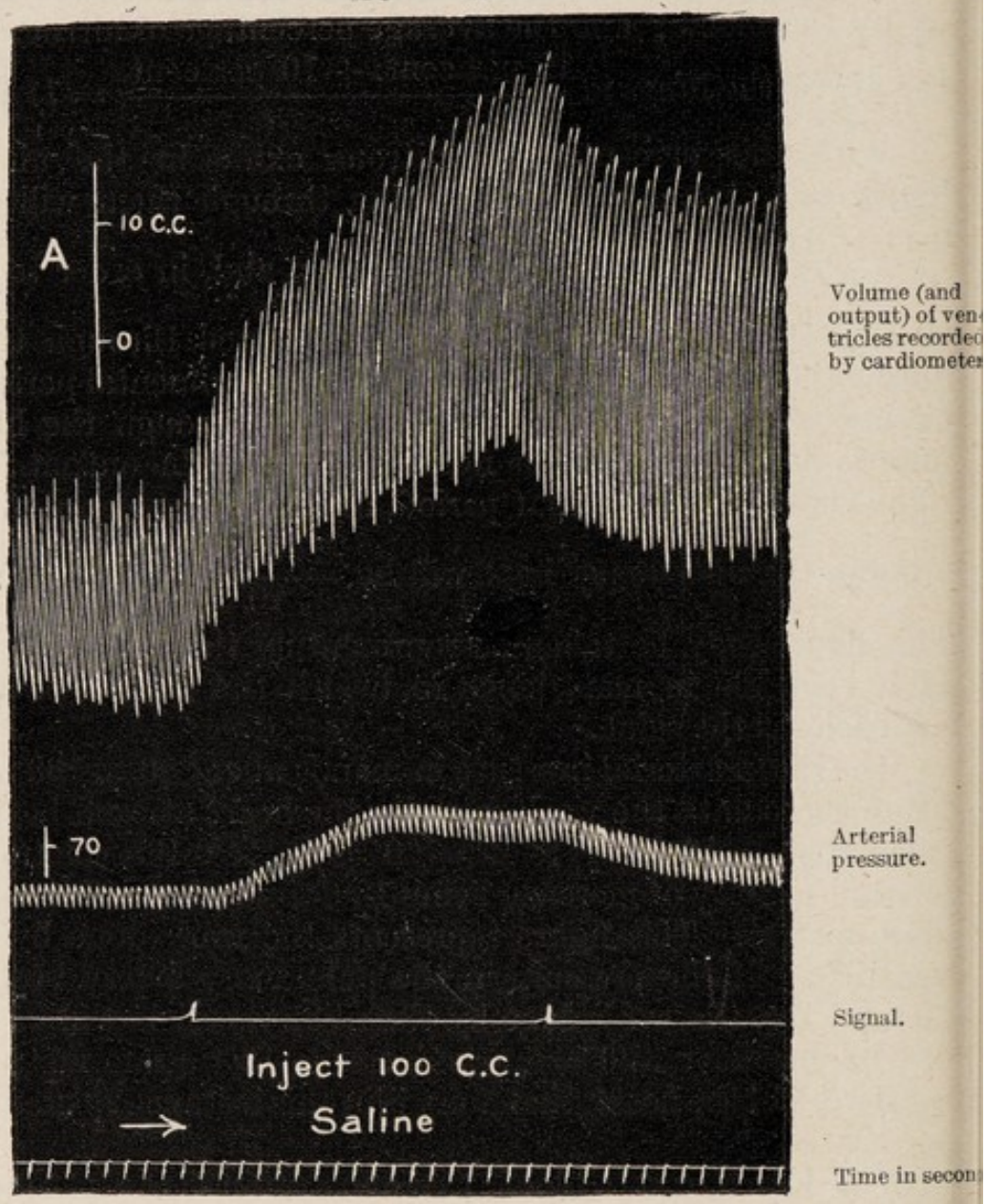


FIG. 100.—Tracing to show the effect of increased diastolic filling of the ventricles upon their output and volume. The venous inflow was increased by injecting saline solution into a vein. The heart was enclosed in a cardiometer: downstroke = systole. A = calibration of cardiometer.

way; but, since the heart is a hollow organ, the initial length of its fibres, that is, their length at the end of diastole, depends upon the amount of blood present in its cavities. If the heart is distended with blood each fibre will be longer than if it contains but little blood, and the greater the initial length of its fibres, the greater will be the force with which it contracts during systole.

The fact that the contractile power of the heart-muscle varies with the length of its fibres at the end of diastole, or, in other words, with the volume of the heart at the end of diastole, has been termed by Starling *the law of the heart.* It follows, therefore, that the amount of blood expelled from the ventricles at each beat is determined by the degree to which they are filled at the beginning of systole; and, if the arterial pressure is steady, this depends on the amount of blood entering the heart during diastole. This amount is increased (1) by deeper respiratory movements, whereby more blood is sent into the heart with each inspiration; (2) by muscular movement, which drives blood along the veins towards the heart; and (3) by any increase in the total volume of the circulating blood, such as is produced by the injection of blood or saline solution into a vein (fig. 100). During muscular exercise, the more forcible respiration and the active muscular movement lead to a much larger flow of blood into the heart and, therefore, to a larger output of blood than during rest.

The output of the heart is not affected, except for a few moments, by alterations in the arterial blood-pressure, unless these are extreme. The first effect of a rise of blood-pressure is that for a few beats the output of the ventricles becomes smaller; and, since the amount of blood entering the heart during each diastole is unchanged, the volume of the heart gradually becomes larger. The greater distension of the ventricle increases the length of its fibres, causing them to contract more and more forcibly during systole and thus to expel more blood into the aorta. The result is that the heart soon becomes so dilated at the end of diastole, and therefore contracts so strongly during systole, that its output per beat becomes as large as it was at the lower arterial pressure (fig. 101). In the normal animal, the presence of the pericardium prevents the risk of over-distension of the heart.

The capacity of the ventricle to maintain its normal output in spite of a greatly raised arterial pressure, and to increase its output when the venous inflow becomes larger, is spoken of as its "reserve" force or "power of compensation," and is of the utmost importance. In its relation to the body as a whole the output of the heart is one of the fundamental facts of the circulation, since it determines the rate at which oxygen can be carried from the lungs to the tissues; and, if the output were diminished whenever the blood-pressure rose, for example during exercise, the high blood-pressure would necessarily involve a smaller, and possibly inadequate, supply of oxygen to the tissues.

The compensatory power of the heart enables it to adapt itself to transient variations in arterial blood-pressure and venous inflow. When the work of the heart is permanently increased, for example,

by a continuously high blood-pressure, the heart-muscle hypertrophies, just as skeletal muscles enlarge as the result of regular muscular work.

When the heart beats rapidly, the diastolic pause is shortened, less blood enters it between the beats, and its output per beat is diminished. Consequently its output in a given time (*e.g.* a minute) is not necessarily greater when the heart is beating rapidly than when it is beating slowly. If the inflow of venous blood to the heart is small, the blood enters the ventricles at a

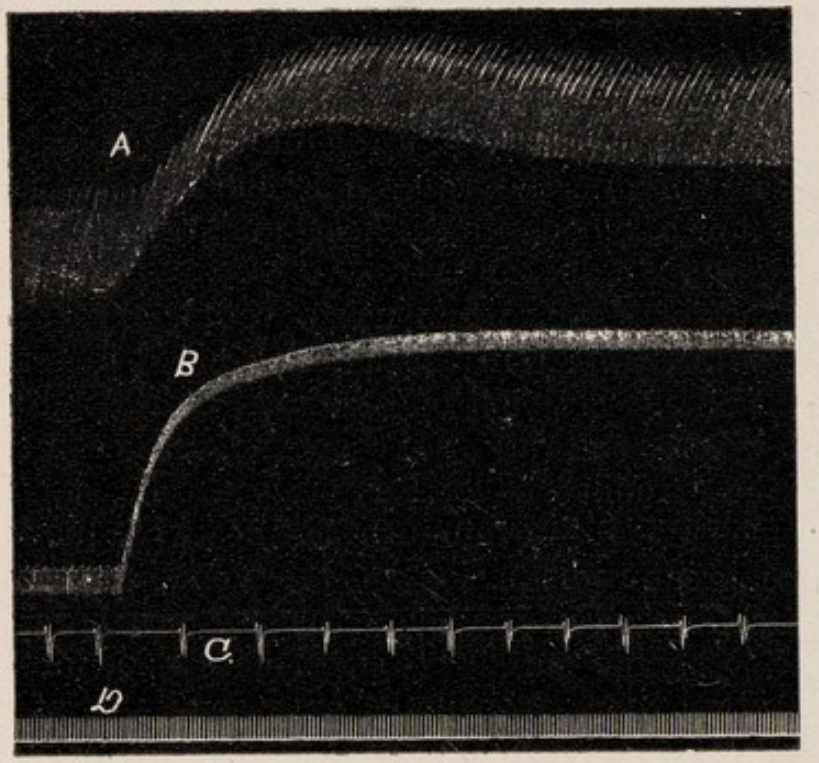


FIG. 101.—Effect of a rise of arterial pressure upon the output of the heart. (Knowlton and Starling.)

A, volume of ventricle; B, arterial pressure; C, output of left ventricle; D, time in seconds.

fairly uniform rate during diastole; and an increase in the rate of the heart merely causes a correspondingly smaller output per beat, the output per minute being almost unaltered (fig. 102, A). If, however, the flow of blood into the heart during diastole is large, the ventricles become almost fully distended with blood early in diastole, and very little additional blood passes into them later in diastole. In these circumstances, an increase of rate, that is to say, a shorter diastole, leads to very little diminution of the output per beat and to a considerable increase in the output per minute (fig. 102, B). Hence, when the venous inflow is large, acceleration of the heart increases its maximum output by enabling it to discharge more blood into the arteries in a given time than would be possible at the slower rate.

The factors which control the output of the heart may be summarised thus :—

(1) If the rate of the heart is constant, the output of the

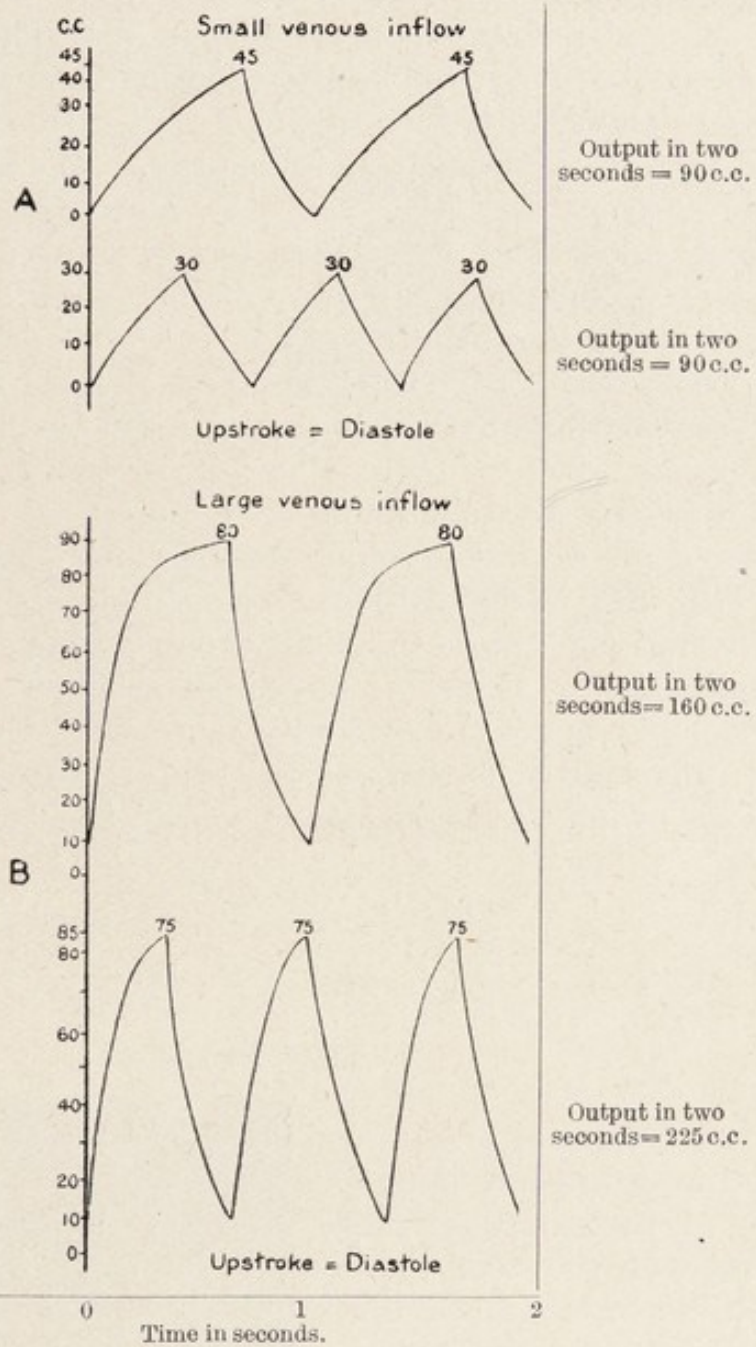


FIG. 102.—Diagram to illustrate the influence of the rate of the heart upon its output, (A) when the venous inflow is small, (B) when the venous inflow is large. The ventricle is assumed to empty itself completely during systole when the inflow is small, but not quite completely when the venous inflow is large.

ventricles varies directly with the venous inflow to the heart during diastole, but is (within wide limits) unaffected by changes of arterial pressure.

(2) If the venous inflow is small, the output per minute is

independent of the rate of the heart; if the venous inflow is large, acceleration of the heart increases its output.

Variations in the Work of the Heart.—Since the work done by the heart is measured by its output, multiplied by the arterial pressure ($Q \times R$), it will be altered either by a rise or fall of arterial pressure or by variations in the output of the heart, or by these two factors varying simultaneously. Whenever the arterial blood-pressure rises, the heart does more work, since the output remains unchanged. Again, increased filling of the heart during diastole, brought about by any of the causes already mentioned, by increasing its output, will add to the work of the heart; and the larger output from the heart tends in itself to raise the arterial blood-pressure, and thus to increase still further the work done. In muscular exercise there is both a rise in arterial blood-pressure and a greater diastolic filling of the heart.

In man, during muscular exercise, the output of the heart per beat may be 90 to 100 c.c. or even more, and, since the heart is beating much more frequently than during rest, its output per minute may be three or four times as great as during rest, its work being thereby enormously increased. These facts indicate how important it is that persons whose hearts have become less efficient owing to disease should refrain from vigorous exercise.

SECTION III

THE PULSE

If the arterial system consisted of a series of rigid tubes, the blood forced into it from the heart would, in accordance with the laws of hydrostatics, cause an instantaneous rise of pressure throughout the whole system, and an equal quantity of blood would at once escape from the distal end of the system. Owing to the fact that the arteries are distensible, only a fraction of the amount of blood entering the arterial system at each systole is forced through the arterioles during the systole, and much of the force of the heart is expended in further expanding the already distended arterial system to accommodate the extra blood sent into it. The expansion of the arteries starts at the root of the aorta, and proceeds as a wave along the whole arterial system, gradually dying away before the capillaries are reached. This wave of expansion constitutes the *pulse*. It travels at a rate of 6 to 8 metres a second, and is independent of the movement of

the main mass of blood along the arteries, the velocity of which rarely exceeds half a metre a second.

The pulse can be felt, and often seen, in the superficial arteries of the body, *e.g.* the radial artery; in order to study it more exactly a graphic record may be obtained by means of an instrument known as a *sphygmograph*, of which many forms exist.

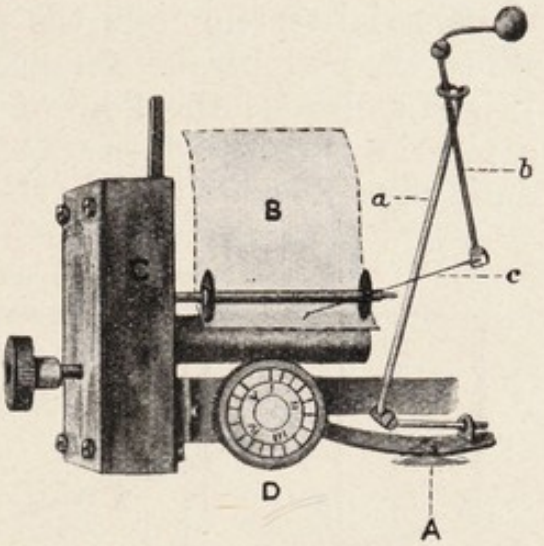


FIG. 103.—Dudgeon's sphygmograph; slightly diagrammatic. Explanation of figure in text.

Dudgeon's sphygmograph, which is illustrated diagrammatically in fig. 103, may be attached by a band round the wrist in such a way that the small metal plate A rests on the skin over the radial artery. The movements of the arterial wall are magnified by the series of levers, *a*, *b*, *c*, and are recorded by the free end of the lever *c*, which writes on a moving strip of blackened (smoked) paper B. The paper is moved by means of a small clockwork arrangement, and the pressure of the plate A on the artery can be adjusted by means of the dial D.

A typical pulse-tracing thus obtained is seen in fig. 104. It shows a sharp rise from *a* to *b*, succeeded by a steady fall, interrupted at *c* by a small notch which is immediately followed by a slight wave. The rise *a* to *b* constitutes the *primary*, or percussion, wave; the wave following *c* is the *dicrotic* wave, the notch just preceding it being the dicrotic notch. Other small waves, some preceding the dicrotic wave (predicrotic), and others following it (postdicrotic), sometimes occur; they are due to slight oscillations of the stretched arterial walls, magnified and distorted by vibrations set up in the sphygmograph. The portion of the wave from *b* to *c* is normally descending, and the pulse is called *katacrotic*; when the primary wave continues to rise almost until the dicrotic notch is reached, the pulse is said to be *anacrotic*.

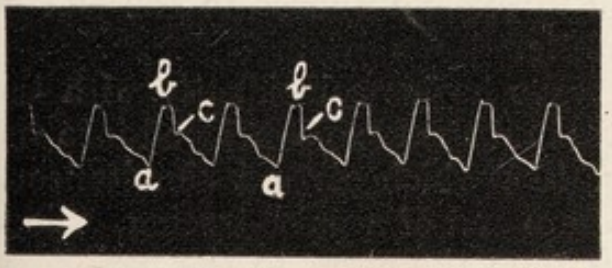


FIG. 104.—Pulse-tracing from the radial artery.

The primary wave is caused by the sudden expansion of the

artery when blood is forced into it during systole, the form of the wave depending upon the peripheral resistance. After the first abrupt expansion of the arteries, the blood usually escapes through the peripheral resistance more rapidly than it enters the arterial system from the heart, and the pulse is katacrotic. When the peripheral resistance is very high, *e.g.* in old age or in Bright's disease, the flow of blood from the arteries into the capillaries is retarded, so that blood continues to enter the aorta during systole more rapidly than it passes through the arterioles ;

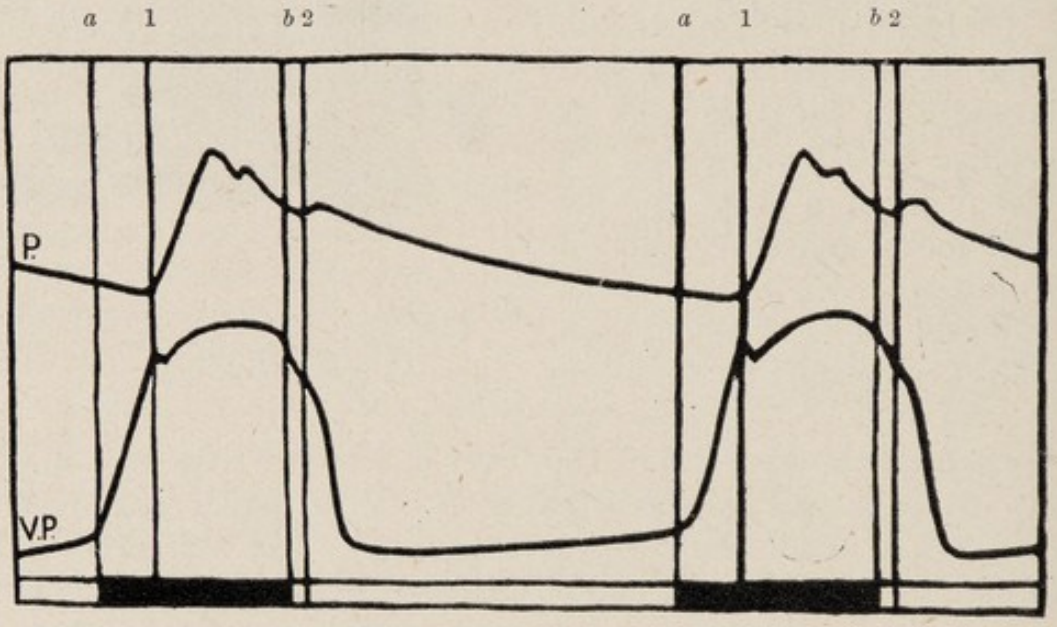


FIG. 105.—Diagram showing simultaneously endocardiac and aortic curves.

P., pulse tracing; V.P., intraventricular pressure. *a*, beginning, and *b*, end of systole. 1, opening of semilunar valves; 2, closure of semilunar valves.

the arteries therefore continue to expand almost to the end of systole, and the pulse is anacrotic.

In the aorta the primary wave begins coincidently with the opening of the semilunar valves and the escape of blood into the aorta, as may be seen in fig. 105, which gives a simultaneous record of the endocardiac pressure and of a pulse-tracing. Since the wave of expansion travels from the aorta to the peripheral vessels, the percussion wave begins in the smaller vessels an appreciable time later than in the aorta. This can be readily observed by taking simultaneously two pulse-tracings, one from the carotid artery and one from the radial artery at the wrist. The tracings are obtained by means of a *polygraph*. A small metal cup is placed over each artery, and each cup is connected by a rubber tube with a tambour provided with a writing lever. The levers are arranged so that one writes directly under the other. The difference in time between the beginning of the

percussion waves is measured with the aid of a time-marker, and the difference in distance from the heart of the points on the arteries at which the pulse-tracings are taken is noted ; from these data the velocity of the pulse-wave can be calculated. Thus, if the difference in time between the onset of the two pulses is 0·1 second and the difference in their distance from the heart is 0·6 metre, the velocity is 6 metres per second. The length of the wave is from 5 to 6 metres.

Fig. 105 also shows that the dicrotic wave occurs immediately after the closure of the semilunar valves, and, as no corresponding wave is present in the endocardiac pressure tracing, the dicrotic wave must have its origin in the arterial system. It was formerly believed that as the primary wave passed along the arteries it was reflected, as a secondary wave, from the obstruction set up wherever the arteries branched, and particularly from the arterioles, where the branchings are very numerous. This small reflected wave, starting at the periphery, was believed to travel back towards the heart as the dicrotic wave. Such a wave is actually produced in an artificial scheme of the circulation where the pulse-wave beats upon a peripheral resistance.

If this view were correct, the distance between the primary and dicrotic waves would naturally be less in the peripheral arteries near the seat of origin of the reflected wave than in the aorta. But the interval between the summits of the primary and secondary waves is of the same length in pulse-tracings taken from the same individual at the same time, whether the artery examined be near, or far from, the heart ; for example, it is the same in the carotid and the dorsalis pedis arteries. Hence the dicrotic wave must arise at the same point as the primary wave, and, since the primary wave starts at the root of the aorta, the dicrotic wave must start there also.

It is brought about in the following manner. When the left ventricle ceases to contract, the column of blood travelling along the aorta continues to move in virtue of its momentum, thereby producing a slight fall of pressure at the root of the aorta ; and the wall of the aorta shrinks a little. The slight fall of pressure immediately causes a reflux of blood against the semilunar valves, closing them, and the blood rebounds from the closed valves, thereby producing a small secondary expansion of the aorta ; this expansion travels along the arterial system, and forms the dicrotic wave. The height of both the primary and the dicrotic waves is largely determined, first, by the distensibility of the arteries, and, second, by the degree of distension of these vessels between successive heart-beats. If the arteries have become rigid (from old age or disease), their capacity for

expansion will obviously be diminished; if they are already greatly distended by a high mean arterial blood-pressure, their capacity for further distension will also be decreased. The conditions most favourable to the appearance of a markedly dicrotic pulse, therefore, are (1) a strongly beating heart, (2) a moderate blood-pressure, (3) highly elastic arteries. These conditions are often very fully realised in young adults during fever.

The rise of pressure caused by the entrance of blood into the arterial system with each heart-beat is greatest where the blood enters the system, namely, at the root of the aorta, and the wave of expansion is largest at this point. Some of this extra pressure is used up in expanding the first section of the aorta, and the force tending to distend the next segment will be slightly less; this process continues from segment to segment along the arterial system, the wave gradually becoming smaller and smaller, until in

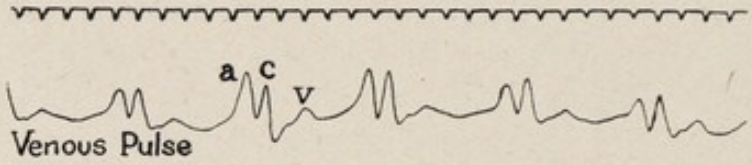


FIG. 106.—Time-marker records $\frac{1}{5}$ sec.

the capillaries it has entirely disappeared, and no trace of any pulse is visible.

VENOUS PULSE

A venous pulse is normally present in the great veins near the heart, and direct observation of the jugular vein shows two visible pulse-waves for each heart-beat. In order to record the venous pulse and to interpret it, a simultaneous tracing of the venous pulse and of the radial pulse is obtained by means of the *polygraph* described on p. 232. One cup is pressed on to the skin over the jugular vein just above the clavicle; the other cup is placed over the radial artery at the wrist. Each cup is connected with a tambour attached to a lever and the two levers are arranged to write one above the other.

Fig. 106 represents a tracing of the venous pulse, taken by this method and shows three waves; the first rise, *a*, corresponds with the auricular systole, the second, *c*, is simultaneous with the beginning of the ventricular systole, and the third, more rounded wave, *v*, is due to the gradual filling of the auricle towards the end of ventricular systole. The waves correspond with the changes of pressure (p. 222) in the auricle, being transmitted along the column of blood in the vein.

The venous pulse is confined to the large veins, and, as the

arterial pulse is extinguished in the arterioles, there is normally no pulsation in the smaller and medium-sized veins. The arterial pulse-wave may, however, extend into the smaller veins under certain conditions. When, for example, the chorda tympani nerve is stimulated, the arterioles of the submaxillary gland become dilated, and not only is the amount of blood flowing through the gland increased, but the pulse-wave extends into the veins coming from the gland. The transmission of the pulse into the veins is due, in this and similar cases, to the diminution of the resistance in the arterioles, resulting from their dilatation.

SECTION IV

THE CAUSATION OF THE HEART-BEAT

We have now to consider how the beat of the heart originates, and the conditions upon which its normal rhythm depends and by which that rhythm can be modified. For this purpose the slowly beating, and relatively simple, heart of the frog has proved to be of great value.

Anatomy of the Frog's Heart.—The frog's heart consists of a sinus venosus, two auricles (atria), a ventricle, and a bulbus arteriosus. The blood from the venæ cavæ enters the sinus, passes into the right auricle, and thence into the ventricle. The blood coming from the lungs enters the left auricle and passes into the ventricle. The ventricle opens into the bulbus arteriosus, from which the aortic arches arise and distribute the blood to the entire body, including the lungs. The cardiac muscle consists of small spindle-shaped fibres showing cross-striation, which is very indistinct, particularly in the sinus venosus.

Two nerves, the right and left vago-sympathetic nerve-trunks, enter the heart at the sinus, and become connected with a small mass of nerve-cells, which lies close to the sino-auricular junction and is known as the *sino-auricular ganglion*. Nerve-fibres from this ganglion pass along the septum between the auricles to enter two similar ganglia (*auriculo-ventricular ganglia*), lying close to the auriculo-ventricular junction. Scattered nerve-cells are also found in the inter-auricular septum and in the basal part of the ventricle, but are absent from its apical half. The fibres issuing from all these groups of nerve-cells end in the muscular fibres of the heart.

THE BEAT OF THE FROG'S HEART

If the brain of a frog be destroyed and the heart be exposed, it can be seen that each beat consists of a regular sequence of

events, namely, contraction of (1) the sinus, followed by that of (2) the auricles, (3) the ventricle, and finally (4) the bulbus arteriosus. When the whole heart is carefully excised from the body and placed in a watch-glass containing salt solution (0·65 per cent. NaCl), it continues to beat in a normal fashion for some time. If the sinus is separated from the rest of the heart by cutting through the sino-auricular junction, the sinus continues to beat as vigorously and at the same rate as before, whereas the auricles and ventricle cease to beat.

After a short time the auricles and ventricle again begin to beat, but at a slower rate than the sinus. If the ventricle is cut away from the auricles, the latter continue to beat, while the ventricle after one or two beats usually comes to a standstill. After an interval of half an hour or more the ventricle may again begin to beat, and it will do so more readily if it is stimulated by an occasional pin-prick. The rate of the ventricular beat is slower than that of the auricles. The apical half of the ventricle, if isolated, will never again start to beat of its own accord. This experiment makes it clear, first, that the rhythmic beat of the heart can be carried on quite independently of the central nervous system, and secondly, that this power of rhythmic contraction is most fully developed in the sinus.

It was formerly supposed that the beat originated in the nerve-cells of the heart, from which a regular series of stimuli was sent out to the heart-muscle, and that the muscular fibres responded to these stimuli by a series of rhythmic contractions. This is the *neurogenic* theory of the cause of the heart-beat. The view now generally held, however, is that the cardiac muscle possesses an inherent power of rhythmic contraction, which is most marked in the sinus and least so in the ventricle, and that this rhythmic power can continue to exist absolutely independently of either the central nervous system or the nerve-cells in the heart, although, as will be seen later, it can be influenced by impulses passing along the nerves to the heart. This view is known as the *myogenic* theory of the heart-beat. The myogenic theory has been accepted for the following reasons.

(1) In the first place, it was shown by Gaskell that a strip of the ventricle of the tortoise, if kept stretched and moist, can be made to beat rhythmically, and will then continue to beat without any external stimulus, although subsequent histological examination of the strip shows that it contains no nerve-cells. In the same way the apical half of the frog's ventricle, which is free from nerve-cells, although it will not beat spontaneously, can be made to contract rhythmically if it is fed with fluid through

a cannula at a pressure sufficient to put tension on the muscle-fibres.

(2) Secondly, it is possible in the frog's heart to remove almost completely the sino-auricular and auriculo-ventricular ganglia without disturbing the cardiac rhythm in any way.

(3) Thirdly, if, in a normally beating frog's heart, successive single stimuli are applied to the ventricle more frequently than the rate at which the heart is beating, the rhythm of the heart can be reversed, so that the beat starts in the ventricle and passes to the auricles, and then to the sinus. Such a reversal of rhythm is quite incompatible with the neurogenic theory of the heart-beat, since it contradicts the general law (law of forward direction) that nervous impulses can pass through a synapse only in one direction (p. 43).

It may be concluded, therefore, (1) that the rhythmic contraction of the heart is myogenic in origin, and (2) that, although all parts of the heart possess some rhythmic power, the beat normally always starts in the sinus, in which this power is most fully developed. The sinus sets the pace of the heart, and the ventricle responds to the stimuli reaching it, doing its work under the control of the sinus.

The Propagation of the Beat.—In the frog the muscular tissue of the whole heart is continuous, but the power of the tissue uniting the sinus and the auricles, and the auricles and ventricle, to conduct impulses is less than that of the rest of the heart. The impulses starting from the sinus are slightly delayed, therefore, in their passage to the auricles, and again in their passage from auricles to ventricle, so that there is a distinct pause between the contractions of the sinus and auricles, and auricles and ventricle respectively.

THE PROPERTIES OF THE CARDIAC MUSCLE

If a fine thread is tied round the apex of the frog's heart and attached to a light lever supported by a spring, a graphic record of the heart-beats can be obtained; this shows a small fall corresponding with each auricular contraction, and a larger fall corresponding with each ventricular systole (fig. 107). A thread, tightly tied at the junction between the sinus and the auricles, will now bring the auricles and ventricle to a standstill for a variable time, since the ligature prevents the passage of the normal rhythmic stimuli from the sinus to the rest of the heart; this is known as the Stannius ligature. The quiescent ventricle may then be used to study the properties of cardiac muscle as compared with those of skeletal muscle.

The contraction of cardiac muscle shows the following characteristics :—(1) When the ventricle is stimulated with single shocks of gradually increasing strength, it is found that with a certain strength of current the heart gives a beat. If a stronger current is used, the resulting beats are not increased in extent or force. The observation that if the heart beats at all in response to a stimulus its contraction is maximal, whatever the strength of the stimulus, is known as the " all or none law." This is due to the fact that the heart-muscle is a syncytium, and that a stimulus applied to any point will, if it is effective, spread over the whole muscular tissue of the heart, and therefore every fibre will contract in response to the stimulus. The heart gives the best beat of which it is capable at any moment, though the force with which it beats varies from time to time, being influenced by various factors, including the nutritive condition of the fibres. The " all or none law " simply means that the heart-beat is maximal for the conditions under which the heart is placed at any moment, and not that it remains constant throughout life. In this respect cardiac muscle behaves like the individual fibres of a skeletal muscle, which also obey the " all or none law " (p. 24).

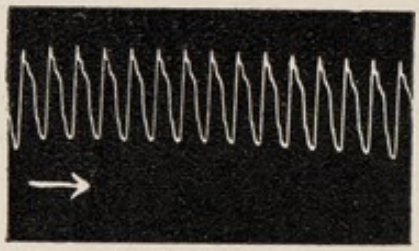


FIG. 107.—Tracing of the normal heart-beat in the frog. Downstroke = systole.

(2) If the resting heart is stimulated by successive induction shocks at an interval of 5 to 10 seconds, the extent of the second contraction is rather greater than that of the first. At the third or fourth contraction a maximum is reached, and succeeding contractions are all of the same extent. This phenomenon is sometimes called the " staircase effect," and is due to the beneficial influence of the first two or three stimuli on the contractile power of the heart-muscle. The same effect may be observed in skeletal muscle in similar circumstances.

(3) When the quiescent heart is made to beat by a single induction shock, and a second shock is sent into the heart during the systole evoked by the first stimulus, the second stimulus produces no visible effect on the heart, which is said to be " refractory." This " refractory period " extends from the instant when the first stimulus is applied until the end of the systolic phase. Owing to the greater length of the refractory period of cardiac muscle as compared with that of skeletal muscle, it is impossible to tetanise the heart, since only those stimuli which fall during the diastolic period are effective.

The refractory period also accounts for the effects observed in the normally beating heart when a single shock is sent into the ventricle at the beginning of diastole. In this case the ventricle responds with an extra beat, and the next stimulus coming down from the sinus to produce a ventricular systole falls within the refractory period of this extra beat and is ineffective. There is consequently a long pause, which is known as the " compensatory pause," between the extra beat and the next beat originating from the sinus (fig. 108).

(4) The force of the contraction is influenced, as in the case of skeletal muscle, by the length of the cardiac fibres (p. 226). If the heart is isolated and perfused with saline solution (0·65

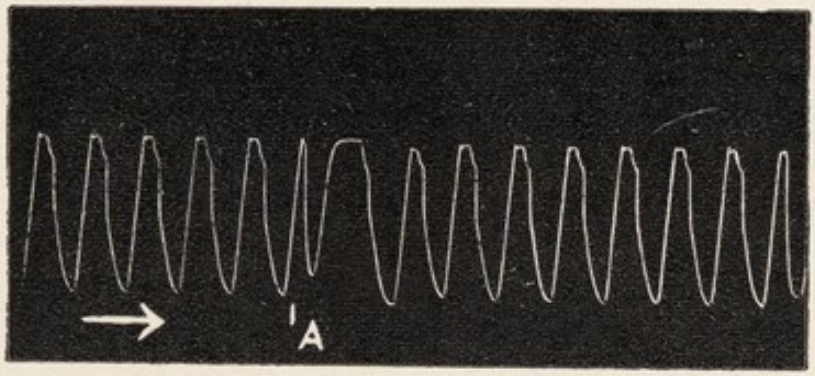


FIG. 108.—Tracing of a normally beating frog's heart. A single induction shock, applied to the ventricle at A, caused an extra systole, followed by a compensatory pause. Downstroke = systole.

per cent. NaCl), the force of the ventricular contraction will vary with the pressure under which the fluid is allowed to enter the heart. The higher the pressure, the greater will be the amount of saline solution entering the ventricle during diastole, and the greater will be the length of each of its fibres at the end of diastole. The greater diastolic length of the fibres enables the heart-muscle to contract more strongly during systole, with the result that the heart empties itself as completely as it did when the pressure of the perfusing fluid was low.

Further, increase of the internal tension to which the fibres are exposed is a stimulus to contraction, and it is for this reason that the apical half of the frog's ventricle contracts rhythmically when it is filled with fluid under pressure. The heart of the snail is so susceptible to this stimulus that it will not beat at all unless its fibres are under tension.

THE MAMMALIAN HEART

In the mammalian heart, the sinus, although present in early embryonic life, does not exist as a separate structure after birth, but is represented by a mass of specialised tissue, lying close to the entrance of the superior vena cava into the heart and extending a little way along the sulcus terminalis of the right auricle. This tissue is known as the *sino-auricular node.*

It has already been mentioned that, connecting the auricles and ventricles, is a band of tissue known as the *auriculo-ventricular bundle* (bundle of His). This bundle starts near the opening of the coronary sinus into the right auricle, its point of origin being called the *auriculo-ventricular node.* It passes along the top of the interventricular septum for a short distance, and then divides into two branches, one of which runs down the right, and the other down the left, wall of the septum immediately under the endocardium. In some animals, *e.g.* the calf, it can be readily dissected out in this part of its course as a thin band, paler than the rest of the ventricular muscle. It soon breaks up into a number of very fine branches which are distributed partly to the papillary muscles, and partly over the rest of the wall of the heart. The extent of this branching is well seen in fig. 109. The main bundle is composed of small, somewhat fusiform fibres, which are faintly striated. It is richly supplied with blood-vessels, and contains nerve-cells and nerve-fibres. The terminal branches of the bundle consist of fibres, called *fibres of Purkinje,* which are larger and paler than ordinary cardiac muscle-fibres. They show striated fibrillar material on the surface, and undifferentiated protoplasm internally. Like cardiaç muscle they are built up of segments, each of which has one or two nuclei in its central protoplasm.

The Rhythm of the Mammalian Heart.—Although the heart is provided with many nerve-cells, and receives in addition a nerve-supply from the central nervous system, its rhythm in the mammal, as in the frog, is in all probability of myogenic origin and depends solely upon the inherent rhythmic power of the muscle itself. It has been shown, for example, that, provided they are adequately supplied with oxygenated blood, strips of mammalian ventricle will continue to beat for some hours although they contain no nerve-cells. Evidence to the same effect is furnished by the heart of an embryo chick, which begins to beat some days before any nerves are present in it.

The impulse normally starts in the sino-auricular node, and,

travelling over the walls of the auricles, reaches the auriculo-ventricular node. From this node, the impulse passes along the auriculo-ventricular bundle to the ventricles ; and any condition which impairs the continuity of the bundle leads to a disturbance of the sequence of contraction of auricles and ventricles. In man the continuity of the bundle may be partially or completely destroyed by disease, the result being known as partial or complete 'heart-block.' In partial heart-block one out of every

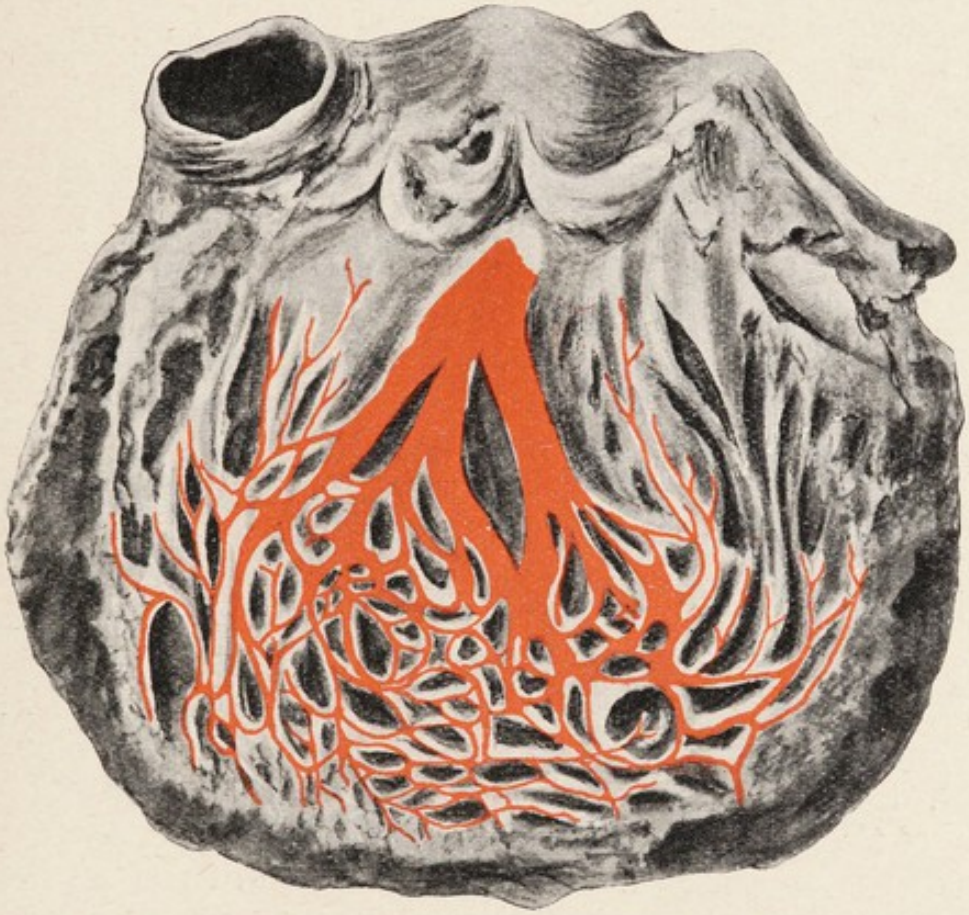


FIG. 109.—Diagram to show the distribution of the auriculo-ventricular bundle (in red) in the wall of the left ventricle. (After Tawara.)

two or three auricular beats is conducted along the bundle to the ventricle, the latter beating at half or a third the rate of the auricles (2 : 1 or 3 : 1 rhythm). In complete heart-block the rhythm of the auricles is unaffected, whereas the ventricles beat at a rate varying from 30 to 40 per minute ; the patient usually exhibits characteristic symptoms (Stokes-Adams disease), and a simultaneous record of the venous and radial pulse, taken with the polygraph (p. 232), shows that the rhythm of the ventricles is quite independent of that of the auricles.

When the bundle is divided in an animal, the rhythm of the auricles remains unaltered, whereas the ventricles immediately begin to beat at a slow rate having no relation to that of the

auricles. Partial heart-block is sometimes seen in asphyxial conditions, even when the bundle is intact. Partial or complete heart-block can also be induced in the frog's heart, although this does not possess an auriculo-ventricular bundle, by compressing the muscular tissue uniting the auricles and ventricle so as to lessen or abolish its conductivity. The mammalian ventricle differs, however, from that of the frog in possessing a more pronounced rhythmic power, and, when functionally isolated from the auricles, it begins to beat almost immediately with its own rhythm.

It is evident that, in the mammalian heart, the auriculo-ventricular bundle is essential for the propagation of the wave of contraction from the auricles to the ventricles.

The Electrical Changes in the Heart.—The time relations of, and the course taken by, the wave of contraction, as it travels from the sino-auricular node over the heart, can be easily demonstrated, not only in the lower animals, but even in man, by studying the electrical changes which take place at the same time. These changes may be recorded by connecting two parts of the heart, for instance the auricles and ventricles, with some form of galvanometer. For this purpose, the string galvanometer (p. 30) is now most generally used.

The resting heart is isoelectric, that is to say, the auricles and the ventricles are at the same potential, and the thread of the galvanometer is at rest. When the auricles contract, a difference of potential is set up between them and the ventricles, and a current passes in the heart from auricle to ventricle, and through the galvanometer from ventricle to auricle. During systole of the ventricles and diastole of the auricles, the current passes in the opposite direction. Contraction of the base of the ventricles while the apex is still at rest also causes a current to flow through the string of the galvanometer. Cardiac muscle thus resembles skeletal muscle in that its contraction is accompanied by an electrical change, the contracting part being galvanometrically negative (but electro-positive) to the resting part. The difference in character of the galvanometric tracings of the electrical changes in the heart and in skeletal muscle is due, partly to the prolonged contraction of cardiac muscle-fibres, partly to the complex arrangement of these fibres in the heart-wall.

In order to obtain a record of the electrical changes in the human heart, one end of the thread of the galvanometer is connected with a vessel containing salt and water, into which the right arm of the subject is placed. The left leg is placed in a similar vessel connected with the other end of the thread. The

right arm conducts the electrical changes at the base of the heart (including the auricles), while the changes occurring at the apex are conveyed down the left leg to the apparatus. The apparatus is so arranged that, in these circumstances, an upward movement of the shadow of the thread on the photographic record means that the base of the heart is negative to the apex, and is therefore contracting while the apex is at rest.

Fig. 110 represents an electro-cardiogram obtained with this instrument, and shows three upstrokes for each cardiac cycle. The first wave, P, corresponds with the systole of the auricles, which, when they contract, become galvanometrically negative to the resting apex. The second wave, R, occurs at the beginning of the ventricular systole, and is due to the systole commencing at the base of the ventricle, which becomes negative to the apex. As the wave of contraction travels to the apex, the thread returns to its resting position and remains steady for a short time, during which the whole ventricle is in contraction. The final rise at T is due to the systole lasting longer at the base than at the apex, particularly round the root of the aorta and pulmonary artery. The systole of the ventricles continues from the beginning of the R wave to the summit of the T wave. The records obtained in the lower animals show the same general form; in the frog and tortoise the prolonged contraction of the ventricle is accompanied by a long period between R and T during which the heart is isoelectric.

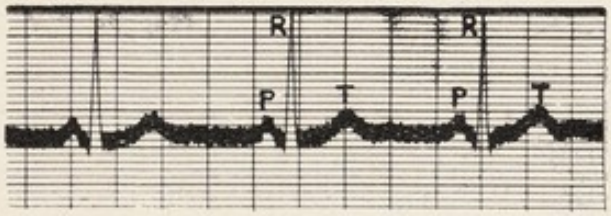


FIG. 110.—Electro-cardiogram from human heart. (Hume.) Explanation of letters in text.

The interval between the vertical lines is $\frac{1}{5}$ sec.

The Nutrition of the Heart-Muscle.—The nutrition of the heart-muscle is dependent on the amount and composition of the nutrient fluid supplied to it; normally this fluid is the circulating blood. The influence of alterations in the composition of the nutrient fluid is very easily studied in the isolated frog's heart, the muscular wall of which is nourished entirely by interchanges between the muscular fibres and the blood flowing through the heart. For this purpose a cannula (Symes'), such as that shown in fig. 111, is tied into an auricle, and the heart is excised. The cannula is attached to a bottle containing a suitable perfusion-fluid, which enters the heart at a pressure of 1 to 2 cm. of water. The fluid expelled through the bulbus arteriosus from the ventricle flows over the surface of the heart, keeping

it moist. The apex of the ventricle is connected by a thread with a recording lever.

The perfusing fluid most commonly used is known as Ringer's fluid, and has the following composition :—

NaCl	0·65 per cent.
KCl	0·03 „
$CaCl_2$	0·02 „
A trace of sodium bicarbonate.	

If 0·1 per cent. glucose is added to this solution, it is called Locke's fluid.

By means of this or similar methods, the influence of changes in the composition of the perfusing fluid upon the rate and force of the beat can be readily ascertained. The muscle of the frog's heart possesses a large store of energy, and will continue to beat for a long time without any fresh supply of nutrient material so long as the perfusing fluid contains oxygen. The force of the beat is dependent, however, not only on the supply of oxygen, but also on the presence or absence of certain salts, and on the reaction of the perfusing fluid.

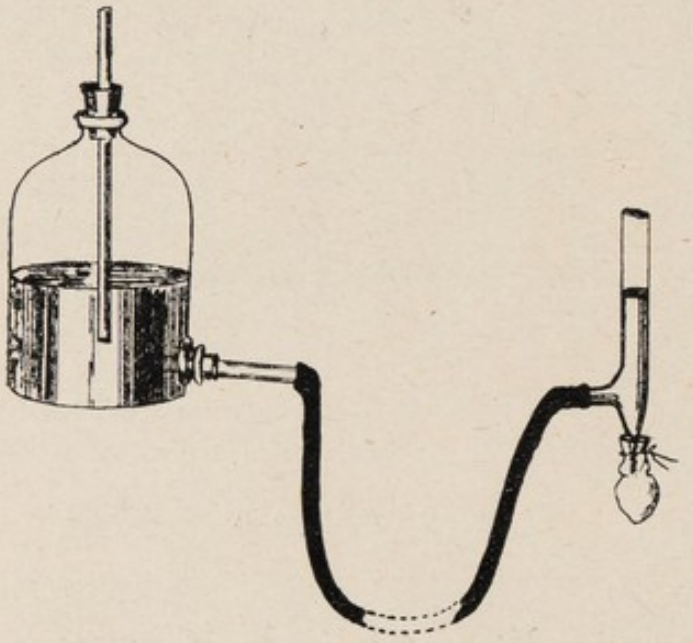


FIG. 111.—Diagram of apparatus for perfusion of frog's heart.

(1) If the heart is perfused with a solution free from calcium, the contractions of the ventricle gradually become feebler, and the heart soon stops in diastole. When calcium, but not potassium, is present, the ventricle after a short time fails to relax completely during diastole, and eventually may come to a standstill in a fully contracted state. The presence of both calcium and potassium, as, for example, in Ringer's fluid, seems to be essential for the maintenance of the normal beat.

(2) The heart is extremely sensitive to slight changes in the reaction, that is, the H ion concentration, of the perfusing fluid. It beats most forcibly when the perfusing fluid is neutral; if the fluid is made slightly acid or slightly alkaline, the beats become smaller.

In the mammal the heart receives its blood-supply through the coronary arteries, along which blood is flowing during both systole and diastole. The conditions which modify the supply of blood to the heart by the coronary vessels can be readily studied in the heart-lung preparation (p. 223), with the addition of a cannula being placed in the coronary sinus, so that the blood flowing through the coronary vessels can be collected and measured. In the first place, the amount of blood flowing through the coronary vessels varies directly with the blood-pressure in the aorta. In the second place, carbonic acid and other metabolic products of the activity of the heart increase the coronary blood-flow since they dilate the coronary vessels. By one or both of these means the supply of blood and, therefore, of oxygen and nutritive material to the heart is increased whenever the heart does more work. The more important factor is the arterial blood-pressure, and a rise of 50 mm. Hg in the arterial pressure may treble the supply of blood to the heart. The coronary blood-flow is also increased by the addition of adrenalin to the circulating blood, since this substance dilates the coronary vessels.

If the supply of oxygen and of nutrient material to the heart becomes inadequate for its needs, the nutrition of the muscle-fibres is impaired, and the contractile power of the heart diminishes. When the supply of blood to the heart (or a large part of it) is abruptly cut off by ligature of a coronary artery, or of one of its main branches, the ventricles almost immediately cease to contract, and the heart cannot be made to beat again.

The force of the mammalian heart-beat can also be influenced by changes in the reaction of the blood, but it is doubtful whether, under normal conditions, the reaction of the circulating blood ever alters sufficiently to affect the force of the heart.

Both in the frog and in the mammal the rate of the heart is increased by a rise, and decreased by a fall, in the temperature of the fluid circulating through it.

SECTION V

THE REGULATION OF THE VASCULAR MECHANISM

In order that the various tissues of the body may receive an adequate supply of nutritive material and oxygen, it is essential that the blood-supply to the different organs should be varied in accordance with their needs. This end is attained by means of the central nervous system, which can modify the rate of the heart and the calibre of the arterioles in response either (1) to external stimuli, or (2) to impulses arising in the different

parts of the body itself, or (3) to changes in the character of the circulating blood. The third factor also directly influences the force of the heart-beat and the calibre of the vessels.

THE INNERVATION OF THE HEART

The nerves supplying the heart are (1) the vagus, and (2) branches from the sympathetic system. In the frog, the pre-ganglionic sympathetic fibres leave the spinal cord in the white ramus of the third spinal nerve, and have their cell-stations in the corresponding sympathetic ganglion. From the ganglion post-ganglionic fibres pass upwards to join the vagus close to

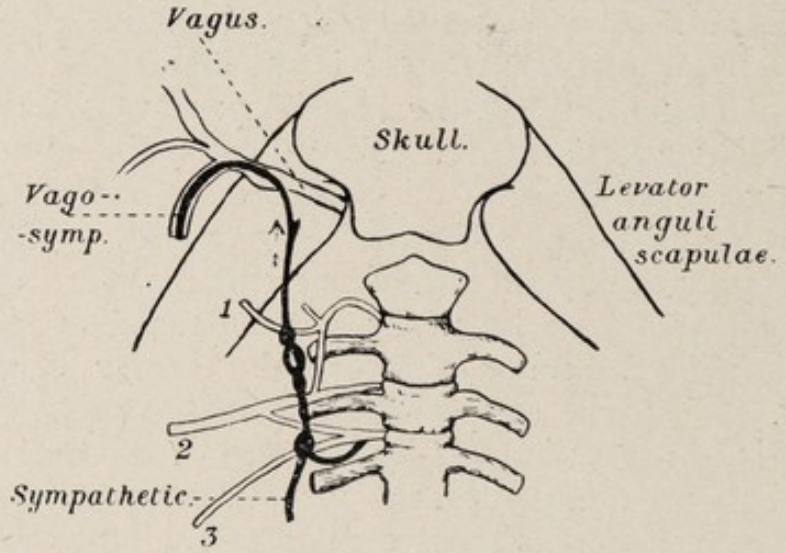


FIG. 112.—Origin of the nerves to the frog's heart.
1, 2, and 3 are spinal nerves.

its exit from the skull; the combined vagus and sympathetic fibres form a single nerve on each side, the vago-sympathetic, which runs to the heart (fig. 112). The fibres of the vagus nerve have their cell-stations in the ganglia of the heart itself.

In the mammal, the vagus gives off branches in the thorax, which run directly to the heart, in which their cell-stations lie. The pre-ganglionic sympathetic fibres leave the spinal cord by the second and third thoracic white rami; their cell-stations are in the stellate ganglion, from which post-ganglionic fibres run directly to the heart.

The Vagus.—When a weak stimulus is applied to the peripheral portion (*i.e.* the end towards the heart) of the divided vago-sympathetic nerve in the frog, the heart immediately beats more slowly: a stronger stimulus brings the heart to a standstill. This effect of the vagus is known as 'inhibition,' since the nerve, when stimulated, checks or inhibits the normal rhythm of the

heart. When the stimulus ceases, the heart begins to beat again, at first feebly, but soon more strongly than before the stimulus was applied.

In the mammal, stimulation of the peripheral part of the vagus produces the same effect, and, if the blood-pressure is being recorded, the tracing shows a marked fall of pressure

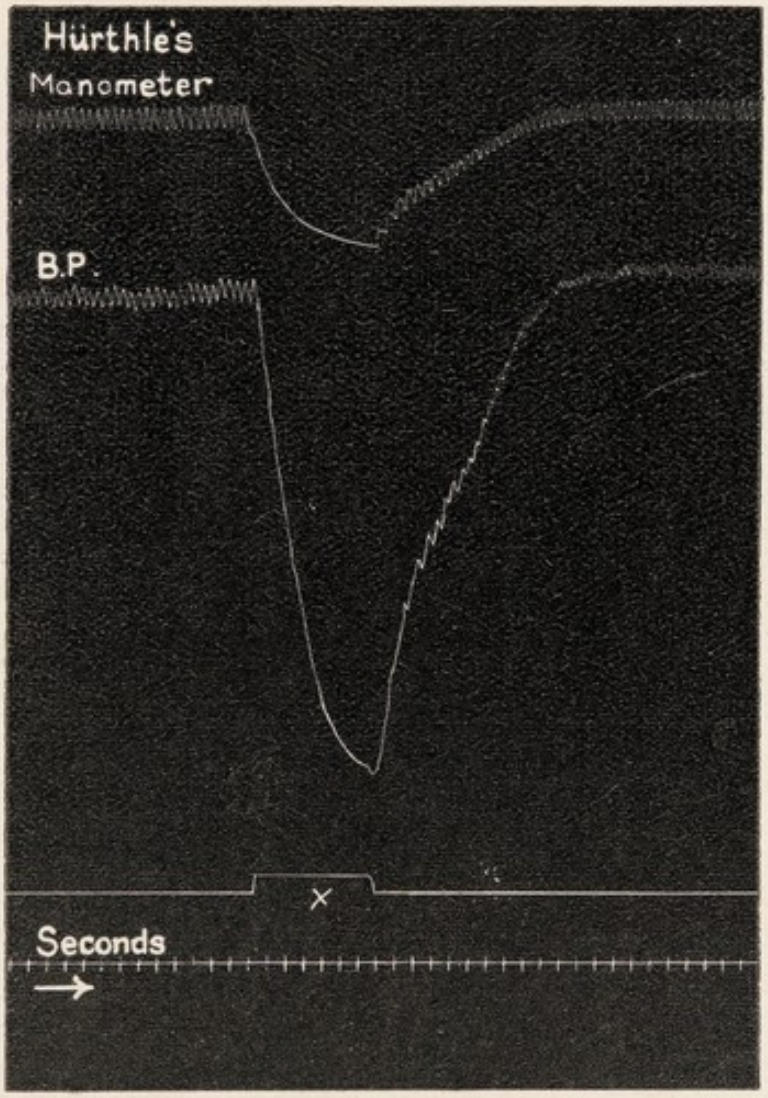


FIG. 113.—Stimulation of peripheral end of one vagus at X.
Note the inhibition of the heart and fall of blood-pressure. B.P., arterial pressure recorded by mercurial manometer.

(fig. 113). When the stimulus is removed, the heart begins to beat again, and the blood-pressure returns to, or even rises above, its original level. Sometimes, especially if the stimulus is prolonged, the ventricle may again begin to beat slowly even during the stimulation. This phenomenon is known as "vagus escape," and is due to the fact that the ventricle is beginning to beat independently with its own normal, slow rhythm.

In the frog the vagus fibres supply not only the sinus and auricles, but also the ventricle. In many, and probably in all, mammals, the vagus fibres are distributed to the auricles, but

not to the ventricles ; stimulation of the vagus in this case affects only the auricles directly, and the ventricles stop beating because they no longer receive the normal stimulus from the auricles. As a rule the vagus affects chiefly the sino-auricular node, inhibiting the impulses normally originating at this point, and the whole heart is brought to a standstill. Occasionally it seems to act mainly by lessening the conductivity of the auriculo-ventricular bundle, and the auricles continue to beat at their usual rate, whereas the ventricles beat infrequently or not at all.

The Sympathetic Fibres.—Stimulation of the sympathetic nerves to the heart, either in the frog or in the mammal, quickens the heart, and for this reason they are called accelerator nerves ; usually the force of the heart is also increased. The effect is

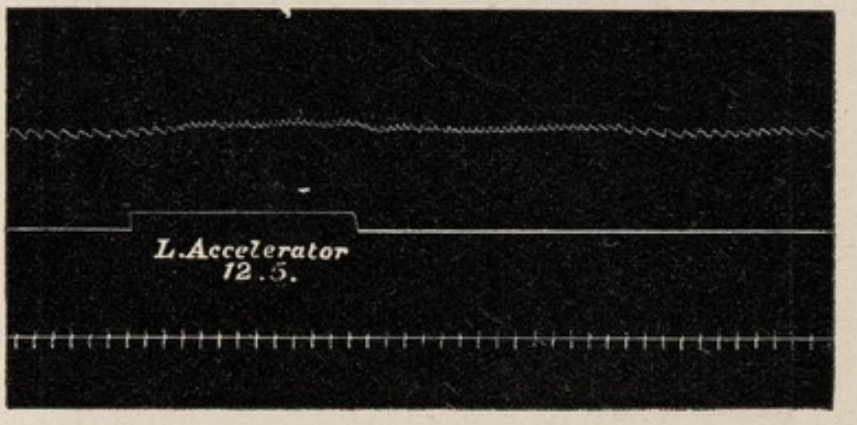


FIG. 114.—Upper tracing shows acceleration of the heart due to stimulation of an accelerator nerve.

only produced after a latent period of some seconds, and lasts for a little time after the cessation of the stimulation (fig. 114). In the mammal the blood-pressure may rise slightly or may be unaffected.

Cardiac Reflexes.—The efferent fibres of the vagus arise from a collection of nerve-cells lying in the medulla oblongata, and known as the vagus centre. In the normal animal a continuous stream of impulses is passing from the centre down the vagus nerve, exerting a restraining force on the rate of the heart-beat and tending to inhibit it. This action of the vagus centre is described as its *tonic* inhibitory action, and is particularly well marked in the dog and horse. Section of the vagus nerves abolishes the tonic action and the heart beats more frequently. The tone of the vagus centre can be reflexly increased or diminished by afferent impulses reaching it from various parts of the body. The most important afferent paths are (1) the depressor nerve, (2) afferent fibres running in the vagus from the heart itself, and (3) many sensory nerves.

(1) The depressor nerve is purely afferent, and, starting in the walls of the aortic arch, it runs up the neck on each side, in some animals (rabbits) as a separate nerve, in others bound up with the vagus trunk, to end in the medulla oblongata. If the nerve is divided, stimulation of its central portion (*i.e.* the end towards the brain) causes a fall of blood-pressure and slowing of the heart. The slowing of the heart is due to a reflexly produced increase of vagus tone, and does not occur when the depressor nerve is stimulated after section of the vagi. In animals in which the depressor nerve-fibres are bound up with the vagus

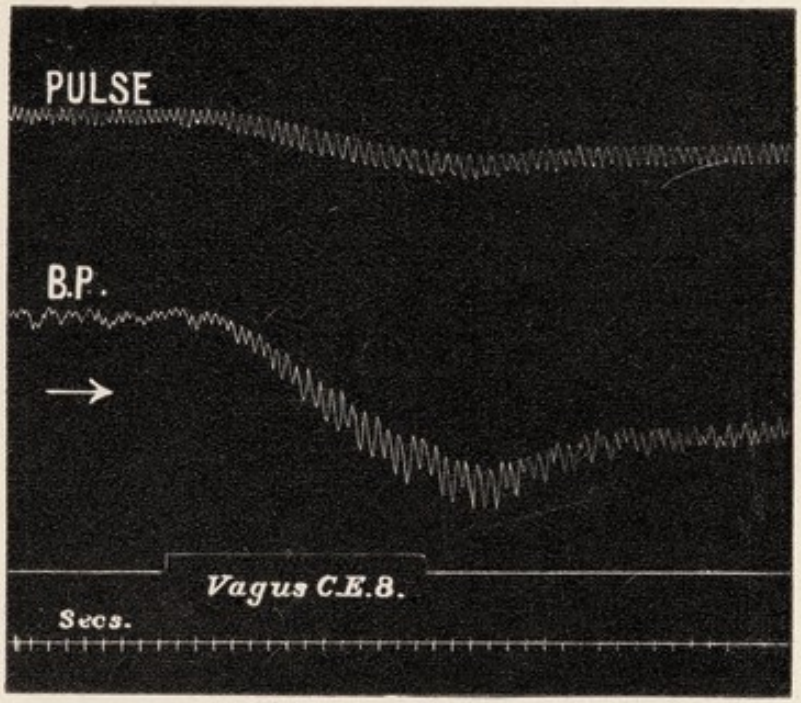


FIG. 115.—Reflex slowing of the heart due to stimulation of central end of one vagus. The other vagus is intact.

nerve, stimulation of the central end of one vagus usually causes slowing of the heart, provided the other vagus is intact (fig. 115).

The tonic action of the vagus centre is also increased when the general blood-pressure is raised, and the heart is slowed, probably because the stretching of the aortic wall stimulates the endings of the depressor nerve-fibres in the aorta and causes impulses to pass along these fibres to the vagus centre. This relationship between the blood-pressure and the pulse-rate is known as Marey's law, which states that "the pulse-rate varies inversely with the blood-pressure." Exceptions to this law are observed during muscular exercise and as a result of painful stimuli (fig. 117).

(2) It has been shown that if the flow of blood to the heart is increased, for instance, by the injection of blood or saline

solution into a jugular vein, the venous pressure rises ; at the same time the pulse-rate quickens (fig. 116), provided the nervous supply to the heart is intact. The acceleration is due chiefly to loss of vagus tone and partly to increase of accelerator tone ; it is brought about reflexly, the afferent impulses probably originating in the heart itself, and passing along the vagi to the medulla oblongata.

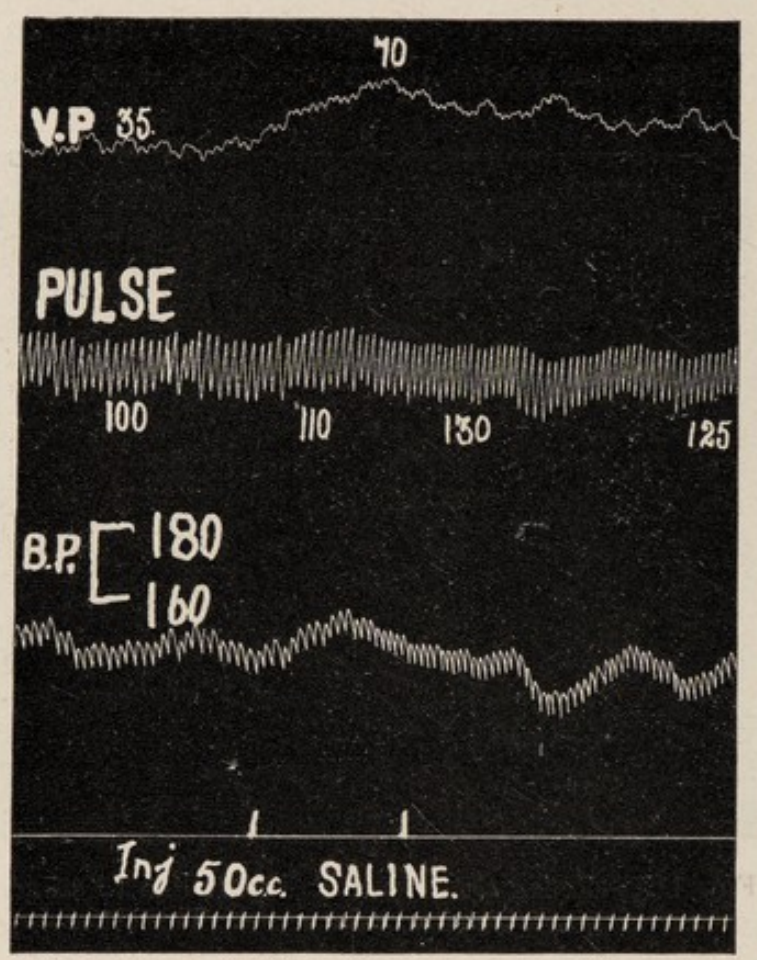


FIG. 116.—Tracing showing acceleration of the heart produced by rapidly increasing the flow of blood to the heart. The figures on the pulse-tracing represent the pulse-rate at each point. V.P., pressure in V. cava at its opening into the right auricle ; the figures represent pressure in mm. water

(3) The stimulation of the central end of almost any sensory nerve which, in a conscious animal, would give rise to pain causes reflex quickening of the heart (fig. 117), owing mainly to diminution of the tone of the vagus centre and partly to reflex stimulation of the accelerator nerves. Stimulation of the central end of the splanchnic nerve or of the fifth nerve, however, causes slowing of the heart, an effect which is sometimes seen to follow a severe blow on the abdomen, and which is also readily produced by irritation of the nasal mucous membrane.

Further, the rate of the heart can be modified by impulses reaching the vagus centre from the higher parts of the brain, the acceleration which takes place during emotion being partly caused in this way.

The Pulse-Rate in Man.—The frequency of the heart-beat in a healthy, resting individual is very constant, being on the average 72 per minute. Some people, however, normally have a slow and others a frequent pulse, the range of variation in different individuals being between 55 and 90 per minute. Alterations in the pulse-rate are continually taking place in daily life, and

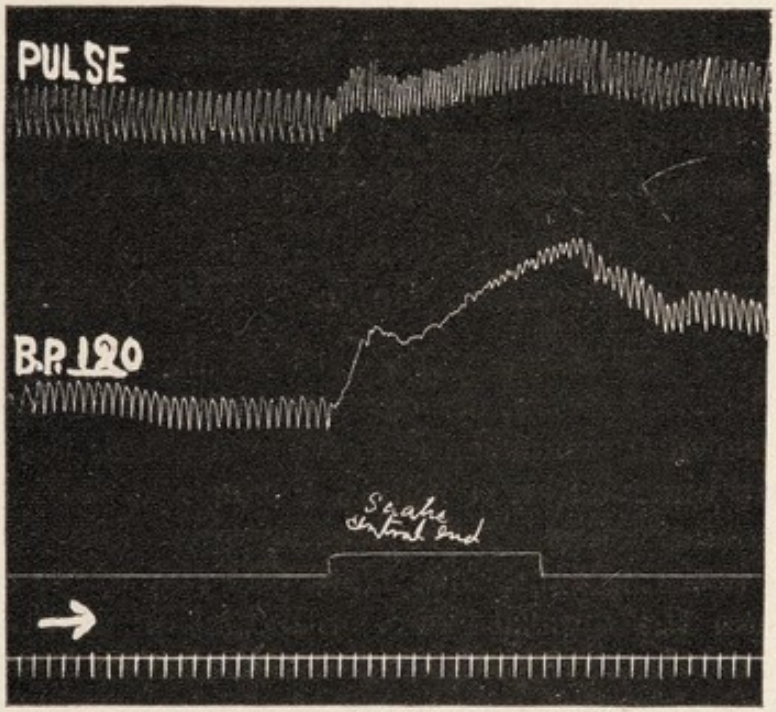


FIG. 117.—Reflex acceleration of the heart and rise of blood-pressure caused by stimulation of central portion of the (divided) sciatic nerve.

are brought about by one or other of the reflex mechanisms just described. The pulse is slightly quickened by the taking of food, and is considerably accelerated by (1) active muscular exercise, (2) emotion, (3) pain; the two latter conditions are often accompanied by muscular movements (unless these are restrained by an effort of the will) and by increased respiratory movements. As a result of the muscular and respiratory movements the inflow of venous blood to the heart may become very large, and the concomitant acceleration of the heart greatly increases its output in a given time, thereby enabling it to send a much larger supply of blood and of oxygen to the various organs and tissues of the body. In this way, acceleration of the heart plays an important part in the adjustment of the circulatory mechanism to the needs of the body.

In health, marked slowing of the pulse-rate is of comparatively infrequent occurrence, though it is often observed in pathological conditions.

The Action of Drugs on the Heart.—The action of drugs on the heart is most easily studied in the frog. The rate of the heart-beat is slowed by pilocarpine or muscarine, which stimulate the vagus endings in the heart; this effect is abolished by atropine, which paralyses these endings, so that after its administration stimulation of the vagi has no effect on the rate of the heart. Atropine has no action on the accelerator nerve-endings. Nicotine first stimulates and then paralyses the cell-stations of the vagus in the heart; and, if it is painted on the heart, stimulation of the vagus trunk is ineffective, since the impulses passing along it are blocked at the cell-stations. Adrenalin stimulates the nerve-endings of the accelerator nerves, thereby increasing both the force and the frequency of the heart-beat.

THE INNERVATION OF THE BLOOD-VESSELS

The Vaso-constrictor Nerves.—If the ears of a rabbit, preferably a light-coloured one, are examined, it will be observed that, when one cervical sympathetic nerve is divided, the ear on that side almost immediately becomes flushed. The central artery and its branches can be seen to become wider, many small vessels previously invisible come into view, and the whole ear becomes warmer than the opposite one. Stimulation of the peripheral end of the cervical sympathetic nerve causes an immediate constriction of the blood-vessels, many of which disappear from view, and the ear becomes paler and cooler than that of the opposite side.

This experiment, which was first carried out by Claude Bernard, shows that the cervical sympathetic nerve contains fibres which run to the blood-vessels of the ear, and which, when stimulated, cause constriction of the arterioles by the contraction of their muscular walls. It proves, further, that normally the muscular coats of the arterioles are neither fully relaxed nor fully contracted, but are in a state of partial contraction, which is spoken of as *tone*. The tone of the arterioles exists only so long as they are in connection with the central nervous system, and is dependent upon impulses passing from the nervous system. The nerve-fibres which carry these impulses to the arterioles, and which, when stimulated, increase their tone, causing them to constrict still further, are called *vaso-constrictor* nerves.

In other organs, the presence of vaso-constrictor nerves, and the effect of section or stimulation of these nerves on the calibre of the arterioles has been ascertained, not by direct ocular observa-

tion, but by determining the amount of blood flowing through the organ in a given time. The volume of blood (V) flowing through an organ in a given time varies directly with the mean arterial pressure (P) and inversely with the resistance (R) in its arterioles, and is represented by the formula $V \propto \frac{P}{R}$. The arterial pressure tends to drive blood through the organ, whereas the resistance offered in the arterioles tends to lessen the amount of blood entering the organ. Hence the rate of blood-flow through a small organ, such as the kidney, may be altered in one of two ways. On the one hand, in the absence of any active change in its arterioles, a rise of the general arterial blood-pressure will

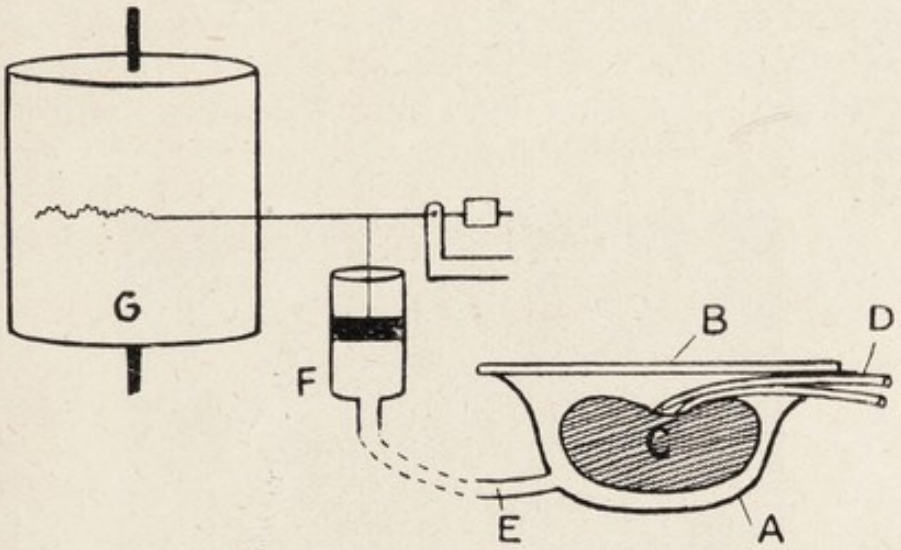


FIG. 118.—Method for recording changes in the volume of an organ.

A, Oncometer, in which lies the kidney C. D, renal vessels. B, glass lid. F, piston recorder. G, revolving drum.

force more blood through the arterioles of the kidney. On the other hand, if the mean arterial pressure remains constant, dilatation of the renal arterioles will lead to an increased rate of blood-flow through the kidney by lessening the resistance to the flow of blood. In experiments on the rate of blood-flow through an organ it is necessary, therefore, to record both the rate of flow and the mean arterial pressure, in order to ascertain whether the alterations in flow are due to local changes in the arterioles, or to changes in the general arterial pressure, or possibly to a combination of these factors.

The amount of blood flowing through an organ in a given time may be directly measured by allowing the blood escaping by the veins to pass along a graduated tube. Thus if 2 c.c. of blood flow into the tube in four seconds, the rate of flow is 30 c.c. per minute. This method is very useful in the case of small organs, such as the kidney or the submaxillary gland.

Changes in the calibre of its arterioles affect not only the rate at which blood flows through an organ, but also the amount of blood present in it, and hence its volume, at any moment. For example, constriction of the arterioles of an organ lessens both its volume and the rate of blood-flow through it. Consequently, alterations in the rate of the blood-flow through an organ can be indirectly ascertained by recording the variations in its volume. For this purpose the following method is employed. The organ is placed in an air-tight box, known as a *plethysmograph*, provided with a small opening which is connected with a piston-recorder arranged to write on a drum (fig. 118). When the organ expands, the air in the box is driven along the tube into the piston-recorder,

FIG. 119.—Oncometer.

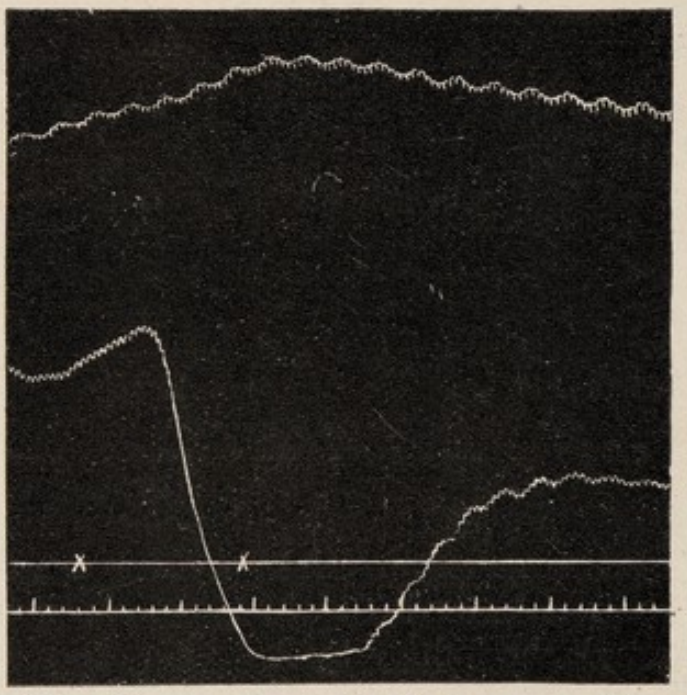


FIG. 120.—Tracing of arterial blood-pressure (1), and kidney volume (2). Between X and X the 10th anterior thoracic nerve-root was stimulated, causing a decrease in kidney-volume. (From *Practical Physiology*, by Pembrey and others.)

thereby raising the lever ; shrinkage of the organ has the opposite effect. The form of plethysmograph varies with the shape of the organ which is being studied. The one generally used for the kidney, and known as an oncometer (fig. 119), is made of vulcanite and has a glass lid ; in one side is a groove through which the renal vessels and nerves can pass. The box is made air-tight by filling the interstices with vaseline. Fig. 120 repre-

sents a record of the volume of the kidney thus obtained, simultaneously with a general blood-pressure tracing, and shows the effect of stimulating the peripheral end of a divided renal nerve.

By one or other of these methods it is found that division of the nerves passing to the kidney produces an increase of its volume and a larger flow of blood through it, whereas stimulation of the nerves has the opposite effect. Since in these experiments the general arterial pressure remains practically unaltered, the changes in the blood-flow produced by section or stimulation of the renal nerves must be brought about by alterations in the calibre of the arterioles of the kidney.

Experiments of this kind show that the arterioles of almost every organ in the body are supplied with vaso-constrictor nerves. The tone of these vessels is controlled by a centre, the *vaso-motor centre*, lying in the medulla oblongata ; nerve-fibres pass from the cells of this centre down the spinal cord to end, in all probability, round cells in the lateral horn in the thoracic region, and round corresponding cells in the lumbar region. These cells give off small medullated fibres, which leave the spinal cord by the anterior roots and enter the white rami communicantes to form part of the sympathetic system ; their subsequent course has already been described (pp. 112 and 114).

The mean arterial pressure depends largely upon the resistance offered by the arterioles to the flow of blood through them ; it rises when they are constricted, and falls when they are dilated. Hence stimulation of the vaso-motor centre, by causing constriction of arterioles all over the body, produces an enormous rise of blood-pressure ; destruction of the centre is followed by dilatation of the arterioles, and the blood-pressure falls to 50 mm. Hg, or less. The centre lies in the floor of the fourth ventricle, its lower limit in the rabbit being about 4 mm. above the apex of the calamus scriptorius and its upper limit about 4 mm. higher. Its position has been ascertained experimentally by observing the effect on the blood-pressure of transection of the brain-stem at various levels. Section through the pons or upper part of the medulla oblongata does not affect the blood-pressure ; when the section passes through the upper end of the centre it produces a slight fall of pressure, and if a section is made a few millimetres lower the fall of pressure is maximal. On division of the spinal cord in the cervical region, all the arterioles are cut off from the vaso-motor centre, and the fall of blood-pressure is as great as after destruction of the centre itself. When the transection is made in the thoracic region, only those arterioles which receive vaso-constrictor nerves from the spinal cord below the

lesion will lose their tone ; and the fall of arterial pressure becomes less marked the lower the level at which the spinal cord is divided, transection in the lower lumbar region having no effect upon the mean arterial pressure.

If an animal is kept alive for some hours or days after transection of the spinal cord, its arterioles gradually recover their tone and the blood-pressure returns to a normal level. This is brought about by means of subsidiary vaso-motor centres in the spinal cord, which are called into play when the medullary centre is put out of action. On subsequent destruction of the spinal cord, the blood-pressure falls almost to zero.

The only arterioles in the body which are not known to be influenced by vaso-constrictor nerves are the cerebral and coronary vessels. The existence of vaso-constrictor nerve-fibres supplying the pulmonary vessels has been demonstrated by means of adrenalin. This substance stimulates the endings of the vaso-motor nerves in the walls of the arterioles, and thus produces the same effect upon the arterioles as does stimulation of the nerves themselves. It follows, therefore, that, if the addition of adrenalin to the blood flowing through an organ brings about constriction of its arterioles, the blood-vessels of that organ must be supplied with constrictor nerve-fibres. Observation has shown that, when the lungs are perfused with blood under a constant pressure, the addition of adrenalin to the blood lessens the outflow from the lungs owing to constriction of the pulmonary arterioles. Hence it may be concluded that vaso-constrictor fibres are distributed to the pulmonary vessels.

The Vaso-Dilator Nerves.—In many parts of the body the arterioles are supplied not only with vaso-constrictor but also with vaso-dilator nerves, stimulation of which produces dilatation of the vessels owing to relaxation of their muscular walls. The chorda tympani nerve, for example, carries vaso-dilator fibres to the vessels in the sub-maxillary gland, and when it is stimulated the blood-flow through the gland is increased, and may become four or five times as large as that taking place before stimulation of the nerve. Since the general blood-pressure remains unaltered, the increase in the blood-flow through the gland must be due to dilatation of its arterioles. Vaso-dilator fibres are also found in the nerves supplying the other salivary glands, the tongue, and other structures in the head. Similar fibres leave the spinal cord by the anterior roots of the second and third sacral nerves ; and stimulation of these nerves, which are called the nervi erigentes, causes dilatation of the blood-vessels of the generative organs and of the rectum.

The vaso-dilator nerves show two important points of differ-

ence from the vaso-constrictor nerves. In the first place, mere section of the nerves produces no obvious effect upon the calibre of the blood-vessels, so that, unlike the vaso-constrictors, the vaso-dilator fibres do not appear to exercise a continuous influence upon the tone of the arterioles. In the second place, the cell-stations for these nerves lie, not in the sympathetic ganglia, but close to, or even within, the organ whose arterioles they supply.

In the instances just given, the nerves contain only vaso-dilator fibres, but in the nerves supplying the limbs both vaso-dilator and vaso-constrictor fibres are present. Stimulation of the peripheral end of a nerve, such as the sciatic, usually causes vaso-constriction, though the existence of vaso-dilator fibres can be demonstrated in one of the following ways :—

(1) If the sciatic nerve is divided and its peripheral end stimulated immediately, the arterioles become constricted, but, when the nerve is stimulated two or three days after section, the arterioles dilate. This result is due to the fact that the constrictor fibres degenerate, and cease to carry impulses, earlier than do the dilator fibres.

(2) If the sciatic nerve is stimulated with single induction shocks repeated at intervals of one or two seconds, these shocks stimulate only the dilator fibres, and the arterioles dilate.

(3) The dilator nerves are excited more readily than the constrictor nerves by mechanical stimuli, such as pinching the nerve.

(4) If a limb is cooled, stimulation of the nerve to that limb is followed by dilatation of the arterioles.

The change in the calibre of the arterioles, thus produced, leads to a corresponding alteration in the amount of blood flowing through the vessels of the limb, and alters the volume of the limb. These changes in volume can be readily recorded by enclosing the distal part of the limb in a plethysmograph of suitable shape, which is connected with a tambour and a recording lever.

Bayliss has shown that the vaso-dilator fibres to the limbs leave the spinal cord by the posterior roots, and that stimulation of the peripheral end of a posterior root causes marked dilatation of the arterioles, and therefore an increase in the volume of the limb (fig. 121). The posterior root fibres starting in the skin and deep tissues normally carry impulses from these structures to the spinal cord and brain. When stimulation of the peripheral end of the posterior root causes dilatation of the arterioles, the impulses must pass towards the periphery, that is, in the opposite direction to that taken by the impulses from the skin. For this reason the impulses running towards the periphery and causing vaso-dilatation have been called *antidromic*.

In normal circumstances a stimulus applied to the skin at A (fig. 122) will give rise to an impulse passing along the sensory nerve B into the spinal cord; in its course each nerve-fibre gives off a collateral branch C, which ends in the wall of an arteriole D of the

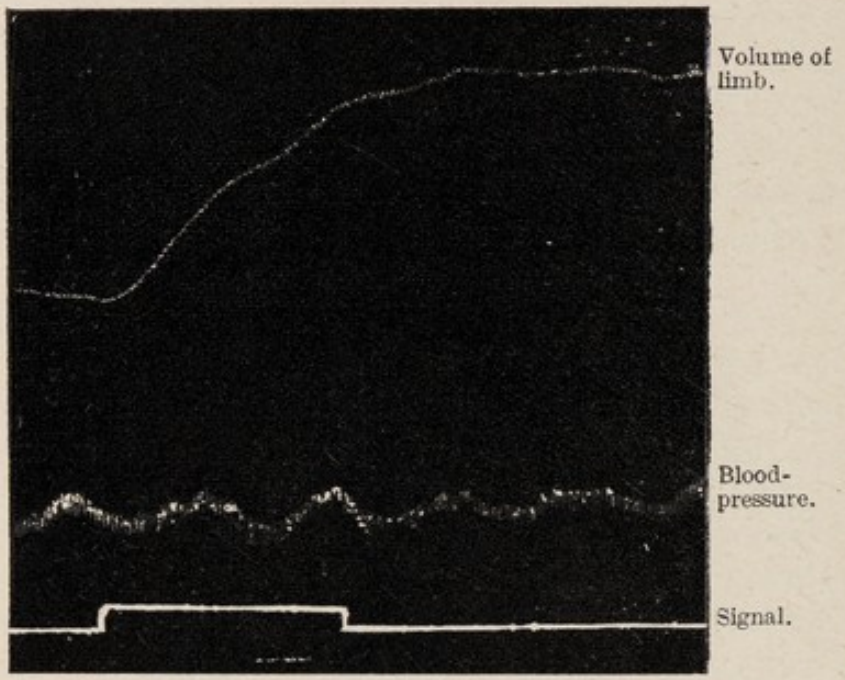


FIG. 121.—Stimulation of peripheral end of 7th lumbar posterior root. (Bayliss.)

limb. The impulse passing along the fibre B also passes along the collateral C to the arteriole D, and causes it to relax. Since nerve-fibres can conduct impulses in both directions, stimulation of the posterior root fibres at E gives rise to an impulse which, travelling down the nerve, passes by the collateral branch C to

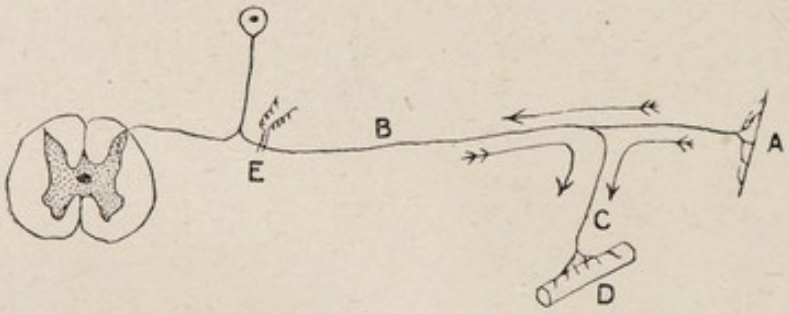


FIG. 122.—Scheme to show path of antidromic impulses (axon-reflex).

the arteriole D, and causes it to relax. We see, therefore, that whether the stimulus is applied at the periphery A or at E, the impulse reaches the arteriole along the branch C. The effect of stimulation at A, which is not a true reflex, is called an *axon-reflex*. If the fibres of the posterior root become degenerated peripherally to the ganglion, the axon-reflex disappears, and

a stimulus applied to the skin at A causes no dilatation of the subcutaneous vessels.

This axon-reflex is of great importance to the body. As is well known, an irritant (*e.g.* a mustard blister) applied to the skin causes it to become red owing to dilatation of the cutaneous vessels. The dilatation of the vessels is one of the means by which the tissues protect themselves against injuries or irritants, and, if the vascular changes fail to occur owing to degeneration of the peripheral sensory fibres, the damage done by the irritant to the tissues may be much more severe.

Vaso-dilator fibres are also present in the sympathetic system itself, although their presence is not readily demonstrated owing to the greater abundance of vaso-constrictor fibres ; but when the endings of the latter are paralysed by the drug ergotoxin, stimulation of the splanchnic nerves causes vaso-dilatation and a fall of blood-pressure.

The vaso-dilator fibres seem to be concerned mainly, though not entirely, with bringing about an increased flow of blood in individual organs, whereas the vaso-constrictor fibres, controlled by the vaso-motor centre, regulate the tone of the arterioles of the body as a whole.

Fig. 123.—Tracing showing the effect upon the blood-pressure of stimulating the depressor nerve. (Bayliss, *Principles of General Physiology.*)

Influences Affecting the Vaso-motor Centre.—The vaso-motor centre is extremely susceptible both to impulses reaching it from other parts of the nervous system, whether these come from the higher parts of the brain or through the peripheral nerves, and to changes in the character and amount of the blood passing to the brain. Its activities are constantly varying in response to these stimuli, in such a way that the mean arterial pressure is raised to meet special needs of the body, and is prevented from falling below the level necessary for the adequate supply of blood to the tissues and more especially to the brain.

(1) *Nervous Stimuli.*—The depressor nerve is a purely afferent nerve, originating in the root of the aorta, and passing to the brain. Electrical stimulation of its central end causes (1) a fall of blood-pressure, and (2) a decrease in the rate of the heart. After section of the vagus nerves, stimulation of the depressor nerve does not affect the rate of the heart, though it still produces a fall of blood-pressure (fig. 123), which in these circumstances

must be due to dilatation of the arterioles. The dilatation is brought about by lessening of the activity of the vaso-motor centre and decrease of the tone of the arterioles ; it is a reflex act, the afferent path being the depressor nerve. In all probability, when the arterial blood-pressure is very high, impulses are set up in the endings of the nerve in the stretched aortic wall which reflexly lower the blood-pressure, and thus lessen the strain placed upon the heart.

Increased activity of the centre and a rise of blood-pressure are brought about by stimulation of most sensory nerves, and also by impulses passing to the centre from the cerebral cortex during muscular exercise and in violent emotional excitement, such as fear or anger.

(2) *The Composition of the Blood.*—The vaso-motor centre is extremely sensitive to changes in the composition of the blood supplying it, being stimulated by a lack of oxygen, or by the presence of an excess of carbonic acid in the blood. The effect of lack of oxygen, and of excess of carbonic acid, is seen in its most extreme form in asphyxia (p. 304), but even a slight excess of carbonic acid stimulates the centre, and leads to constriction of the arterioles and a rise of arterial pressure. The same effect is produced when the reaction of the blood, measured by its H ion concentration, becomes less alkaline ; and the injection into the blood-stream of small amounts of an acid, such as lactic acid, may produce a considerable rise of arterial pressure. Further, the vaso-motor centre is stimulated whenever the amount of blood passing through the brain in a given time diminishes.

During asphyxia the blood-pressure tracing sometimes shows, in addition to the oscillations caused by the heart-beat and respiration, other waves much slower in rhythm and larger in amplitude than the respiratory waves. These waves, known as *Traube-Hering curves*, are not due to the influence of muscular or respiratory movements upon the return of blood to the heart, since they may occur in a curarised animal. They are brought about by slow rhythmic variations in the activity of the vaso-motor centre ; and their occurrence not only during asphyxia, but also after severe hæmorrhage or in anoxæmia, suggests that the activity of the vaso-motor centre assumes a rhythmic character as the outcome of impairment of its nutrition consequent upon an inadequate supply of oxygen.

The subsidiary vaso-motor centres, unlike the chief centre, are extremely insensitive to either nervous or chemical stimuli, and probably they take little or no part in the vascular changes normally occurring in the body, though their activity can be excited by asphyxia.

The Splanchnic Area.—In whatever way the activity of the

vaso-motor centre is increased or lessened, the resulting constriction or relaxation of the blood-vessels is most pronounced in the abdominal organs. The splanchnic nerves send constrictor fibres to the blood-vessels of almost the whole of the abdominal viscera, and the total capacity of these vessels is so large that the amount of blood contained in them forms a great proportion of the total blood in the body. Further, the general arterial pressure is more markedly altered by section or stimulation of the splanchnic nerves than of any other nerve in the body.

When the arterioles of the abdominal organs become constricted in response to stimulation of the splanchnic nerve, the splanchnic viscera naturally contain less blood than before, and more blood has to be accommodated in other parts of the vascular system. As a consequence the large and medium-sized arteries are more fully distended with blood, and in this way the general arterial blood-pressure is raised. Constriction of the arterioles of the abdominal organs thus leads to a rise of blood-pressure in two ways, (1) by the increased peripheral resistance, and (2) by the diminished capacity of these vessels to contain blood; the first of these is the more important.

Hence the maintenance of the mean arterial pressure at a constant level, in spite of the varying influences which are brought to bear upon the vaso-motor centre in daily life, is largely effected by changes in the degree of constriction of the arterioles supplied by the splanchnic nerves, and constituting the *splanchnic area*. For example, when the depressor nerve is stimulated, the fall of pressure which occurs is due mainly to the dilatation of the arterioles in the splanchnic area. When the blood-supply to the vaso-motor centre is deficient, the resulting rise of blood-pressure is caused primarily and chiefly by constriction of the arterioles of the abdominal organs. During muscular exercise an increased flow of blood through the skeletal muscles is required and takes place, and the vessels in the splanchnic area are constricted, more blood being diverted into the muscular system. On the contrary, during digestion, the digestive organs require an abundant blood-supply, and the vessels of the skin are constricted, while the arterioles of the digestive tract are relaxed. It is for this reason that severe exercise taken immediately after a meal tends to disturb digestion.

Influence of Gravity on the Circulation.—If a thin-walled, cylindrical rubber bag is filled with fluid and held with its long axis vertical, the fluid, under the influence of gravity, tends to accumulate at, and to distend, the lower end of the bag. In the body also, the blood tends to accumulate in the most dependent parts, and if a rabbit is held up by the ears the blood accumulates

in the abdominal area, particularly in the large veins, and the arterial blood-pressure falls (fig. 124). As a result, the amount of blood passing through the brain in a given time is inadequate, and its functions are seriously interfered with, so much so that it is said to be possible to kill a hutch rabbit by holding it up in this position for a short time, death being due to anæmia of the brain.

The influence of gravity is antagonised completely in man, and to a lesser extent in most animals, by means of a compensating action on the part of the vaso-motor centre. When a man rises from the horizontal to the standing position, the blood tends

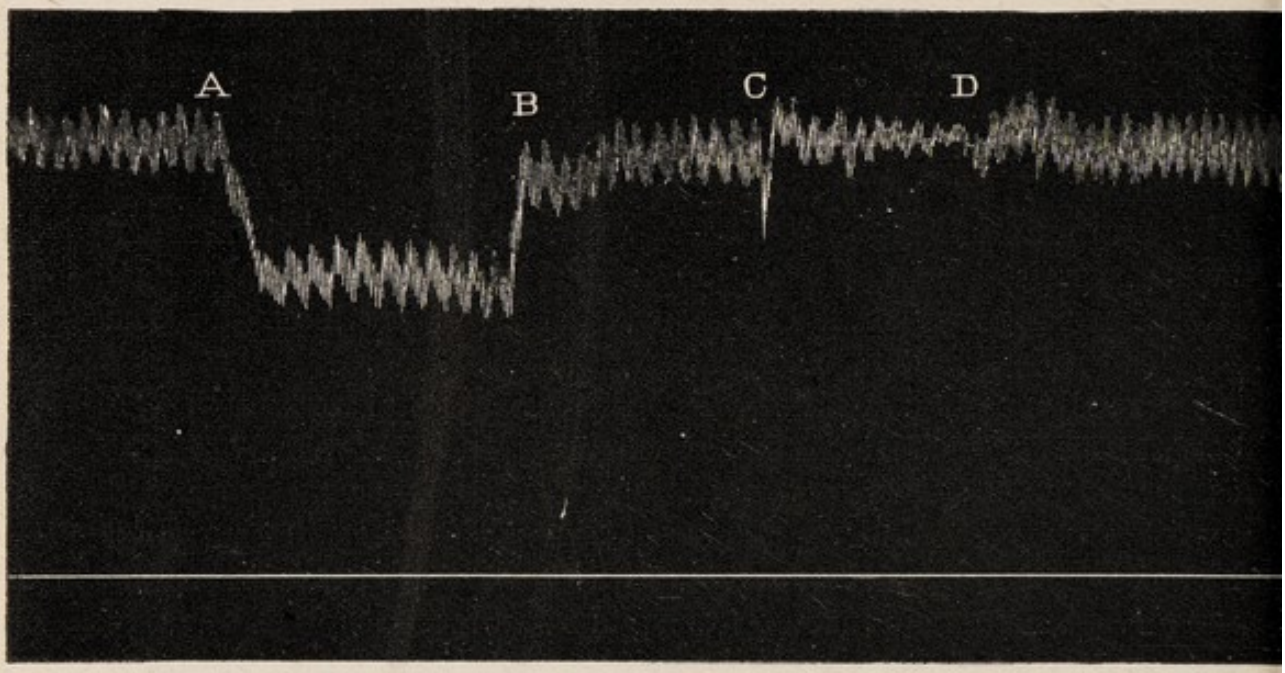


FIG. 124.—Aortic blood-pressure of a dog. Effect of posture. (L. Hill.)
(From *Practical Physiology*, by Pembrey and others.)
A-B, vertical, head up; B, horizontal; C, vertical, head down; D, horizontal.

to accumulate in his abdomen, and the supply of blood to the brain is diminished. This diminution at once stimulates the extremely sensitive vaso-motor centre, which sends out impulses constricting the arterioles of the splanchnic area, thereby forcing the blood out of this area into the rest of the body, including the brain. Conversely, the splanchnic arterioles relax to some extent whenever an individual changes from the vertical to the horizontal position.

This reaction on the part of the vaso-motor centre to any change in the position of the body as regards gravity is so rapid and complete that we are not normally aware of its existence. The temporary giddiness, which is often noticed by individuals who are anæmic or in poor health, on changing suddenly from a horizontal to a standing position, is due to the fact that the

response of the vaso-motor centre to the change of position is slower than usual, and that for a few moments the brain is inadequately supplied with blood. In the same way "fainting" is in many cases caused by temporary diminution of the activity of the vaso-motor centre, so that the blood-pressure falls and the blood-supply to the brain is deficient, causing loss of consciousness. The compensating action of the vaso-motor centre for the effect of gravity is also inefficient in anæsthetised persons.

In the horizontal position, the pressure in the brachial and femoral arteries is almost the same, but, owing to the influence of gravity, the arterial pressure in the femoral artery of an individual in the erect position is much higher than that in the brachial artery. The constriction of the arterioles of the legs, however, is so great that the pressure in the capillaries and veins of the leg and foot is no higher than that in the hands. The flow of blood from the foot and leg back to the heart against the force of gravity is greatly assisted, and indeed made possible, by muscular movement; each muscular movement squeezes the blood along the veins towards the heart, and the valves prevent any reflux. In persons who are habitually compelled to stand for any length of time, or in whom the valves are defective, blood tends to accumulate in the veins of the legs, and the veins are apt to become dilated and varicose.

The Effect of Hæmorrhage.—Any considerable loss of blood from the body lessens the amount present in the vascular system, and the output of the heart at each beat decreases; the arterial pressure falls, and the supply of blood to the brain becomes inadequate. The vaso-motor centre is at once stimulated, causing increased constriction of the arterioles; at the same time fluid passes from the tissues into the blood, and the arterial pressure rapidly regains its normal level. After a very severe hæmorrhage these compensatory mechanisms are inadequate, and the blood-pressure remains low.

The Influence of Adrenalin.—The structure and functions of the suprarenal glands are dealt with later (p. 458), but it is necessary to mention at this point their influence on the circulation. These glands produce a substance, adrenalin, which can be extracted from them and obtained in a pure form. A minute amount of adrenalin (*e.g.* 0·01 or 0·02 mgr.), injected into a vein, stimulates the nerve-endings of all the fibres of the sympathetic system, including those which supply the arterioles, and causes extreme constriction of all the arterioles except the coronary vessels, which are dilated, and the cerebral vessels, which are unaffected; and if the vagus nerves have been divided, a rise of arterial pressure is produced. The suprarenal glands

receive fibres from the splanchnic nerves, and, when a splanchnic nerve is stimulated, some of the adrenalin present in the suprarenal gland passes into the suprarenal vein and so into the blood-stream, giving rise to the effects just described.

It is clear, therefore, that, whenever a splanchnic nerve is stimulated, the ensuing rise of blood-pressure is partly due to the increased peripheral resistance brought about by the direct action of the splanchnic nerve on the abdominal blood-vessels, and is partly caused by the constriction of arterioles all over the body by the adrenalin set free into the blood-stream. The influence of these two factors is seen in the form of the blood-pressure tracing, which often shows, as it rises, a small notch or step (fig. 125) ; the first part of the rise is due to constriction of the abdominal blood-vessels, the rise above the notch is due to

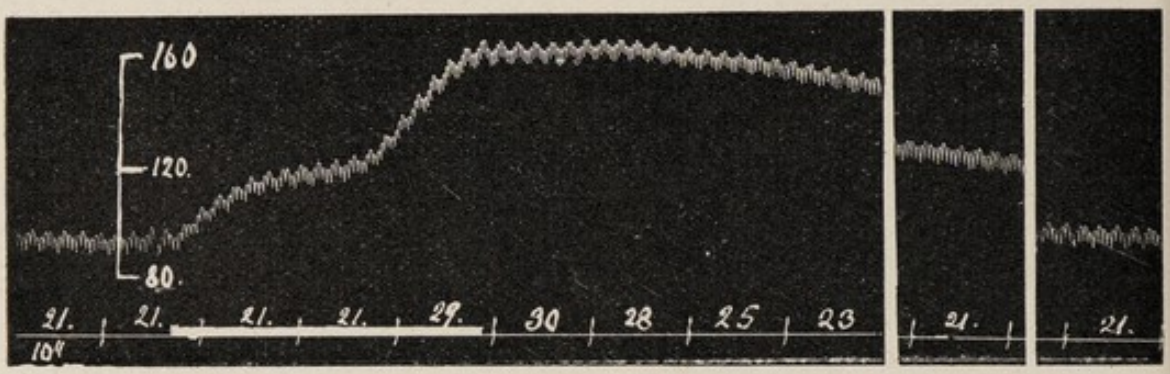


FIG. 125.—Arterial blood-pressure tracing, showing effect of stimulation of left splanchnic nerve. (von Anrep.)

adrenalin. Owing to the setting free of adrenalin, stimulation of a splanchnic nerve may cause diminution in the volume of the limbs. These effects are produced not only when a splanchnic nerve is divided and its peripheral end is directly stimulated, but also when the impulse passing along the splanchnic nerve originates in the vaso-motor centre itself, as in asphyxia. After extirpation of the suprarenal glands, adrenalin can no longer be set free into the blood-stream, and stimulation of a splanchnic nerve causes a much smaller rise of blood-pressure ; the vaso-constriction is limited to the abdominal vessels, and the blood-vessels of the limbs are passively dilated by the higher arterial pressure (fig. 126).

Shock.—After severe injuries or profuse hæmorrhage an individual may pass into the condition known as shock. Its most characteristic symptom is a low arterial blood-pressure ; the pulse is rapid and feeble, the respiration is shallow, and the temperature is low. A similar condition sometimes occurs after surgical operations, and can be experimentally produced in

animals. There is reason to believe that, in shock, a part of the blood stagnates in the capillaries in various parts of the body, the total volume of blood entering the heart, passing through the lungs, and circulating round the body being thereby reduced. Owing to the diminution in the amount of blood which is actually circulating round the body, both the return of blood to the heart and its output are very small, the arterial system contains comparatively little blood, and the arterial pressure is therefore very low. In consequence of the low arterial pressure, the various tissues of the body receive an inadequate supply of blood and of oxygen, and their nutrition is impaired. The brain, which is

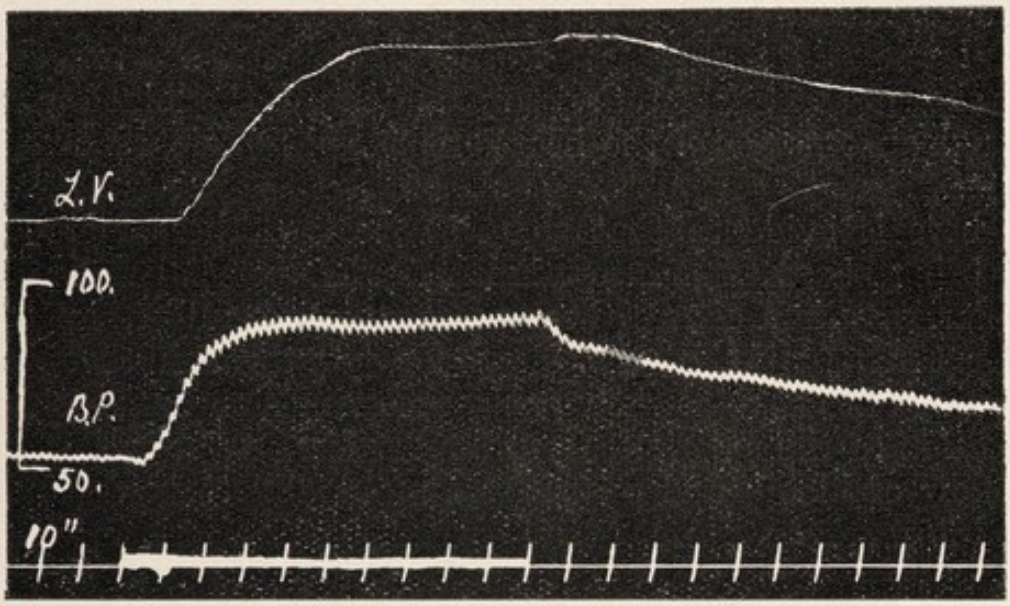


FIG. 126.—Stimulation of a splanchnic nerve after removal of the suprarenal glands. (von Anrep.)

L.V., volume of leg enclosed in a plethysmograph; B.P., arterial blood-pressure.

very readily damaged by lack of oxygen, suffers most in this respect.

The volume of the circulating blood and, consequently, the arterial pressure, may be restored by injecting into the circulation either blood from another individual or a 6 per cent. solution of gum arabic in normal saline. The advantage of gum-saline solution is that, unlike a simple saline solution, it is retained in the blood-vessels. The reasons for this difference are, first, that gum is a colloid, and second, that the osmotic pressure of gum in 6% solution is approximately the same as that of the proteins in blood-plasma. Hence, when a solution of gum is injected into the circulation, the gum, being a colloid, remains in the blood-vessels and, in virtue of its osmotic pressure, it attracts water from the lymph and tissues into the blood, thereby keeping up the blood-volume and arterial pressure for a long time.

Local Changes in the Arterioles.—The variations in the activity of the vaso-motor centre, brought about by the means already described, are chiefly directed to regulating the mean arterial pressure and to providing an efficient supply of blood to the brain. Alterations in the calibre of the arterioles in any one organ of the body, as distinct from the body in general, can also be brought about by vaso-dilator nerves, as, for example, the chorda tympani. There is, however, another factor of great importance. Generally speaking, increased functional activity of any organ of the body is accompanied by dilatation of its arterioles and an increased flow of blood through it; this is brought about by the direct action upon the walls of the arterioles of the waste products (metabolites) formed by the organ during its activity. These include carbonic acid, lactic acid, and probably other substances, and experiment has shown that, when they are added to the blood passing through an organ, *e.g.* the heart or skeletal muscle, its arterioles dilate.

There is evidence that some at least of these metabolites also bring about some alteration in the endothelial walls of the capillaries, which causes them to dilate more fully than before under the pressure of the blood flowing through them. The widening of the capillary channels, occurring simultaneously with dilatation of the arterioles, still further lessens the resistance to the flow of blood, and contributes materially to increasing the blood-flow through an active organ. This local mechanism provides a means by which the increased demands of an active tissue for nutritive material and oxygen are met by an increase in the amount of blood passing through it.

THE CEREBRAL CIRCULATION

The circulation of the blood through the brain is peculiar in two respects. In the first place, the brain is enclosed in a rigid case, the skull, which it almost completely fills, and, in the second place, there is at present no conclusive evidence that the arterioles of the brain are under the control of the vaso-motor centre, although the existence of nerve-plexuses round them has been observed histologically. The presence of cerebro-spinal fluid in the skull allows for a slight increase in the volume of the blood in the cerebral blood-vessels, since a rise of pressure within these vessels distends them to a certain extent, and forces some of the cerebro-spinal fluid out of the skull into the sheaths of the nerve-trunks. Apart from this increase, which amounts only to 2 or 3 c.c., the amount of blood in the cerebral vessels cannot be increased, since

the capacity of the skull is constant, and the brain which, together with the blood-vessels, practically fills it, is incompressible.

Any increase or decrease in the amount of blood supplying the brain is brought about entirely by variations in the *velocity* with which the blood flows through the cerebral vessels. It has already been pointed out that, if the width of the bed through which the blood is flowing remains constant, the velocity of the flow will vary directly with the pressure which tends to drive the blood along the vessels. In the body this pressure is the mean arterial pressure, and, since the volume of the cerebral vessels remains constant, the velocity of the flow of blood through them will depend entirely on the arterial pressure, provided there is no obstruction to the escape of blood from the cerebral veins. If the arterial pressure rises, the arteries become rather more distended and occupy more space, and, as the total volume of the cerebral vessels remains unaltered, the expansion of the arteries must be accompanied by narrowing of the capillaries and veins. The narrowing is not sufficient to cause any obstruction to the escape of blood through these vessels, and the amount of blood flowing through the brain is greatly increased. If the general arterial pressure falls, the velocity of the blood-flow through the brain diminishes, and the amount of oxygen reaching it in a given time is correspondingly decreased. When the supply of oxygen falls, the vaso-motor centre is stimulated, causing constriction of the splanchnic arterioles, and thereby raising the blood-pressure to such a level that the flow of blood through the brain is again sufficient to provide an adequate supply of oxygen. Thus the blood-supply to the brain is determined almost entirely by conditions outside the brain itself, being increased whenever the abdominal vessels are constricted, and diminished when these dilate. The brain is protected from lack of oxygen by the vaso-motor centre in the manner just described.

If the blood-supply to the brain becomes inadequate, the respiratory centre is also stimulated, and the increased respiratory movements bring more blood to the heart, thereby enabling it to expel more blood at each beat and thus to assist the vaso-motor centre in raising the blood-pressure.

The pressure of the cranial contents upon the wall of the skull is just below that within the capillaries of the brain. It cannot be greater than the capillary pressure, since, in these circumstances, the capillaries would collapse and the flow of blood through the brain would cease. The intra-cranial pressure can be raised by any obstruction to the escape of blood from the cerebral veins, or by the presence within the skull of a foreign body, such as a blood-clot. In the latter case the pressure within the skull may

rise sufficiently to compress the capillaries, or even actually to obliterate them. Such compression, which inevitably diminishes the blood-supply to the brain, may cause loss of consciousness and other serious symptoms.

THE ESSENTIAL FEATURES OF THE CIRCULATION

The primary factors on which the efficient working of the circulatory mechanism depends are (1) an adequate output of blood from the heart, and (2) the peripheral resistance in the arterioles. An adequate cardiac output is required in order that the blood may travel through the lungs and round the body in sufficient amount, and sufficiently rapidly, to meet the needs of the body for oxygen and nutrient material, and to remove waste products. The peripheral resistance normally maintains the arterial pressure at such a height as to provide an abundant supply of blood to the brain, and to the heart itself. Aided by the elasticity of the arteries, it also ensures a slow, steady flow of blood through the capillaries.

The adjustment of these factors to the varying needs of the body is mainly effected through the central nervous system, which controls the rate of the heart and the degree of peripheral resistance. When the venous inflow to the heart is large, for example, its output is increased by acceleration of the heart. Again, a rise of arterial pressure stimulates the endings of the depressor nerve and causes reflex dilatation of the arterioles, thereby lowering the arterial pressure and lessening the work of the heart. If the arterial pressure falls, it is restored to the normal level by increased activity of the vaso-motor centre, which is assisted in many cases by an increased output of blood from the heart.

These and other regulative mechanisms depend for their efficiency upon the nutrition of the heart itself, and upon the maintenance of its normal rhythm. Broadly speaking, the rate of the heart is determined by the influence of the nervous system, and the force of the beat by the length of the cardiac muscular fibres at the beginning of systole and by the state of their nutrition. The latter depends almost entirely upon the amount and character of the blood supplied to the heart by the coronary vessels ; if its nutrition is impaired, the heart beats more and more feebly, fails to expel its contents into the aorta, and finally the circulation may come to a standstill. Thus the nutrition of the heart-muscle is ultimately the most important feature of the circulatory mechanism.

SECTION VI

THE FORMATION OF LYMPH

Except in the spleen and the liver, the blood does not come into direct contact with the cells of the tissues. It is separated from them not only by the walls of the capillaries, but also by a fluid called lymph or tissue-fluid, which lies between the capillaries and the tissue-cells themselves. From these spaces the lymph passes into narrow channels (lymphatic vessels) lined by endothelial cells. These channels unite and finally end in a single vessel, the thoracic duct, which opens into the junction of the left jugular and subclavian veins, and conveys the lymph from the greater part of the body into the blood-stream. The lymph from the right side of the head and neck and the right fore-limb, passes into a vessel which opens into the junction of the right jugular and subclavian veins.

The lymph has been described by Foster as a " middle-man," since, on the one hand, it receives from the blood oxygen and dissolved nutrient materials and passes them on to the tissue-cells, and, on the other hand, it receives from the tissue-cells carbonic acid and other waste products and returns them to the blood-stream. The interchange of material between the blood and the tissues takes place by diffusion (p. 16), and in this way the tissues are nourished without any change necessarily occurring in the amount of tissue-fluid.

THE COMPOSITION OF LYMPH

Lymph can be collected by placing a cannula in the thoracic duct of an animal, such as a dog or horse. If the animal has not been recently fed, the lymph is a clear, colourless fluid having a specific gravity of about 1015 ; it usually clots when allowed to stand. It contains some lymphocytes, 4 to 5 per cent. of protein, the proteins being the same as those in blood-plasma, and also various salts and extractives. After a meal the lymph is milky in appearance, owing to the presence of large numbers of minute fat-globules. The fat is derived from that taken in the food, which, after absorption from the digestive tract, passes into the intestinal lymphatic vessels (lacteals). In their course the vessels pass through the lymphatic glands, in which lymphocytes are formed ; the lymphocytes enter the lymph-stream and are carried into the blood.

THE FORMATION OF LYMPH

Although the exchange of material between the blood and the tissues does not necessarily increase the amount of lymph in the tissue-spaces, it is found that, in point of fact, lymph is constantly being formed in the body, and, after passing along the lymphatic vessels, is returned to the blood-stream along the thoracic duct. The formation of lymph has been attributed by some writers to secretion by the walls of the capillaries, and by others to the action of purely physical processes such as filtration and osmosis. If the latter view is correct, a rise in capillary pressure should lead to an increase in the formation of lymph ; and this is found to be the case.

The pressure in the capillaries is not greatly influenced by alterations in the mean arterial pressure, but is very readily affected by changes in venous pressure ; a rise in venous pressure, by obstructing the escape of blood from the capillaries, at once raises the capillary pressure. Hence a large rise in capillary pressure can be produced by ligaturing the inferior vena cava or the portal vein ; and this is followed by a great increase in the flow of lymph from the thoracic duct.

Again, when a large quantity of saline solution is injected into the circulation, the blood is not only increased in amount, but becomes more watery, the condition being called *hydræmic plethora.* The arterial pressure remains almost unaltered, but the veins are distended to contain the greater part of the fluid added to the circulation, and the venous pressure rises ; as a result the pressure in the capillaries also rises, and the flow of lymph from the thoracic duct becomes very profuse.

Hydræmic plethora may also be produced by injecting into the blood a strong solution of glucose or other crystalloid body ; this raises the osmotic pressure of the blood, and water passes by osmosis from the tissues into the blood, thereby increasing its volume and raising the capillary pressure. In these circumstances a great increase takes place in the flow of lymph from the thoracic duct, as is seen in the following table :—

HYDRÆMIC PLETHORA

Periods of Ten Minutes.	Arterial Blood-Pressure.	Pressure in Inferior Vena Cava.	Flow of Lymph.
1	100 mm. Hg	12 mm. water	3·0 c.c.
40 grm. glucose dissolved in 50 c.c. water injected into a vein.			
2	105 mm. Hg	180 mm. water	33·0 c.c.
3	120 „ „	50 „ „	31·0 „
4	118 „ „	25 „ „	20·0 „

From these experiments it may be concluded that the walls of the capillaries form a membrane through which lymph can be filtered off, and that the amount of fluid which passes through the membrane in a given time depends directly upon the capillary pressure.

Another factor in the formation of lymph is the variable readiness with which filtration takes place through the capillaries in different parts of the body under the same pressure. The least permeable capillaries are those of the limbs, the most permeable are those of the liver ; and almost all the lymph flowing from the thoracic duct of a resting animal is formed in the liver and digestive tract. The permeability of the capillaries can be increased by the injection of various poisonous substances called *lymphagogues*, including peptone and leech-extract. The injection of one or other of these substances into the blood-stream leads to an increased formation of lymph, although the capillary pressure, after a short time, is almost unaltered. The additional lymph is derived almost entirely from the liver, as is shown by the fact that, if the lymphatic vessels of the liver are ligatured, the subsequent injection of peptone does not increase the formation of lymph. Hence these lymphagogues act by damaging the capillaries of the liver, and thus increasing their permeability.

The permeability of the capillaries is also increased when their nutrition is impaired, *e.g.* by lack of oxygen, and such an impairment may give rise to dropsy.

The formation of lymph is also dependent upon the metabolism of the tissues themselves. The injection into the blood of bile-salts, for example, leads to the secretion of bile by the liver, and the flow of lymph from the thoracic duct is increased. This is not due to raised capillary pressure, or to changes in the permeability of the capillaries, but is brought about in the following manner. In normal circumstances the osmotic pressure of the tissue-cells, the lymph, and the blood is almost the same. When the metabolism of the liver is increased, metabolic products are formed in the liver-cells and diffuse into the lymph, raising the osmotic pressure of the liver-cells and the lymph as compared with that of the blood. Consequently water passes from the blood into the lymph, and this fluid is increased in amount, giving rise to a larger flow from the thoracic duct. Similar results have been observed in other organs, and probably increased functional activity of any tissue in the body leads to increased formation of lymph.

We may conclude, therefore, that lymph-formation is not a secretory process, but is brought about by purely physical processes, namely, filtration and osmosis ; and the factors concerned

in its production are (1) the capillary pressure, (2) the degree of permeability of the capillary walls, and (3) the metabolic activity of the tissues. There is no reason to suppose that, in health, the permeability of the capillaries alters, and therefore the formation of lymph is increased chiefly by variations in the first and third of these factors.

ABSORPTION FROM THE TISSUES

If a saline solution containing some readily recognisable substance, such as potassium iodide, is injected under the skin or into the pleural or peritoneal cavity, it rapidly disappears, and the presence of potassium iodide can be demonstrated in the blood or urine some time before it appears in the lymph flowing from the thoracic duct. This experiment makes it clear, first, that water and substances in solution can be readily absorbed from the tissue-spaces, and, secondly, that the absorption does not take place into the lymphatic vessels, but through the capillary walls directly into the blood. Similarly, tissue-fluid may be absorbed through the capillary walls; after hæmorrhage, for instance, the volume of the blood is rapidly brought back to the normal by the passage of fluid from the tissue-spaces into the blood. This process depends upon the fact that proteins exert an osmotic pressure, which, though very small in comparison with that of a solution of crystalloid bodies, is yet appreciable. The osmotic pressure of the crystalloids in blood and lymph is much the same, but, owing to the percentage of protein in blood being higher than that in lymph, the blood has a slightly higher osmotic pressure, and fluid tends to pass from the lymph into the blood. At the same time, fluid is being filtered through the capillary wall from the blood into the lymph at a rate varying with the capillary pressure. These two processes, namely, absorption and filtration, tend to balance one another and to keep the volume of the blood constant. The balance may be disturbed either by a rise or by a fall of capillary pressure. In the former case, the amount of tissue-fluid is increased; whereas, if the capillary pressure falls, for instance after severe hæmorrhage, the amount of fluid absorbed exceeds that which is filtered through the capillary walls, and the volume of the blood is restored at the expense of the lymph and tissues.

THE FLOW OF LYMPH

Various factors are concerned in bringing about the flow of lymph from the periphery to the thoracic duct. The first of these is the pressure under which lymph is filtered from the

blood-capillaries, the "filtration-pressure"; this is considerably higher than the pressure in the thoracic duct. Where the duct opens into the great veins the pressure is at most 2 to 3 mm. Hg, and may be negative. Other and more important factors promoting the movement of lymph are muscular and respiratory movements. Every muscular movement, by compressing the lymphatic vessels, forces the lymph on towards the thoracic duct. The contraction of the strands of smooth muscle in the intestinal villi drives the contents of the central lacteal of each villus into the lymphatic vessels. Further, with each inspiration, the abdominal pressure rises and the intestinal lymphatic vessels are compressed; at the same time, the pressure on the thoracic duct becomes negative, and lymph is sucked into it. The effect of these movements is assisted by the presence of valves in the larger lymphatic vessels, which prevent any backward flow of lymph. The flow of lymph from the tissues to the junction of the thoracic duct with the venous system is thus brought about partly by a *vis a tergo*, namely, the filtration-pressure, plus the effect of muscular contraction, aided by the pumping action of the intestinal villi and by increased abdominal pressure during inspiration; and partly by a *vis a fronte*, this being the suction action of the inspiratory movements upon the thoracic duct and great veins in the thorax.

CHAPTER VIII

THE RESPIRATORY SYSTEM

SECTION I

Respiration consists in the transference of oxygen from the atmospheric air to the tissues of the body, and of carbonic acid from the tissues to the outer air. In man and most vertebrates, the oxygen and carbonic acid are carried to and from the tissues respectively by the blood, which, on the one hand, receives oxygen in the lungs and gives it up to the tissues, and, on the other hand, receives carbonic acid from the tissues and gives it up in the lungs. In fishes and many invertebrates, the lungs are replaced by gills. The transference of oxygen from the atmosphere into the blood, and of carbonic acid from the blood into the atmosphere, is called *external* respiration, the interchange of gases between the blood and the tissues being termed *internal or tissue* respiration.

THE STRUCTURE OF THE AIR-PASSAGES AND LUNGS

The respiratory system consists of the lungs and the air-passages leading to them, namely, the mouth and lower half of the nasal cavity, the upper part of the pharynx, the larynx, trachea, and bronchi. The *trachea* is a wide tube about 4½ inches in length in man, and is lined by stratified epithelium, the cells of the inner layer being columnar and ciliated. The epithelium rests upon a thick basement-membrane, beneath which is a layer of elastic fibres running longitudinally ; external to this is areolar tissue in which lie many small glands, which secrete mucin ; outside this is a fibrous coat, strengthened by C-shaped hoops of cartilage. The posterior wall of the trachea contains a layer of unstriped muscle, most of the fibres of which run transversely between the free ends of the cartilages. The cartilaginous hoops keep the lumen of the trachea patent, and prevent its occlusion by external pressure. The fluid formed by the small mucous glands moistens the inner surface of the trachea, and serves also to catch bacteria or particles of dust, which may be carried in

with the inspired air; the cilia, by their movement, carry the fluid up the trachea towards the pharynx.

The main bronchi are similar in structure to the trachea.

In the lungs the bronchi branch in a tree-like manner, the final ramifications opening into the pulmonary air-cells. The *larger intra-pulmonary bronchi* are lined by columnar, ciliated epithelium resting on a basement-membrane. Lying under the basement-membrane are longitudinally disposed elastic fibres with loose

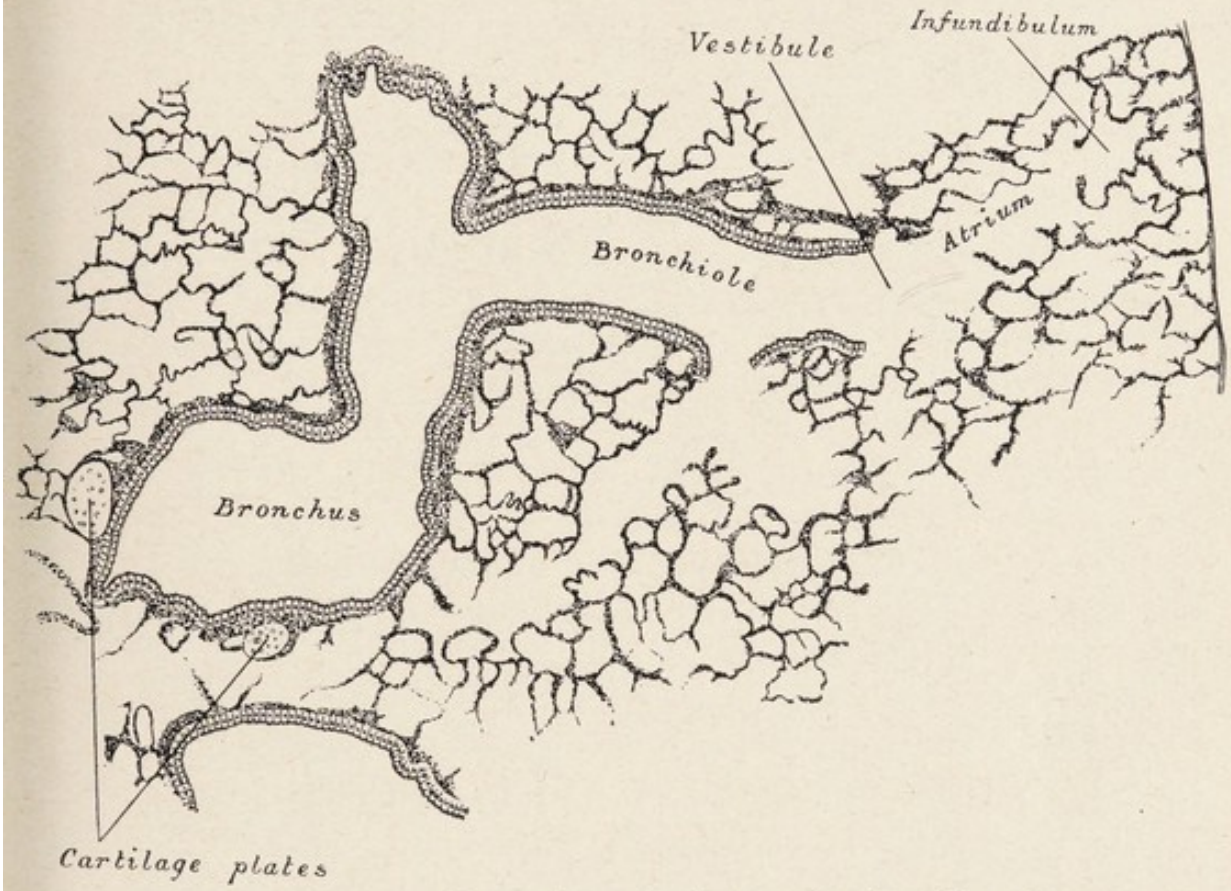


FIG. 127.—Section of lung of cat, showing termination of bronchus. (From Gray's *Anatomy*.)

connective tissue. More externally is a layer of smooth muscle-fibres arranged circularly, the bronchial muscle. External to the bronchial muscle is a fibrous coat containing scattered, irregular plates of hyaline cartilage.

The *smaller bronchi* (bronchioles) have no cartilaginous plates, but their muscular coat is well marked.

Each bronchiole leads into a small number (three or four) of wider thin-walled spaces, lined by flattened epithelium, and called *atria* (fig. 127). Out of each atrium open two or three blind diverticula, each of which is called an *infundibulum*. The walls of the infundibula are studded with hemispherical sacs known as *alveoli*, which are lined by flattened, non-nucleated, epithelial cells. Between adjacent alveoli there is a dense network of capillaries,

supported by a small amount of fine connective and elastic tissue; the network of capillaries is thus common to the two adjacent alveoli, and the blood in the capillaries is separated from the air in the alveoli merely by two thin layers of epithelium. In birds, even the alveolar epithelium appears to be absent, the blood and air being separated solely by the capillary wall.

The branches of the pulmonary artery accompany the bronchi, and open into the alveolar capillary network, from which blood is carried back to the left auricle by the pulmonary veins. Oxygenated blood is supplied to the bronchi by the bronchial arteries.

The lungs nearly fill the thoracic cavity, the space between them being occupied by the heart, great vessels, and other structures. Each lung is covered by a thin membrane, consisting of a superficial layer of flattened epithelium resting on connective tissue with many elastic fibres; the membrane is known as the *pleura*, and is reflected at the root of the lung on to the chest-wall. Each pleura forms a closed sac, the walls of which are normally in apposition; their inner surfaces are moistened by a small amount of fluid, resembling lymph, and glide over one another with every movement of the chest-wall and lung.

THE RESPIRATORY MOVEMENTS

The thorax is a completely closed box, which alters in shape and size with each respiratory movement; with inspiration it becomes larger in all its diameters, vertical, antero-posterior, and transverse, returning to its former size during expiration. The increase in size is brought about partly by the upward movement of the ribs, partly by the descent of the diaphragm.

The diaphragm consists of a muscular sheet with a tendinous central portion. In the position of rest it forms a dome projecting towards the thoracic cavity and when it contracts the summit of the dome, namely the tendinous portion, is drawn downwards from 1 to 2 cm., thereby increasing the vertical diameter of the chest. The extent to which the central tendon can be drawn downwards is limited by the resistance of the abdominal viscera, and, when the limit is reached, the direction of the pull of the costo-sternal muscle-fibres of the diaphragm is reversed, so that the lower end of the sternum and the movable ribs are raised. The spinal fibres of the diaphragm, the lower attachment of which is a fixed point, exert a downward pull upon the central tendon throughout the inspiratory period.

The Ribs.—At the beginning of inspiration the first pair of ribs and the manubrium sterni are fixed by the resistance of the cervical structures, and the second to the fifth pairs of ribs are

drawn upwards by the contraction of the external intercostal muscles and the serratus posticus (posterior) superior. Since the ribs slant downwards and forwards from their vertebral articulation, this upward movement carries the sternum forward and increases the antero-posterior diameter of the chest. At the same time the ribs rotate slightly round the axis represented by a line drawn from their vertebral to their sternal attachments, and their lower borders, which in the expiratory position are inverted, become everted. The costo-chondral angle is also opened out. By these means the transverse diameter of the chest is enlarged.

The lower ribs are raised partly by the external intercostal muscles, partly also by the contraction of the diaphragm, and partly by the interchondral portion of the internal intercostal muscles.

Thus the muscles concerned in quiet inspiration are the diaphragm, the external intercostal muscles, the interchondral portion of the internal intercostal muscles, and the serratus posticus (posterior) superior. The entrance of air into the lungs is also assisted by widening of the glottis, and, if the breathing is at all laboured, by dilatation of the alæ nasi. In forced inspiration other muscles, such as the trapezius, pectoral muscles, sterno-mastoid, and rhomboids, are called into play.

During quiet expiration, the chest returns to its former shape and size, mainly on account of the elasticity of the chest-wall and lungs and of the abdominal wall and abdominal contents; the downward movement of the ribs during expiration is also assisted by the contraction of the costal part of the internal intercostal muscles. In forced expiration, the accessory muscles employed are mainly those of the abdominal wall.

Quiet respiration in men is carried out principally by the movements of the diaphragm. In women, the larger part is played by the movements of the upper ribs, chiefly on account of the wearing of tight clothing, which interferes with the movement of the diaphragm and lower ribs.

THE EFFECTS OF THE RESPIRATORY MOVEMENTS ON THE LUNGS

The passage of air into, and out of, the lungs during respiration is brought about by purely mechanical causes, which can be roughly illustrated by the aid of an artificial model. A thin-walled, rubber bag is placed in a glass vessel closed by a cork; the bag is attached to a glass tube, which passes through the cork and is open at the top. The bottle is connected by another tube

with a mercury manometer, and by a third tube with a suction-pump, by means of which air can be sucked out of it (fig. 128).

At the outset of the experiment the air in the bottle is at the same pressure as that of the atmosphere, and the bag is collapsed. If a little air is sucked out of the bottle, the pressure falls and, since the pressure within the rubber bag remains unaltered, a difference of pressure is set up on its inner and outer surfaces. The bag therefore expands, air being sucked into it along the glass tube to fill the extra space thus provided, until the pressure within it and outside it becomes nearly equal; but the pressure outside the bag is finally a little less than atmospheric pressure, because a part of the pressure on the inner surface of the bag is used up in overcoming the tendency of its stretched elastic wall to collapse. When more air is sucked out of the bottle, the rubber bag expands still further, but the pressure in the bottle remains negative, that is, less than atmospheric pressure. When the bottle is opened, the bag collapses because the pressure on each side of it becomes the same.

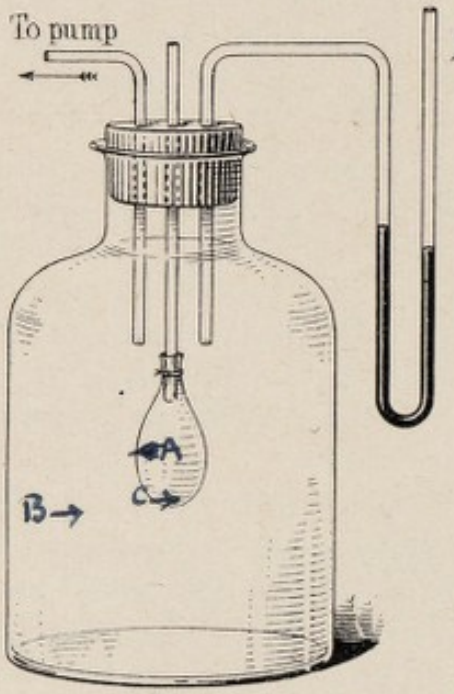


FIG. 128.—For explanation see text.

In the body the lungs take the place of the bag, the bottle is represented by the chest, and the changes in the pressure on the outer surface of the lungs are brought about by alteration in the size of the chest-cavity. If a small tube, connected with a manometer, is passed through the chest-wall of an animal into the pleural cavity, the pressure within the chest is seen to be lower than that of the atmosphere; at the end of expiration the difference is usually about 6 mm. Hg. When the chest enlarges during inspiration, the pressure on the outer surface of the lungs diminishes, and, as the pressure within them remains unchanged, they expand. Owing to the greater force required to bring about this expansion of the lungs, the pressure in the pleural cavity is further diminished, and amounts on an average to 730 mm. Hg. The negative pressure in the pleural cavity thus varies from — 6 mm. Hg during expiration to — 30 mm. Hg or more during inspiration, and represents the pressure required to overcome the tendency of the expanded lungs to collapse by virtue of their elasticity. When the lungs expand during inspiration, air rushes in to fill

the additional space; during expiration air is expelled. The expansion of the lungs during inspiration is due almost entirely to the enlargement of the infundibula and atria, and the portions of the lungs which expand most are those in contact with the diaphragm and ribs; the dorsal and mediastinal surfaces, and the apices are much less expansile.

If the chest is opened, either during life or after death, the pressure on both the outer and the inner surfaces of the lungs is that of the atmosphere, and owing to their elasticity the lungs collapse. In the new-born infant, the lungs, even in their collapsed condition, fill the chest. As the child grows, the capacity of the chest increases more rapidly than does the size of the lungs; and the lungs of the adult are considerably expanded even at the end of expiration.

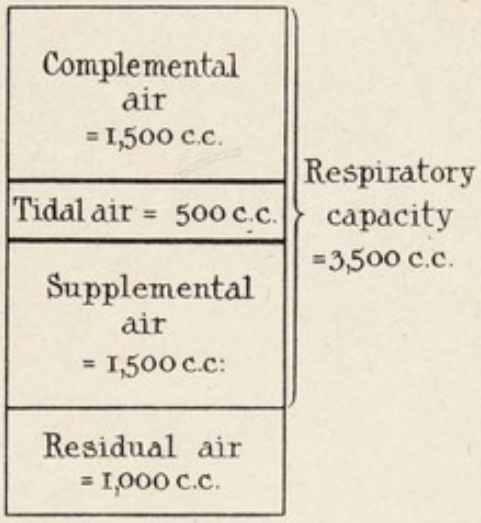


FIG. 129.

Since with each expansion of the chest the lungs increase in size so as to fill completely the extra space thus provided, the amount of air entering the lungs at each breath varies with the extent of the respiratory movement. In quiet respiration it amounts to 350 to 500 c.c., and is spoken of as *tidal* air. The additional volume of air which can be taken into the lungs by forced inspiration amounts on an average to about 1500 c.c., and is called *complemental* air. The largest amount of air which can be expelled from the lungs by the most violent expiration, made at the end of an ordinary breath, is termed *supplemental* air; it varies in different individuals from 1000 to 1500 c.c. The total volume of air which can be taken into and expelled from the lungs by the most forcible inspiration and expiration, namely, the sum of the tidal, complemental, and supplemental air, is termed the *vital capacity* of the chest, and is from 3000 to 3500 c.c. These figures are obtained by allowing the individual to breathe into a spirometer, which is a small gasometer provided with a graduated scale. When the subject breathes into, or out of, the spirometer, the air-chamber rises or falls, the increase or decrease of its contents, thus produced, being read off on the scale.

Even after the most forcible expiration a considerable amount of air—usually about 1000 c.c.—still remains in the lungs, and is spoken of as *residual* air (fig. 129).

is the chest wall C, consequently A becomes more positive to overcome in, & B's in comparison less more negative.

The normal rate of respiration in adults is 15 to 18 a minute. Expiration follows inspiration immediately, and is succeeded by a slight pause before the next inspiration begins. Children breathe more rapidly, the rate in the infant being about 40 per minute.

Ordinary quiet breathing is usually called *eupnœa*, and an increase in the depth of the respiratory movements is called *hyperpnœa*; if these movements are not only deeper, but also laboured, the term *dyspnœa* is applied to them. A temporary cessation of breathing is known as *apnœa*.

If the ear is placed in contact with the chest-wall, a faint sound—the vesicular murmur—is heard during inspiration; it is believed to be produced by the passage of air through the larger respiratory passages, the sound being modified in its conduction through the substance of the lung to the surface of the body. On listening over the trachea and large bronchi, the sound is louder, and is audible both during inspiration and expiration. The character of the sound is altered in disease of the lungs or pleura.

SECTION II

THE CHEMISTRY OF RESPIRATION

The composition of expired air differs considerably from that of the atmosphere, the average difference being as follows :—

	Nitrogen.	Oxygen.	Carbonic Acid.
Inspired air . . .	79	20·96	0·04
Expired air . . .	79·4	16·50	4·10
		4·46	4·06

The increased percentage of carbonic acid in expired, as compared with inspired, air is 4·06, the difference between the percentage of oxygen in inspired and expired air being 4·46, so that the total volume of the air expired is less than that inspired. It is for this reason that the *relative* amount of nitrogen in expired air is slightly increased, although the actual amount is the same as in inspired air. The ratio of the volume of carbonic acid leaving the body to the volume of oxygen taken into the body and not reappearing in the expired air is known as the *respiratory quotient*, and is usually expressed as $\frac{CO_2}{O_2}$. In

the table it is $\frac{4{\cdot}06}{4{\cdot}46} = 0{\cdot}90$. Its significance will be discussed subsequently.

In addition to containing less oxygen and more carbonic acid, the expired air is fully saturated with water, and is at the body temperature. It has been stated that small quantities of poisonous substances are also present in expired air, and that the accumulation of these substances in crowded and ill-ventilated rooms is the cause of the headache and other uncomfortable symptoms experienced in these circumstances. Careful experiments have shown that this is not the case, and that the symptoms are due partly to the accumulation of carbonic acid in the air, and make their appearance when this reaches 0·1 per cent. or more, and partly, as Leonard Hill suggests, to a high temperature and lack of currents of air in the room. They may be avoided by constant renewal of the air in rooms by adequate ventilation.

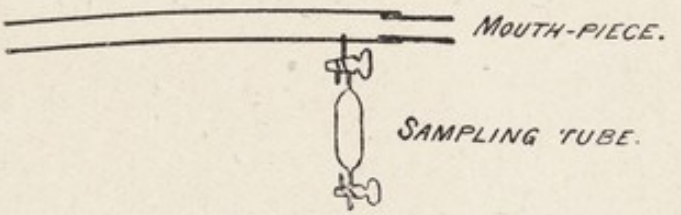


FIG. 130.

The expired air comes partly from the lungs, partly also from the respiratory passages, namely the bronchi, trachea, pharynx, and nose. Since the air in these passages undergoes very little change in composition during respiration, they are known as the "dead space," the capacity of which varies from 130 to 150 c.c., and is very constant for the same individual. The air contained in the dead space is expelled during the first part of expiration, the air expelled during the latter part of expiration, particularly if this is forcible, coming directly from the alveoli of the lungs. Since the interchange of oxygen and carbonic acid between the blood and the air in the lungs takes place solely in the alveoli, it is of great importance to ascertain the composition of the alveolar air.

Haldane has devised a simple apparatus for collecting samples of *alveolar air* in man. It consists of a piece of rubber tubing about 1 inch in diameter, 3 or 4 feet long, and provided with a mouthpiece. About 2 inches from the mouthpiece the tube is connected with a sampling tube (fig. 130), which has previously been made vacuous. The subject breathes normally for a few moments, and then, at the end of a normal inspiration, he expires deeply through the mouthpiece and instantly closes the mouthpiece with his tongue. The part of the tube near the mouthpiece is now full of alveolar air. The upper tap of the sampling tube

is at once opened, and alveolar air rushes into it from the tube; the tap is then closed, and the sample can be analysed. A second similar experiment is made, in which the subject expires deeply at the end of a normal expiration, and another sample of air is obtained. The mean of the analyses of the two samples gives the average composition of the alveolar air.

The reason for taking two samples is that at the end of inspiration the lungs contain a maximum percentage of oxygen, whereas at the end of expiration they contain a maximum percentage of carbonic acid. The amount of carbonic acid in alveolar air obtained by this method varies from 5 to 6 per cent. in different individuals, but is remarkably constant in the same individual; the amount of oxygen is usually 13 to 14 per cent. Alveolar air thus contains considerably less oxygen, and more carbonic acid, than ordinary expired air, the reason being that, in the expired air, the alveolar air is mixed with the contents of the dead space, the composition of which differs but little from that of the atmosphere.

The air is analysed by shaking up a known volume with caustic potash, which absorbs the carbonic acid; the diminution in volume represents the amount of carbonic acid present in the air. The air is then shaken up with pyrogallic acid, which absorbs oxygen, and the diminution in volume is again measured. The residual gas is regarded as being nitrogen.

THE GASES IN THE BLOOD

Before discussing the means by which the interchange of oxygen and carbonic acid between the blood and air in the lungs is effected, it is necessary to determine, first, the amount of these gases in the blood, and, secondly, the conditions in which they are held in it.

GASES IN THE BLOOD (DOG)

		Oxygen.	Carbonic Acid.	Nitrogen.
100 volumes of	Arterial blood yield .	20 vols.	40 vols.	1–2 vols.
	Venous blood yield .	8–12 ,,	46–48 ,,	1–2 ,,

If blood is exposed to a vacuum, there is a considerable evolution of gas, which may be collected and analysed. For this purpose, some form of gas-pump is usually employed, the composition of the gas being subsequently ascertained by exposing

it first to potash, which absorbs carbonic acid, and secondly to pyrogallic acid, which absorbs oxygen. By this means it is found that 100 volumes of blood give off about 60 volumes of gas, the composition of which varies according to whether the blood is arterial or venous.

The above method necessitates the use of comparatively large quantities of blood (10 to 20 c.c.) in order to give accurate results ; and Barcroft has devised an apparatus, by means of which the estimation of the blood-gases can be carried out with very small quantities (1 c.c. or even 0·1 c.c.) of blood. The method has the advantage of being readily applicable to man, and depends upon the fact that, when potassium ferricyanide and a trace of alkali (usually ammonia) are added to blood, all the oxygen previously in combination with hæmoglobin is evolved, and the amount of oxygen given off from a known volume of blood can be measured. The hæmoglobin then takes up oxygen from the reagents, being converted into methæmoglobin.

On subsequent treatment of the sample of blood with tartaric acid, all the carbonic acid present in the blood is given off and its amount can be measured. Recent observations indicate that the following figures represent approximately the amount of oxygen and carbonic acid present in 100 volumes of human blood :—

	Oxygen.	Carbonic Acid.
Arterial blood . . .	18–18·5 vols.	45 vols.
Venous blood . . .	12–13 ,,	50–51 ,,

The total quantity of oxygen which 100 volumes of blood can take up and give off is called its *oxygen capacity*.

Barcroft's differential apparatus (fig. 131) consists of a manometer, of which the bore is 1 mm., and which is provided with a scale graduated in millimetres. Attached to each limb is a small bottle, which is detachable, and by means of taps each bottle can be connected with, or shut off from, the outer air. The manometer is partially filled with clove oil.

(1) To determine the *oxygen capacity* of a sample of blood, 2 c.c. of dilute ammonia and 1 c.c. of the blood to be examined are placed in each bottle, and the bottles are shaken until the blood is thoroughly laked and saturated with oxygen ; 0·2 c.c. of a saturated solution of potassium ferricyanide is then placed in the reservoir in the stopper of one bottle A. The bottles are then attached to the manometer and placed in a water-bath. When the reading of the manometer becomes constant, the taps are closed, thereby excluding the bottles and the

manometer from the outer air, and the apparatus is tilted so that the ferricyanide runs into the blood in A, which gives off its oxygen. The oxygen evolved in the bottle A exerts pressure on the clove oil, forcing it down in that limb and up in the opposite limb of the manometer. The difference in the level of the clove oil in the two limbs is proportional to the amount of oxygen evolved, and, by multiplying this difference by a constant, the actual amount of oxygen set free can be ascertained. If, for example, the difference of level is 60 mm., and the constant is 3, the amount of oxygen evolved from 1 c.c. of blood is 0·18 c.c., *i.e.* 18 volumes from 100 volumes of blood, and this is its oxygen capacity.

(2) To determine the *amount* of oxygen present in a given sample

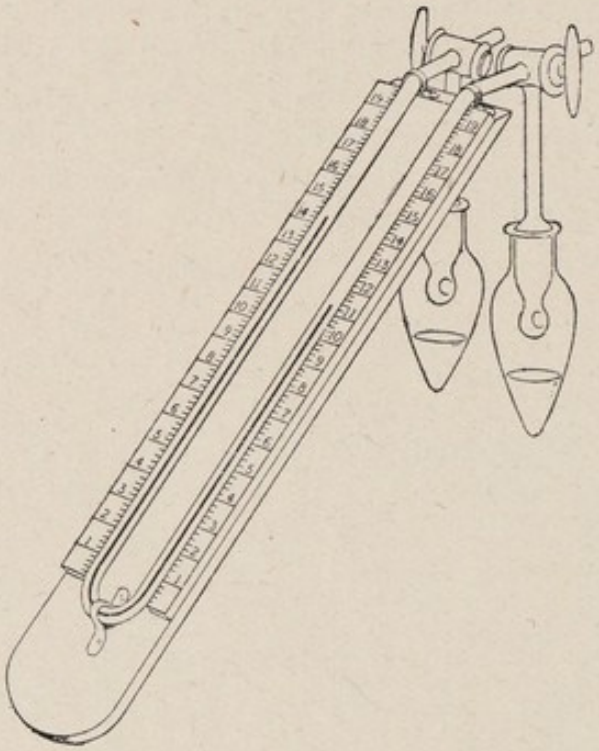


FIG. 131.—Barcroft's blood-gas apparatus. (From Barcroft, *Respiratory Function of the Blood.*)

of blood, 2 c.c. of dilute ammonia are placed in each bottle; 1 c.c. of the blood to be examined is carefully placed under the ammonia at the bottom of one bottle A, and thus kept from contact with the air. 1 c.c. of fully oxygenated (saturated) blood is placed in the bottle B, and the bottles are attached to the manometer; the bottles are placed in a water bath, and when the readings are constant the taps are closed, and the apparatus is shaken in order to lake the blood in each bottle. The blood in bottle B being already fully saturated, takes up no more oxygen when brought into contact with the air in the bottle. If the blood in the bottle A is already fully saturated with oxygen, it takes up no more oxygen, and the reading of the manometer remains unchanged; but, if it is not fully saturated, it takes up some oxygen, and the level of the clove oil rises in that limb of the manometer. The difference in the level of the clove oil in the two limbs represents the amount of oxygen taken up by the blood, and, if the total oxygen

capacity is ascertained, the degree to which the blood was previously saturated can be calculated.

Thus, if the oxygen capacity of 1 c.c. blood was 0·18 c.c., and it took up in the foregoing experiment 0·06 c.c. oxygen, it must have previously contained 0·12 c.c., and its percentage saturation was $100 \times \frac{0 \cdot 12}{0 \cdot 18} = 66$ per cent.

THE CONDITION IN WHICH THE GASES ARE HELD IN THE BLOOD

Theoretically, the gases in the blood might be either simply dissolved in it or chemically combined with some constituent of the blood. In order to decide which of these possibilities is the correct one, it is necessary to consider first the conditions which modify the amount of any gas present in a fluid such as water. On exposing water to the air, a certain amount of oxygen and nitrogen is dissolved in it. Confining our attention to oxygen, the amount dissolved in a known volume of water depends upon (1) the capacity of water to dissolve oxygen, (2) the pressure exerted by the oxygen upon the surface of the water, and (3) the temperature of the water. The capacity of water to dissolve any gas is constant for the same gas, provided the pressure of the gas and the temperature of the water remain unchanged. Some gases, such as carbonic acid, are very soluble in water, others, such as oxygen and nitrogen, are only slightly soluble. The *coefficient of solubility* of a gas is defined as the amount of that gas which is dissolved at a given temperature in 1 c.c. of the liquid, when the pressure of the gas on the liquid is 760 mm. Hg.

Since the capacity of water to dissolve any gas is constant, the amount of the gas dissolved at a given temperature (which will be assumed to be constant) varies directly with the pressure of the gas on the surface of the liquid. When water is exposed to pure oxygen at atmospheric pressure, the pressure of oxygen on the water is 760 mm. Hg ; if it is exposed to atmospheric air, both the oxygen and nitrogen exert a pressure, which is proportional to their percentage in the air. In such a mixture of gases, the proportion of the total pressure exerted by the oxygen on the walls of the vessel containing it, or on the surface of a fluid, is called the *partial pressure* or *tension* of oxygen, and it is measured by determining (1) the percentage of oxygen in the gaseous mixture, and (2) the total pressure of the mixture. The partial pressure of oxygen in atmospheric air is therefore 20·96 per cent. of 760 mm. Hg, namely 159 mm. Hg.

The Tension of Gas in a Fluid.—When water is exposed to a

gaseous mixture containing oxygen, the molecules of oxygen tend to pass into the liquid and be dissolved ; at the same time, the molecules of oxygen already in solution tend to pass from the water into the gaseous mixture. The tendency of the molecules of oxygen to leave the fluid is called the *tension* of oxygen in the fluid. When these two opposing processes are equal, the gaseous mixture and the fluid are in equilibrium, and the amount of oxygen dissolved in the fluid remains constant. In these circumstances, the tension of oxygen in the fluid is equal to the partial pressure of the oxygen in the gaseous mixture to which the fluid is exposed.

The tension of oxygen in a fluid cannot be measured directly, but is determined by placing samples of the fluid in a series of closed vessels, containing oxygen at various known partial pressures, and finding in which vessel the fluid neither gives off nor takes up oxygen. The tension of oxygen in the fluid in this vessel is equal to the partial pressure of the oxygen in the gaseous mixture to which the fluid is exposed ; if the amount of oxygen in the gaseous mixture is 5 per cent. and the total pressure of the gaseous mixture is 760 mm. Hg, the partial pressure of oxygen is 38 mm. Hg, and this is equal to the tension of oxygen in the fluid. The forms of apparatus which have been devised for measuring the tension of a gas in a fluid are called *aërotonometers*.

The Tension of Oxygen in Blood.—In the case of water, oxygen is held in simple solution, and, if the temperature is constant, the amount of oxygen dissolved in the water varies directly with the partial pressure of oxygen in the air to which it is exposed. If the pressure of oxygen is doubled, twice as much is dissolved in the water. When similar experiments are carried out with blood, the amount of oxygen present in the blood, as determined either by exposing it to a vacuum in a gas-pump or by Barcroft's apparatus, is not proportional to the partial pressure of oxygen in the gaseous mixture to which the blood is exposed. For example, when the blood is in equilibrium with air containing oxygen at a partial pressure of 100 mm. Hg, it will contain about 18 volumes of oxygen per 100 volumes of blood. If the partial pressure of oxygen is reduced to 50 mm. Hg, the blood will contain 14·5 volumes of oxygen per 100 volumes of blood.

Since the amount of oxygen in blood is not *directly* proportional to the partial pressure of oxygen in the air to which the blood is exposed, it is evident that oxygen is not held in blood simply in solution. Further, a given volume of blood can take up many times as much oxygen as an equal volume of water. Hence it is clear that oxygen must form an unstable compound with some constituent of the blood ; this constituent is hæmoglobin, and a

solution of pure hæmoglobin can take up from the air as much oxygen as blood containing the same amount of hæmoglobin. 1 gram of hæmoglobin can combine with approximately 1·34 c.c. oxygen, though this figure varies slightly in different animals, probably on account of slight differences in the character of the protein part of the hæmoglobin molecule.

If 100 c.c. of blood are exposed to an atmosphere of pure oxygen in a closed vessel at atmospheric pressure, they take up about 20 c.c. of oxygen. When the oxygen is slowly withdrawn from the vessel, so that the pressure on the surface of the blood gradually falls, the blood remains almost unaltered until the pressure falls to about 100 mm. Hg. With a further fall of pressure the blood rapidly gives off its oxygen, and, when the pressure falls to zero, all the oxygen has been evolved. Evidently the combination of hæmoglobin with oxygen is a reversible one ; hæmoglobin gives off its oxygen when the pressure of oxygen is low, and takes it up when the pressure is high. This reversible action is usually indicated thus, $HbO_2 \rightleftarrows Hb + O_2$. It is to this power that hæmoglobin owes its value for respiration. In the alveoli of the lungs the partial pressure of oxygen is relatively high, and the blood becomes almost fully saturated with oxygen. The partial pressure of oxygen in the tissues is almost zero, and, when the blood is carried round in the circulation to the tissues, the oxyhæmoglobin dissociates, the oxygen set free being taken up by the tissues. The effect of a varying partial pressure of oxygen upon the combination between hæmoglobin and oxygen is shown in fig. 132. The curve shows the percentage of hæmoglobin present as oxyhæmoglobin with varying pressures of oxygen ; when all the hæmoglobin is in the form of oxyhæmoglobin, it is said to be fully saturated. For pressures above 100 mm. Hg, the curve becomes almost a straight line.

This curve, which is known as the *dissociation-curve* of hæmoglobin, is obtained in the following manner. A small quantity of blood is placed in an aërotonometer containing a mixture of oxygen and nitrogen at atmospheric pressure. A suitable form of tonometer is that shown in fig. 133 ; it consists of a glass cylinder, which can be rotated in water kept at a constant temperature. When the cylinder is rotated, the small amount of blood, previously placed in it, spreads out into a thin film over the inner wall of the cylinder, and after a short time the blood and gas come into equilibrium, and the blood neither takes up nor gives off oxygen. The cylinder is removed from the water-bath, and the percentage of the total hæmoglobin which is present as oxyhæmoglobin in the blood is estimated

by Barcroft's blood-gas apparatus. If, for example, the partial pressure of oxygen in the mixture of gases placed in the aërotonometer is 40 mm. Hg (corresponding with about 5 per cent.

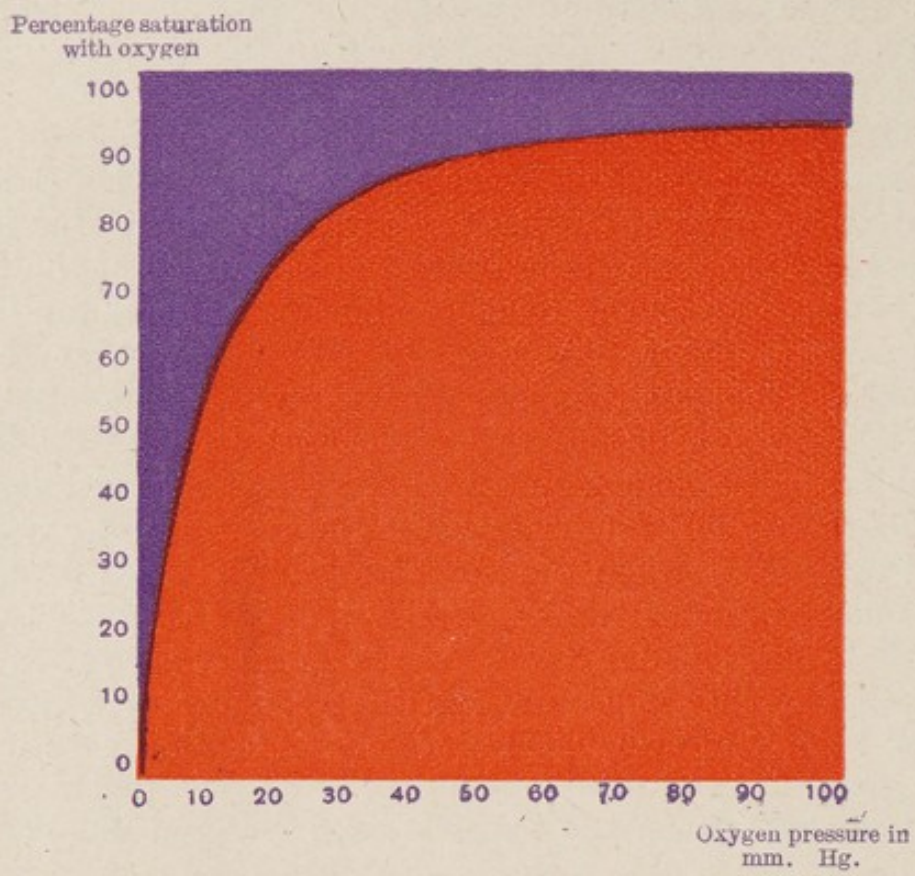


Fig. 132.—Dissociation-curve of hæmoglobin dissolved in water at 37° C. (From Barcroft, *Respiratory Function of the Blood.*)
Oxyhæmoglobin is red, and reduced hæmoglobin is purple.

of oxygen), and the hæmoglobin in the blood, when in equilibrium with this mixture, is 70 per cent. saturated with oxygen, that point can be marked on the chart. By making a series of such observations, and using varying percentages of oxygen in the gaseous mixture, a series of points is determined and plotted out. The line joining these points is the dissociation-curve, which is simply a graphic representation of the influence of the tension of oxygen upon the combination of hæmoglobin with oxygen.

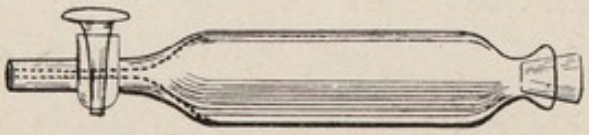


Fig. 133.—Barcroft's tonometer.

The form of the curve can be greatly altered by varying circumstances, and the dissociation-curve of blood differs considerably from that of a solution of pure hæmoglobin, as may be seen in fig. 134. A comparison of the two curves shows that oxyhæmoglobin dissociates more readily in blood than when simply dissolved in water. When the partial pressure of oxygen

is 20 mm. Hg, blood contains only 30 per cent. of its hæmoglobin in the form of oxyhæmoglobin, whereas in a watery solution of pure hæmoglobin 72 per cent. exists as oxyhæmoglobin. This difference is chiefly due to the presence of salts, particularly potassium salts, in the blood, which render the combination between hæmoglobin and oxygen more unstable; when hæmoglobin is dissolved in water containing the same salts as those normally present in blood, its dissociation-curve is identical with that of blood.

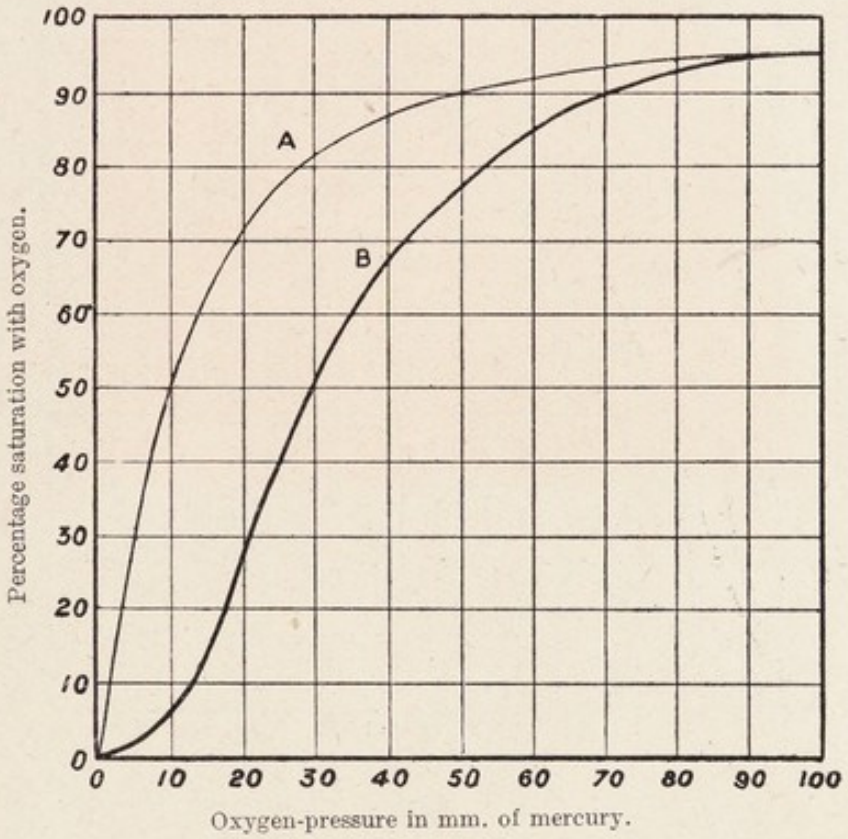


FIG. 134.—Dissociation-curves (A) of hæmoglobin dissolved in water at 37° C., and (B) of blood at 37° C.

The other factors which alter the form of the dissociation-curve of blood are (1) the temperature of the blood, and (2) the presence of carbonic or other acids. The higher the temperature of the blood and the greater the amount of carbonic or other acids in the blood, the more readily does the oxyhæmoglobin dissociate. The effect of carbonic acid and of lactic acid is shown in fig. 135. These factors modify not only the *extent* to which oxyhæmoglobin dissociates at the same partial pressure of oxygen, but also the *rate* at which it loses oxygen and becomes reduced. When an indifferent gas, such as nitrogen, is bubbled through a solution of fully oxygenated blood, the oxyhæmoglobin gradually dissociates, and is reduced to hæmoglobin; the dissociation is much more *rapid* if the blood is warmed, or if it contains an

excess of carbonic acid or a small amount of lactic acid (fig. 136). The influence of carbonic or other acids on the readiness with which oxyhæmoglobin dissociates, when the pressure of oxygen to which it is exposed is low, is of great physiological importance, since the time occupied by any one portion of the blood in traversing the capillaries is very short, being approximately one second. As the blood passes through the capillaries, it not only gives off oxygen, but also receives from the tissues carbonic acid and

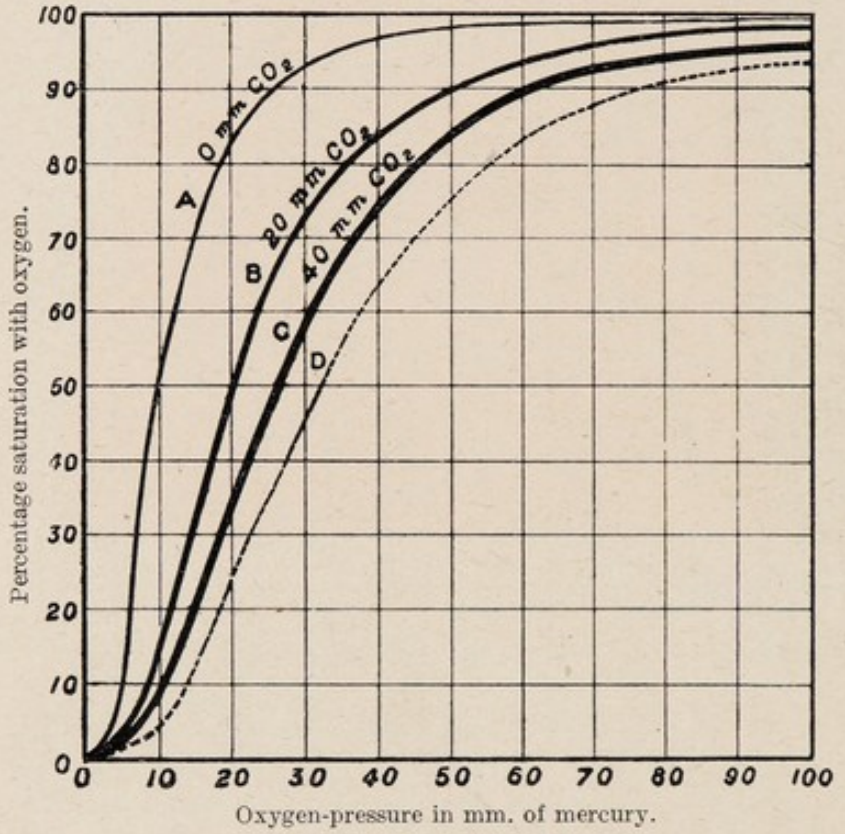


FIG. 135.—A, B, and C show the effect of varying tensions of CO_2 in blood on the dissociation-curve of oxyhæmoglobin. The dotted line D is the dissociation-curve of oxyhæmoglobin in blood to which 0·025 per cent. lactic acid was added.

frequently lactic acid. The greater ease with which the oxyhæmoglobin dissociates in these circumstances increases the amount of oxygen set free and therefore available for the tissues; and this effect will be especially marked and beneficial when the tissues are functionally active and are giving out large amounts of carbonic acid and require a larger supply of oxygen.

Although these conditions profoundly influence the rate of transference of oxygen from the blood to the tissues, they do not appreciably affect the amount of oxygen taken up by the blood as it passes through the lungs. The partial pressure of oxygen in the lungs is normally just over 13 per cent. (about 105 mm. Hg), and a consideration of fig. 135 shows that at this

pressure of oxygen the saturation of the blood will be practically the same, whether the blood is normal or whether it contains an excess of carbonic acid or a trace of lactic acid.

In addition to the oxygen thus combined with hæmoglobin, the blood contains oxygen in simple solution in the plasma, amounting at the body temperature to about 0·36 c.c. oxygen per 100 c.c. of blood.

Carbonic Acid in Blood.—The tension of carbonic acid in

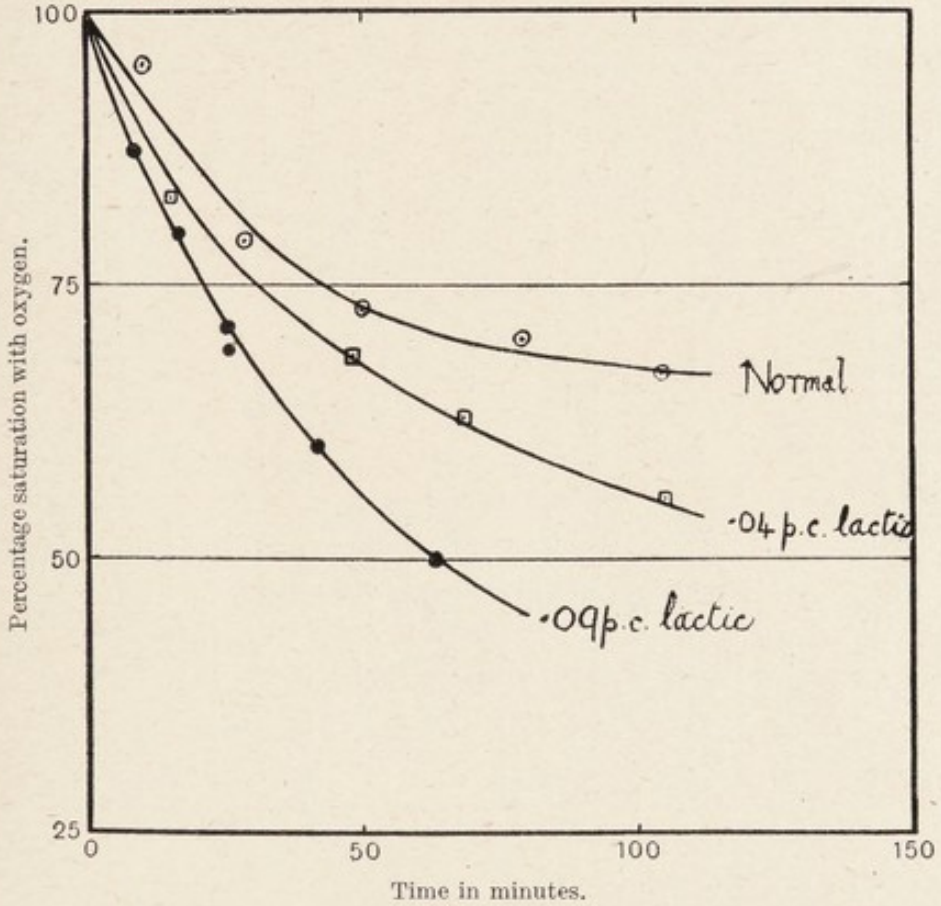


FIG. 136.—Curves showing the rate at which oxyhæmoglobin is dissociated by bubbling nitrogen through blood, and the effect of the presence of lactic acid in the blood in increasing the rate of dissociation. (Mathison.)

blood, when determined by means of an aërotonometer, is equal to a partial pressure of about 5 per cent. of carbonic acid. If all the carbonic acid were simply dissolved in the blood, the latter would contain at this tension only about 2½ volumes of carbonic acid per 100 volumes of blood ; but, since 100 volumes of blood, when exposed to a vacuum, give off from 45 to 50 volumes of carbonic acid, most of this must be in a state of chemical combination.

There are two views as to the form in which the combined carbonic acid exists in the blood, and is conveyed from the tissues to the lungs. According to one view, the whole of the combined

carbonic acid is in the form of sodium bicarbonate. The proteins of the red cells and plasma are also combined with sodium, and when carbonic acid enters the blood from the tissues, it reacts with the sodium-protein compound to form sodium bicarbonate and free protein. As the blood passes through the lungs it loses carbonic acid, and the sodium thus set free again combines with protein.

Other authorities believe that carbonic acid is combined partly as sodium bicarbonate, partly with hæmoglobin and partly

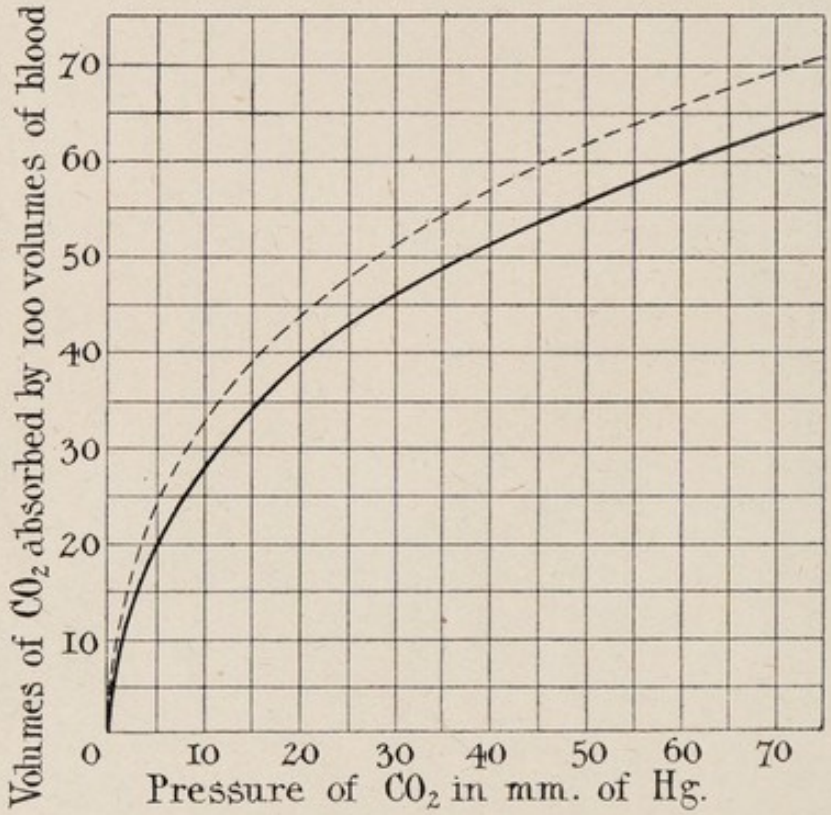


FIG. 137.—Dissociation curve of CO_2 in blood. (From Christiansen, Douglas and Haldane.)

Lower curve: blood exposed to CO_2 and air. Upper curve: blood exposed to CO_2 and hydrogen.

with the proteins of the plasma, but that the sodium bicarbonate in the blood takes no part in the transport of carbonic acid from the tissues to the lungs. They hold that this is effected chiefly by hæmoglobin, and to a slight extent by the proteins in the plasma; these unite with carbonic acid, as the blood flows through the tissues, to form an unstable compound which undergoes dissociation when the blood traverses the lungs, the carbonic acid escaping into the alveolar air. On this view the combination between hæmoglobin and carbonic acid resembles that between hæmoglobin and oxygen. It is of interest, therefore, that the dissociation-curve of carbonic acid in blood exposed to varying partial pressures of carbonic acid in the surrounding air has the

same general form as that of oxyhæmoglobin (fig. 137); the dissociation is most rapid when the partial pressure of carbonic acid varies from 0 to 30 mm. Hg. Since oxygenated blood gives off its carbonic acid more readily than deoxygenated blood, the oxygenation of the blood as it flows through the lungs probably facilitates the escape of carbonic acid from the blood into the alveolar air.

The blood also contains about $2\frac{1}{2}$ volumes of carbonic acid in solution per 100 volumes of blood.

THE EXCHANGE OF GASES IN THE LUNGS

The air in the lungs is separated from the blood by the walls of the pulmonary capillaries and by the alveolar epithelium. The membrane formed by these two layers of epithelium is extremely thin, and permits oxygen and carbonic acid to pass through it.

It is generally held that the passage of oxygen through this membrane from the alveolar air into the blood, and of carbonic acid from the blood into the alveolar air, takes place by the purely physical process of diffusion. If this view is correct, the tension of oxygen in the arterial blood leaving the lungs can never exceed that in the alveolar air, since diffusion will cease when the tension of oxygen in the blood equals that in the alveolar air.

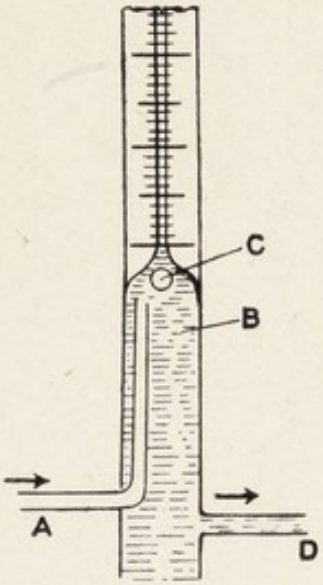


FIG. 138.—Krogh's tonometer.

Krogh has devised an aërotonometer which can be used to measure the tension of oxygen in circulating arterial blood, and the lower part of it is shown in fig. 138. It consists of a cannula A, which is attached to the central end of an artery; the blood flows from the cannula into a bulb B, from the top of which passes off a narrow graduated tube. A small air bubble C is placed in the bulb, and the blood flows through the bulb, and is returned to the distal end of the artery by the tube D, clotting being prevented by the injection of hirudin. An interchange of gases takes place between the blood and the bubble, and, owing to the small size and relatively large surface of the latter, the gases in the blood and the bubble soon come into equilibrium, this being reached when the size of the bubble remains constant; it is then withdrawn into the graduated tube, and its composition is analysed.

Since the oxygen of the blood is in equilibrium with that in

the bubble, the tension of oxygen in the blood can be ascertained by determining the percentage of oxygen in the bubble and the total pressure to which it is exposed. If the arterial pressure is 100 mm. Hg, and the bubble contains 10 per cent. of oxygen, the partial pressure of oxygen is 10 per cent. of 860 mm. Hg (atmospheric + arterial pressure), namely 86 mm. Hg. The tension of

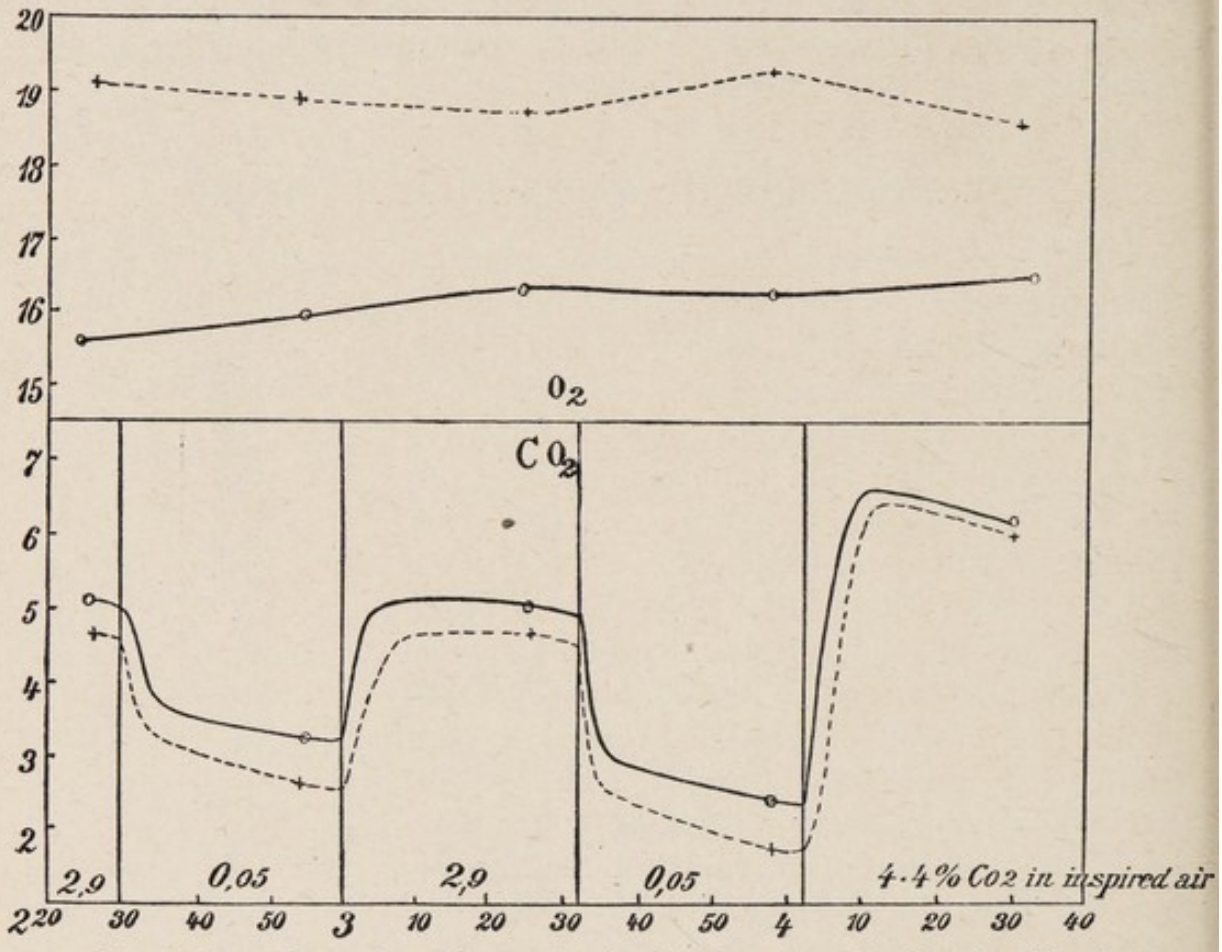


FIG. 139.—The tension of gases in the alveolar air and in blood. (Krogh.) (From Barcroft, *Respiratory Function of the Blood.*)

The upper half shows tension of oxygen, and the lower half tension of carbonic acid. The dotted lines represent the tension in the alveolar air, and the continuous lines show the tension in the blood. During three periods the amount of carbonic acid in the inspired air was increased.

oxygen in the blood is thus equal to 86 mm. Hg, or about 11·3 per cent. of oxygen at atmospheric pressure.

By means of this apparatus, it has been found that, in animals, the tension of oxygen in arterial blood is distinctly less than that in alveolar air, the difference being usually 1 to 3 per cent. of an atmosphere (fig. 139). It has been estimated that, in man, the oxygen-tension of venous blood is about 40 mm. Hg, whereas the partial pressure of oxygen in alveolar air is usually about 105 mm. Hg. The difference between the oxygen-tension in alveolar air and that in the venous blood is so great that oxygen rapidly diffuses through the pulmonary epithelium into the blood, where it combines with hæmoglobin, until the tension of oxygen in the

blood becomes almost equal to that in the alveolar air. Further, the structure of the alveoli is such that, as it flows through the lungs, an enormous surface of blood is exposed to the air in the lungs; and this greatly assists the diffusion of oxygen into the blood. Taking into account first the rate at which oxygen can diffuse through a membrane similar to that separating the blood from the alveolar air, and secondly the surface area of the alveoli, it has been calculated that the difference in the tension of oxygen in the lungs and in the venous blood respectively is more than sufficient to provide for the passage of the oxygen required by the body into the blood by simple diffusion.

Although this view is generally accepted, some authorities are still of opinion that it is true only for the resting individual, and that during exercise, when the need for oxygen is greater, or at high altitudes, when the supply of oxygen is deficient, the tension of oxygen in the blood is higher than that of alveolar air, this difference being due to the secretion of oxygen into the blood by the pulmonary epithelium.

Similarly, it has been found that the tension of carbonic acid in venous blood is very slightly higher than that in alveolar air (fig. 139). If the tension of carbonic acid in alveolar air is raised, the tension in the blood shows a corresponding rise, and still remains slightly higher than that in the alveolar air.

In man, the difference between the tension of carbonic acid in venous blood and in alveolar air is probably about 6 mm. Hg. This difference is much smaller than that between the tension of oxygen in alveolar air and venous blood respectively, but carbonic acid can traverse a membrane such as that separating the air in the lungs from the blood twenty-five times as quickly as oxygen; and the difference between the tension of carbonic acid in venous blood and in alveolar air, slight though it is, is sufficient to allow carbonic acid to pass from the blood into the air in the lungs by simple diffusion.

Owing to the difference in the tension of oxygen and of carbonic acid in the blood and in alveolar air, the blood, as it flows through the lungs, takes up oxygen and leaves the lungs almost fully saturated with oxygen; at the same time it loses 5 or 6 volumes of carbonic acid per 100 volumes of blood.

SECTION III

THE REGULATION OF THE RESPIRATORY MOVEMENTS

Oxygen is continually passing from the alveolar air into the blood, and is replaced by the entrance of air from the atmosphere

during respiration. Similarly, carbonic acid is constantly diffusing from the blood into the alveolar air, and with each expiration a certain amount is expelled from the lungs. Assuming that the amount of air entering and leaving the lungs with each breath is 400 c.c., and that the expired air contains 4 per cent. of carbonic acid, then, with each respiration, 16 c.c. of carbonic acid are removed from the body. Since the composition of alveolar air remains constant, it is evident that 16 c.c. of carbonic acid must, in the same time, have passed from the blood into the air in the lungs. When an additional amount of carbonic acid is formed in the body and taken up by the blood, it passes into the alveolar air and tends to raise the percentage of carbonic acid in alveolar air. Hence, if the percentage of carbonic acid in alveolar air is to remain constant, as it actually does under normal conditions, the amount of air passing into and out of the lungs at each breath must be correspondingly increased. If 32 c.c. of carbonic acid pass from the blood into the alveolar air during a breath, they can be removed if the amount of expired air is 800 c.c., containing 4 per cent. carbonic acid. In the same way, the need of the body for more oxygen is met by a larger amount of air entering the lungs at each inspiration. This process, whereby any accumulation of carbonic acid, or deficiency of oxygen, in the alveolar air, and consequently in the blood, is prevented, is under the control of the central nervous system, and is regulated in such a way that an excess of carbonic acid, or a lack of oxygen, leads to deeper and more frequent respiratory movements.

The Respiratory Centre.—The rhythmic alternation of inspiration and expiration is brought about by the contraction and relaxation of the respiratory muscles, which are controlled and co-ordinated by a centre—the respiratory centre—lying in the grey matter of the floor of the fourth ventricle. From this centre impulses pass along the nerves supplying the respiratory muscles, namely, the vagus to the muscles of the larynx, the cervical nerves to the muscles of the neck, the intercostal nerves to the intercostal muscles, and the phrenic nerves to the diaphragm.

The centre is bilateral, the two halves being connected by commissural fibres and each half controlling the muscles of the corresponding side. Its position has been determined by observing the effect upon the respiratory movements of transection of the brain-stem or spinal cord at various levels. Recent observation indicates that the centre extends along almost the whole length of the floor of the fourth ventricle. When a section is made through the brain-stem at any point above the level of

the fourth ventricle, respiration is unaffected. A section made a little below this point causes some slowing of respiration; transection at, or just below, the level of the striæ acusticæ leads to pronounced changes in respiratory rate and rhythm. If the spinal cord is divided at the upper end of the cervical region, the respiratory muscles supplied by nerves above the section, *e.g.* those which dilate the alæ nasi, continue to contract. Destruction of the medulla oblongata in the region of the apex of the calamus scriptorius is at once followed by cessation of all respiratory movements. The region occupied by the centre is not sharply defined, but it is undoubtedly closely connected with the sensory nuclei of the vagus nerves.

There is no evidence of the existence of subsidiary centres in the spinal cord.

The centre continues to send out rhythmic impulses to the respiratory muscles when it is cut off from afferent impulses reaching it either from the higher parts of the brain or from the spinal cord. If, however, the brain-stem is divided below the pons, and the vagus nerves are also divided, the respiratory movements are replaced by a series of inspiratory spasms, and the animal dies after a short time. It is doubtful, therefore, whether the centre can be regarded as acting automatically in the absence of all afferent impulses, though this view has been taken by some writers.

The question is one of theoretical rather than practical interest, since, in ordinary circumstances, a constant stream of afferent impulses is reaching the centre and modifying its activity; and hardly any nervous centre in the body is more easily influenced in this way than the respiratory centre. For instance, the mere directing of one's attention to the respiratory movements is sufficient to alter their rate or depth. The respiratory centre, like the vaso-motor centre, is also extremely sensitive to any changes in the composition of the blood supplying it. These two factors which modify its activity, namely, (1) the composition of the blood and (2) nervous impulses from the higher centres or from the peripheral nerves, will be considered separately. The former affects primarily the depth, and the latter the rate, of respiration.

Methods of Recording Respiratory Movements.—In order to study these changes, it is desirable to obtain a graphic record of the rate and depth of the respiratory movements; and numerous methods have been devised for this purpose.

(1) In man the respiratory movements can be recorded by a *stethograph*, one form of which consists of a small metal cylinder, provided with a lateral opening and closed at each end by a rubber

membrane; the lateral opening is connected by rubber tubing with a tambour. Strings are attached to the centre of each rubber membrane, and are passed round the chest and tied. Each expansion of the chest causes the strings to pull upon the rubber membrane, so that the capacity of the cylinder increases and the lever of the tambour falls: during expiration the membranes return to their former position. The same apparatus can be used to record the respiratory movements in the lower animals.

(2) Another method, used in animals, is to connect the side-piece of a cannula, inserted into the trachea, with a tambour; with each inspiration air is sucked out of the tambour, and the lever falls.

(3) In rabbits, a small slip of the diaphragm on each side is inserted into the xiphisternum: and, by separating the xiphisternum from the sternum, this strip of muscle can be isolated without interfering with its vascular or nervous connections. It contracts synchronously with the rest of the diaphragm, and, by connecting the xiphisternum with the membrane of a tambour by means of a thread, each contraction of the slip can be recorded, and serves as an index of the movements of the diaphragm as a whole (Head's method).

THE CHEMICAL REGULATION OF RESPIRATION

The two most important changes in the composition of the blood which alter the respiratory movements are: (1) variations in the tension of carbonic acid, and (2) a fall in the tension of oxygen.

(1) **The Tension of Carbonic Acid.**—If an animal is allowed to breathe air containing 2 to 3 per cent. carbonic acid, the respiratory movements become much deeper, and after a short time usually more frequent; such an experiment is illustrated in fig. 140. If the experiment is made on man, it is further found that the percentage of carbonic acid in the alveolar air remains almost unchanged. The immediate effect of breathing air containing an excess of carbonic acid is to increase the percentage of carbonic acid in the alveolar air, thereby diminishing the passage of carbonic acid by diffusion from the blood into the air in the lungs. As a result, the tension of this gas in the blood rises slightly; the increase in tension stimulates the respiratory centre to greater activity, and the amount of air passing into and out of the lungs with each breath may be doubled or trebled. In this way a larger amount of carbonic acid is expelled from the lungs with each expiration, and the mean tension of this gas in the alveolar air is thereby kept almost at its normal level.

The effect of carbonic acid in stimulating the respiratory centre is also seen during muscular exercise. During exercise the muscles form a large amount of carbonic acid, which passes into the blood and raises the tension of this gas in the blood. This rise of tension stimulates the respiratory centre, and the respiratory movements become deeper and more frequent, with the result that a larger amount of carbonic acid is carried off in the expired air. The response of the respiratory centre to the stimulus of carbonic acid is so delicately adjusted that the tension of carbonic acid in the blood and alveolar air rises very slightly

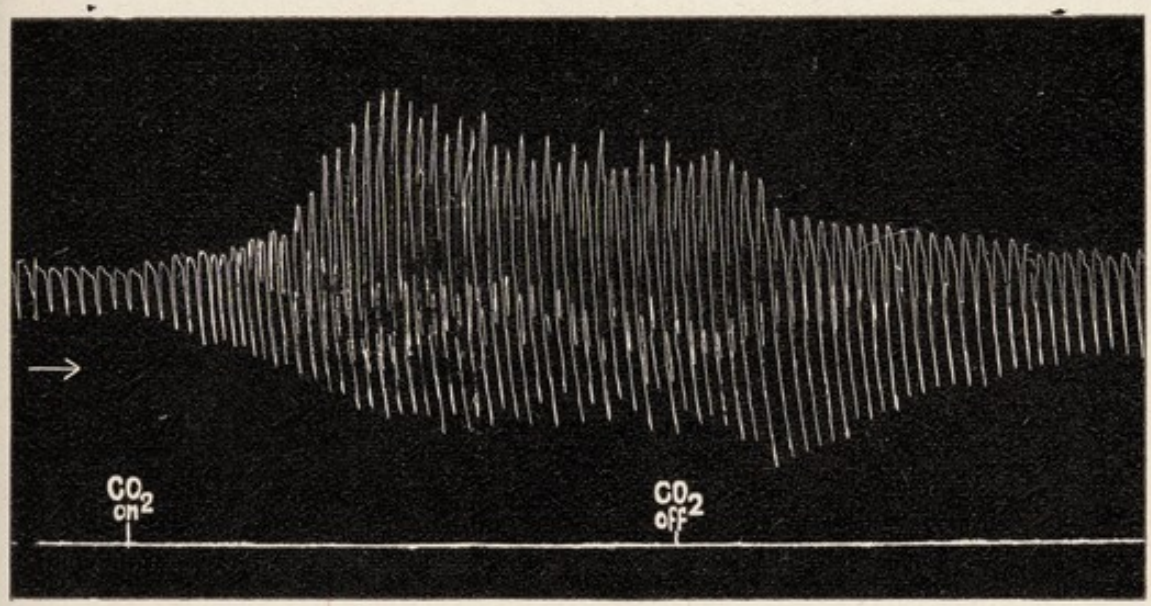


FIG. 140.—The effect of CO_2 on the respiratory movements in the normal animal. The inspired air contained 3 per cent. CO_2 during the period marked on the tracing.

during exercise. In one series of experiments, the following figures were obtained :—

	Percentage of CO_2 in Alveolar Air.
Rest	5·06
Exercise	5·10

Since the slightest rise in the tension of carbonic acid in the blood increases the respiratory movements, a diminution might be expected to lessen the respiratory movements by diminishing or abolishing the stimulus to the centre ; and such is found to be the case. When an individual takes a number of deep breaths (forced respiration), more carbonic acid is removed from the lungs than is entering them from the blood. Hence the tension of carbonic acid in alveolar air, and in blood, falls to such a level that it no longer stimulates the respiratory centre ; and respiration ceases for a short time (apnœa). During the period of apnœa, carbonic acid continues to reach the blood from the tissues, and

its tension in the blood and in the alveolar air gradually rises, until it again reaches a level sufficient to stimulate the respiratory centre ; when this occurs respiration recommences (fig. 148).

Apnœa can also be produced in animals by repeated ventilation of the lungs, whereby carbonic acid is, so to speak, washed out of the lungs and its tension in the blood and alveolar air falls.

These observations show that the activity of the respiratory centre and, consequently, the amount of air passing into and out of the lungs are dependent on the tension of carbonic acid in the blood. It has been pointed out, however (p. 189), that the reaction of the blood, that is to say, its H ion concentration, depends almost entirely on the relative amount of dissolved carbonic acid and of sodium bicarbonate present in the blood-plasma. This relationship can be expressed by the equation :—

$$C_H(\text{H ion concentration}) = \frac{K^* \times H_2CO_3}{NaHCO_3}$$

Since the amount of carbonic acid dissolved in the plasma varies directly with the tension of carbonic acid in the blood, it is clear that every change in the tension of carbonic acid will alter the reaction of the blood, provided the amount of bicarbonate remains constant. If the tension of carbonic acid rises, the blood will tend to become acid, whereas, if the tension falls, the blood will become more alkaline. It has, in fact, been shown that the carbonic acid dissolved in the plasma stimulates the respiratory centre, not in a specific manner, but because, being an acid, it increases the concentration of hydrogen ions in the blood.

It follows, therefore, that the addition of any acid to the circulating blood will lead to greater activity of the respiratory centre. If, for example, 0·02 to 0·04 per cent. lactic acid is rapidly added to the blood, it neutralises part of the sodium bicarbonate of the plasma and thereby alters the *ratio* $\frac{H_2CO_3}{NaHCO_3}$ in such a way that the H ion concentration of the blood rises. The respiratory centre is at once stimulated and the breathing becomes more vigorous until sufficient carbonic acid has been removed from the blood to restore the normal ratio ; the reaction of the blood is then normal although it contains less carbonic acid and sodium bicarbonate than usual.

It may be concluded, then, that the activity of the respiratory centre is normally evoked and controlled by the H ion concentration of the blood ; when this exceeds a certain level, respiration becomes more vigorous, and when it falls below this level apnœa occurs. The centre is so sensitive that the

* K is a constant.

slightest rise in the H ion concentration of the blood leads to hyperpnœa, which continues until sufficient carbonic acid has been removed from the body to bring back the reaction of the blood to its normal level, and the most trivial fall in the H ion concentration decreases or abolishes the respiratory movements until the blood regains the H ion concentration necessary to excite the respiratory centre and evoke normal quiet breathing. In this way, the respiratory centre serves as an extremely delicate and efficient mechanism for keeping the reaction of the blood constant. The importance of this function of the respiratory system lies in the fact that any considerable change in the reaction of the blood, whether this change be towards the acid or towards the alkaline side, at once throws into disorder the working of the body and rapidly brings its functions to a standstill.

(2) **The Tension of Oxygen in the Blood.**—The normal tension of oxygen in alveolar air is 105 to 110 mm. Hg. At this tension the blood leaving the lungs is almost fully saturated with oxygen, and the dissociation-curve of blood (p. 287) shows that, even when the oxygen tension is reduced to 70 mm. Hg, the blood still contains 90 per cent. of its hæmoglobin as oxyhæmoglobin. Experiment shows, in fact, that atmospheric air containing only 12 to 13 per cent. oxygen, which corresponds with about 8 per cent. oxygen in the alveolar air, can be breathed without discomfort and without any alteration in the respiratory movements. When the percentage of oxygen in alveolar air falls below this figure, the breathing often becomes deeper, and considerable hyperpnœa may be produced. At the same time, the individual becomes cyanosed and may feel giddy, or may even lose consciousness.

These symptoms are the result of the imperfect oxygenation of the blood. The mere lack of oxygen in itself does not act as a stimulus to the respiratory centre, and the hyperpnœa is caused indirectly in two ways. In the first place, a marked lack of oxygen renders the respiratory centre more sensitive to the stimulus furnished by the H ion concentration of the blood, so that it can be excited by a smaller tension of carbonic acid in the blood than that normally present. Hence, if the tension of carbonic acid in the blood is normal, it stimulates the abnormally excitable centre very strongly, and hyperpnœa occurs. In the second place, if the lack of oxygen is at all prolonged, the H ion concentration of the blood is increased. Lactic acid is normally formed in the body, and, in the presence of an adequate supply of oxygen, it is subsequently oxidised to carbonic acid and water; when the supply of oxygen is insufficient, the lactic acid passes into the blood, and, by increasing its

H ion concentration, stimulates the respiratory centre, and the respiratory movements become deeper. The deeper breathing raises the tension of oxygen in the alveolar air, and thus increases the amount of oxygen which can be taken up by the blood. In one experiment, for example, the inspired air contained 11·6 per cent. oxygen, which would correspond (if no hyperpnœa occurred) with 5 per cent. oxygen in the alveolar air ; but the respiratory movements increased to such an extent that the alveolar air actually contained 6·8 per cent. oxygen. Hence hyperpnœa helps to protect the tissues from the ill effects of a lack of oxygen in the inspired air.

The presence of an excess of oxygen in alveolar air has no effect on the respiratory movements, and wide variations may occur in the partial pressure of oxygen in the alveolar air without any appreciable change taking place in the respiration ; even when pure oxygen is breathed for a short time, respiration is unchanged in a healthy individual. It is evident, therefore, that, provided the supply of oxygen is adequate, the depth of the respiratory movements is normally regulated by the tension (partial pressure) of carbonic acid in the alveolar air and in the blood.

Effect of Changes in Partial Pressure of Oxygen and Carbonic Acid

	Barometric Pressure.	Percentage of CO_2 in Dry Alveolar Air.	Percentage of O_2 in Dry Alveolar Air.	Alveolar Pressure of CO_2 in Percentage of an Atmosphere.	Alveolar Pressure of O_2 in Percentage of an Atmosphere.
1	646·5 mm. Hg	6·61	13·19	5·23	10·41
2	755 ,,	5·95	13·97	5·53	13·06
3	1260 ,,	3·52	16·79	5·64	28·84

Further, this tension is extremely constant in the same individual, though, as shown in the foregoing table, the actual percentage of carbonic acid in the lungs varies with the barometric pressure. For example, when the barometric pressure is 1260 mm. Hg, the alveolar air contains 3·52 per cent. carbonic acid; this represents a partial pressure of $\frac{3{\cdot}52 \times 1260}{760} = 5{\cdot}6$ per cent. at 760 mm. Hg pressure.

ASPHYXIA

The effects of lack of oxygen in the blood are seen in their most extreme form in asphyxia, and affect not only the respiratory, but also the circulatory, system. Asphyxia may be brought

about by occlusion of the trachea, by the absence of oxygen in the air breathed, and in other ways, and three stages are usually described.

(1) **Stage of Hyperpnœa.**—During this period, which lasts from ½ to 1 minute, the respiratory movements gradually increase in depth, and soon involve not only the muscles usually employed in respiration, but also the accessory muscles. The respiratory movements during this stage are co-ordinate, and show an alternate inspiratory and expiratory rhythm. Consciousness is lost at the end of this stage; the expiratory movements become more and more exaggerated, and the first stage passes into

(2) **The Stage of Expiratory Convulsions.**—During this period every muscle which can assist expiration is called into action, and at the same time convulsive movements of the limbs take place. This period lasts about 1 minute, and is succeeded by

(3) **The Stage of Exhaustion,** during which the animal lies passive, the muscles are flaccid except for an occasional deep inspiration, the pupils are widely dilated, and all reflexes are absent. Death takes place from 3 to 4 minutes after the onset of asphyxia. The blood after death is almost free from oxygen.

If the arterial pressure is observed in an animal during asphyxia, the vagi being cut, it may be seen that towards the end of the first stage the blood-pressure rises rapidly, and soon reaches a very high level, which is maintained for a short time; towards the end of the second stage it begins to fall, and continues to fall steadily until the animal dies.

The sequence of events in asphyxia is brought about in the following manner. At the outset, carbonic acid accumulates in the blood and excites the respiratory centre, producing hyperpnœa. Towards the end of the first stage the increasing deficiency of oxygen begins to make itself felt, leading to still greater activity of the respiratory centre and to loss of consciousness. In the second stage, the lack of oxygen increases the excitability of the whole of the central nervous system, giving rise to the general convulsions which are observed; this effect is soon succeeded by paralysis, resulting from the prolonged deficiency of oxygen, and ending in death. All these effects are most pronounced when the supply of oxygen is cut off abruptly and completely; if the lack of oxygen is brought about gradually, the respiratory changes may be comparatively slight.

The same sequence of events may be observed even if, during asphyxia, there is no mechanical obstruction to the escape of carbonic acid from the lungs and therefore no *actual* increase of this gas in the blood. In these circumstances, the hyperpnœa is due to the greater

excitability of the respiratory centre, which is produced by acute and extreme lack of oxygen.

The vascular changes are also caused partly by excess of carbonic acid, partly by lack of oxygen, as is shown in figs. 141 and 142. These tracings make it clear that a rise of blood-pressure similar to that seen in asphyxia (fig. 141, A) is produced either when the animal is allowed to breathe air containing no oxygen and no excess of carbonic acid (fig. 141, B), or when it breathes air containing an adequate supply of oxygen and a large excess of carbonic acid (fig. 142, A), or, finally, when lactic acid is injected into the circulation (fig. 142, B).

The rise of arterial pressure is due to stimulation of the vasomotor centre, which produces general constriction of the arterioles; adrenalin also is set free into the blood-stream, and contributes to the rise of pressure. By enclosing a loop of intestine in a plethysmograph it may be shown that, with the onset of asphyxia, the volume of the loop diminishes owing to constriction of its blood-vessels, and that this constriction persists until the death of the animal. The final fall of blood-pressure must be due, therefore, to failure of the heart; owing partly to the resistance offered by the high blood-pressure, partly to the direct effect of lack of oxygen upon the nutrition of the heart itself, the output of the heart gradually diminishes, it becomes more and more dilated, and finally ceases to beat. When the vagus nerves are intact, the vaso-constriction leads to reflex slowing of the heart, and the rise of arterial pressure is smaller; the slowing of the heart lessens the strain thrown upon it, and life is prolonged for a minute or so longer. During asphyxia the conductivity of the auriculo-ventricular bundle is often diminished, producing a condition of heart-block, so that the auricles may beat twice or thrice as frequently as the ventricles.

The increased activity of both the respiratory and vasomotor centres in asphyxia is, undoubtedly, the result of increased H ion concentration in the blood; it must be noted, however, that the respiratory centre is the more sensitive, and may be excited by an excess of carbonic acid too slight to affect the vasomotor centre.

THE NERVOUS REGULATION OF RESPIRATION

The respiratory centre can be influenced by nervous impulses reaching it (1) along the vagus, (2) from the higher parts of the brain, and (3) from other afferent nerves; the impulses affect primarily the frequency of the respiratory movements.

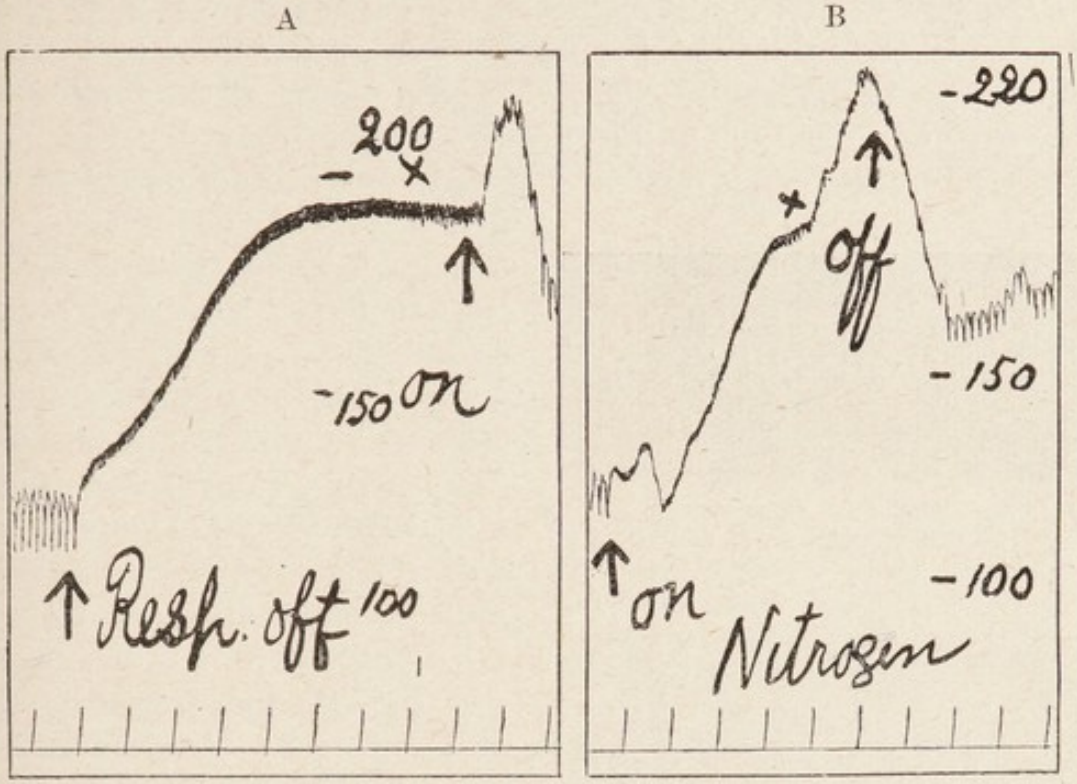


FIG. 141.—Tracing of arterial pressure. (Mathison.)

A shows the effect of asphyxia; B shows the effect of breathing pure nitrogen. The figures represent arterial pressure in mm. Hg.

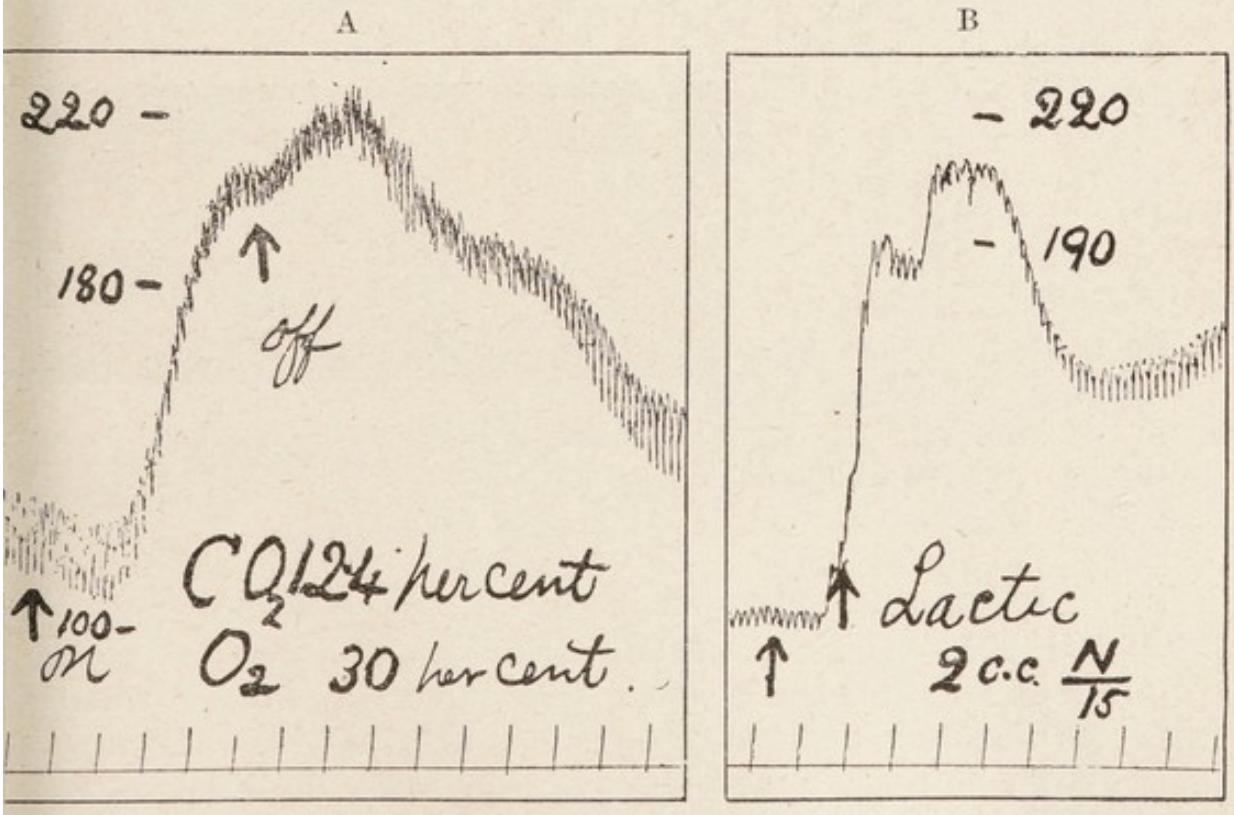


FIG. 142.—Tracing of arterial pressure. (Mathison.)

A shows the effect of excess of CO_2 in inspired air; B shows the effect of injecting lactic acid into the circulation.

(1) **The Vagi.**—The influence of the vagus nerves is most easily studied in the rabbit, by recording the movements of an isolated slip of the diaphragm (p. 298). When a record of the respiratory movements is obtained by this method, it may be seen that division of the vagus nerves is followed by a decrease in the frequency of respiration, although each breath is deeper than before. Electrical stimulation of the central end of one vagus may then produce one of two effects upon the respiratory movements. Sometimes, especially with a weak stimulus or with a constant ascending current, the inspiratory movements are inhibited (fig. 143) and the slip of diaphragm remains in the expiratory position, that is, it is relaxed. More often the inspiratory movements are increased, or the diaphragm may remain in the inspiratory position (fig. 144).

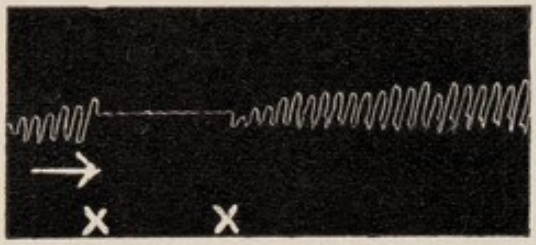


FIG. 143.—Stimulation of central end of one vagus between X and X. The slip of diaphragm remains in the relaxed, expiratory condition.

Downstroke = inspiration.

These experiments make it clear, first, that the vagus nerves contain afferent fibres carrying impulses to the respiratory centre, which modify the rate of respiration; and, secondly, that these impulses are of two kinds, one tending to cause inspiration and the other expiration. These fibres have their origin in the lungs, and their endings can be stimulated either by inflating the lungs, or by sucking air out of them. Fig. 145 illustrates the effect of suddenly distending the pulmonary alveoli with air; the diaphragm remains relaxed, and inspiratory movements cease. This effect, which is produced only when the vagus nerves are intact, and lasts only as long as the distension persists, is known as *vagus apnœa*. Conversely, when air is sucked out of the lungs (negative ventilation), the diaphragm is thrown into contraction and the inspiratory movements are increased.

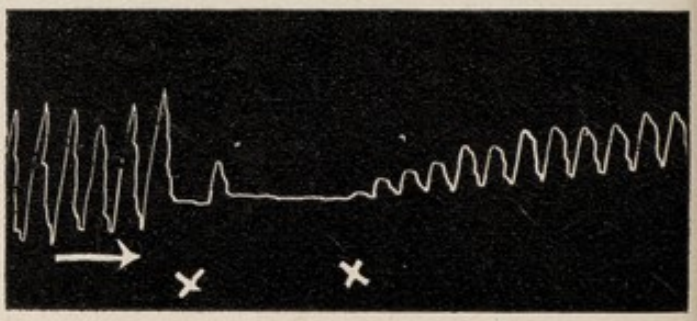


FIG. 144.—Stimulation of the central end of one vagus between X and X. The diaphragm enters into continued contraction (inspiratory position).

Downstroke = inspiration.

It is evident that distension of the pulmonary alveoli stimulates the endings in the lungs of afferent fibres which pass up the

vagus to the respiratory centre. These fibres convey impulses which inhibit inspiration and bring about expiratory movements. On the contrary, collapse of the pulmonary alveoli stimulates the endings of afferent fibres running in the vagi and conveying impulses to the respiratory centre whereby inspiratory movements are evoked.

The existence of such impulses can be further demonstrated by connecting the vagus with a string galvanometer. With each inspiration a deflection of the thread takes place, indicating the passage of an impulse along the nerve ; and, under certain conditions, a similiar deflection may also be observed during expiration.

In normal respiration these two sets of fibres are alternately stimulated, each inspiration sending impulses along one set of fibres and reflexly causing expiration, whereas each expiration gives rise to impulses which bring about another inspiration. The electrical variations in the vagus seem to show that the impulses leading to expiration are the more important and more pronounced.

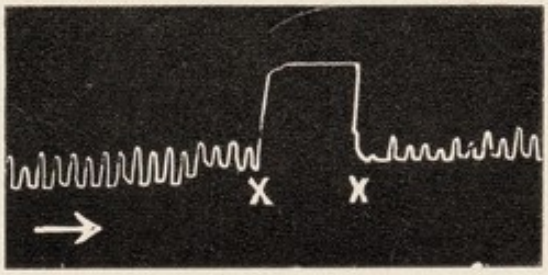


FIG. 145.—Apnœa produced by sudden distension of the lungs between X and X. The vagi are intact.
Downstroke = inspiration.

Although these impulses help to maintain the normal rhythm of the respiratory movements, respiration continues after they are prevented from reaching the respiratory centre by division of the vagi. Their principal function seems to be that of rendering the centre more sensitive to the normal stimulus of carbonic acid, and of controlling the strength of the impulses sent out from the respiratory centre to the respiratory muscles. In their absence, the respiratory centre is not stimulated until the tension of carbonic acid in the blood rises higher than in the normal animal, although each respiration, when it does occur, is exceedingly forcible.

Further, after division of the vagi, the normal adjustment of the respiratory movements in response to any considerable increase in the tension of carbonic acid in alveolar air and blood is no longer efficiently carried out. During muscular exercise, for example, a normal animal breathes not only more deeply, but also more frequently, and is thus able to expel from the lungs almost all the additional carbonic acid reaching them from the blood ; after section of the vagi the *rate* of respiration remains unaltered, the ventilation of the lungs is inadequate, and the

percentage of carbonic acid in the alveolar air rises. The same result is seen when an animal, with its vagi divided, breathes

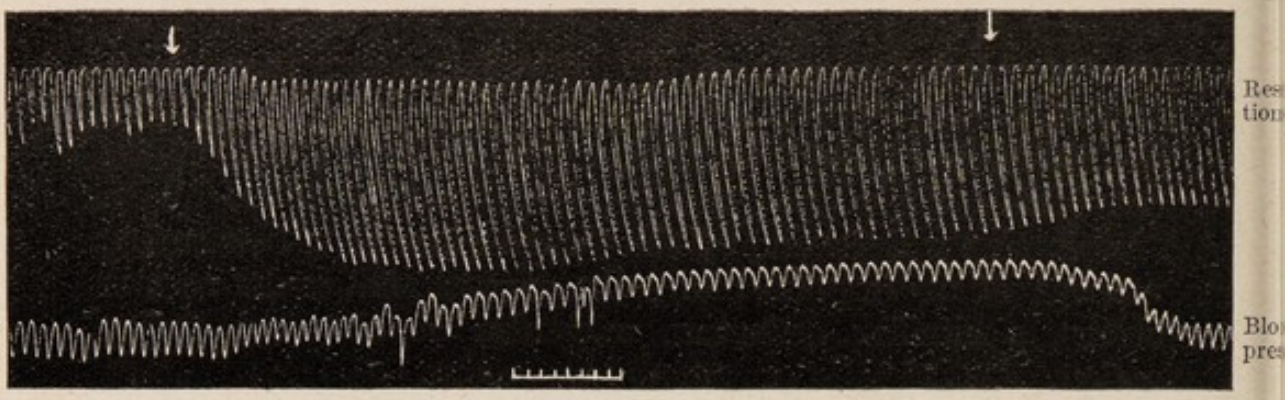


FIG. 146.—Respiratory movements in rabbit with vagi divided. Between the arrows the inspired air contained 10 per cent. CO_2. Note that the *rate* of respiration is not increased. (Scott.)

air containing an excess of carbonic acid (fig. 146), the ventilation of the lungs being much less than in the normal animal, as is seen in the following table :—

VENTILATION OF THE LUNGS

Composition of Inspired Air.	Total Ventilation per Minute.	
	Normal Rabbit.	Rabbit with Vagi Divided.
(1) Atmospheric air	1368 c.c.	1305 c.c.
(2) Air to which 8·6 per cent. CO_2 was added	2813 ,,	1596 ,,

(2) **Impulses from the Higher Parts of the Brain.**—In an anæsthetised animal, the brain-stem may be divided at the level of the pons without any obvious change being produced in the respiratory movements. Nevertheless, impulses from the higher parts of the brain can greatly modify respiration, and the effect on respiration of emotions, such as anger or excitement, is often very marked.

Again, the respiratory movements become deeper and more frequent at the very beginning of muscular exercise ; even the first breath taken after the onset of muscular work is much deeper than the respiration during rest (fig. 147). These changes occur too quickly to be brought about by an increase in the tension of carbonic acid in the blood, and observation shows that they are due to impulses passing from the cerebral

cortex to the respiratory centre, which render it more sensitive than before to the hydrogen ion concentration of the blood. Hence the normal tension of carbonic acid, acting on the unusually excitable centre, calls forth deeper and more rapid respirations. By this means the amount of oxygen entering the lungs and passing to the blood and tissues is increased at the very beginning of exercise, and the muscles are able to take up from the blood, without delay, the additional oxygen which they need for their increased activity.

(3) The respiratory movements may also be modified by impulses reaching the centre from almost every region of the body. Painful stimuli usually produce hyperpnœa, whereas impulses

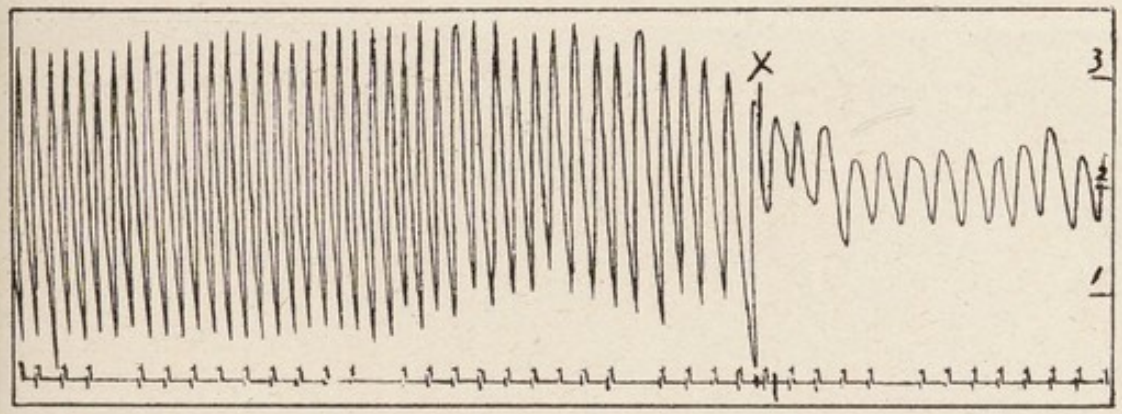


FIG. 147.—Effect of muscular work on the respiratory movements (Krogh.)
The work begins at X. Tracing to be read from right to left.

passing along the fifth nerve and the nerves from the upper respiratory passages tend to inhibit respiration; these nerves may be stimulated by irritant vapours, such as that of ammonia. The superior laryngeal nerve supplies sensory fibres to the glottis, and stimulation of its endings, for instance, by the entrance of a crumb into the glottis, inhibits inspiration and causes violent expiratory efforts. Electrical stimulation of the central part of the divided nerve brings about the same effect.

Summarising the various factors which influence respiration, we see, first, that the normal stimulus to the respiratory centre is the tension of carbonic acid in the blood passing to the centre: an increase of this tension stimulates the centre, and when the tension falls respiration ceases. Secondly, when the blood is deficient in oxygen, not only is the centre more readily excited by carbonic acid, but lactic acid passes into the blood and also stimulates the centre. Thirdly, impulses passing along the vagus nerves from the lungs help to maintain the normal rhythm of respiration, and make the centre more sensitive to the chemical stimulus of carbonic acid. Finally, impulses from the higher parts of the brain,

or impulses reaching the centre by afferent nerves, can modify the respiratory movements.

APNŒA

Reference has already been made to the inhibition of the respiratory movements, which is known as apnœa. The most important condition which gives rise to apnœa is a fall in the tension of carbonic acid in the blood. This occurs whenever the ventilation of the lungs is increased without any corresponding rise in the production of carbonic acid in the body, and may therefore be brought about either, in man, by voluntary, forced breathing (fig. 148), or, in animals, by vigorous artificial respiration. In

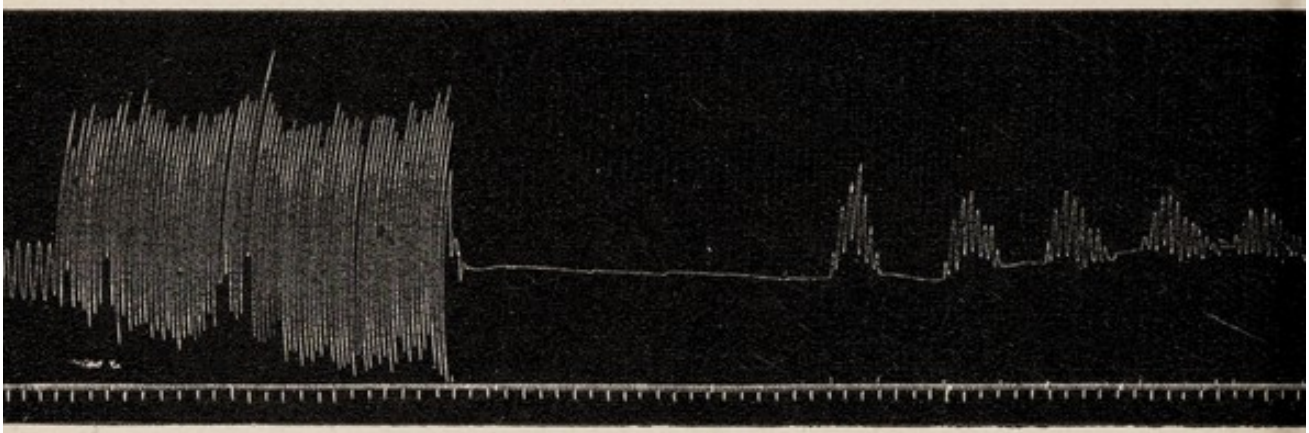


FIG. 148.—Forced breathing in man, followed by apnœa and subsequently by Cheyne-Stokes breathing. (Haldane and Douglas.)

these circumstances the apnœa may last for 1 or 2 minutes, respiration beginning again as soon as the tension of carbonic acid in the alveolar air returns to its normal level. That it is due solely to a fall in the tension of carbonic acid is clearly shown by the fact that, when the inspired air contains an excess of carbonic acid, forced breathing is not followed by apnœa.

A totally different form of apnœa is that produced by sudden distension of the lungs, and known as vagus apnœa (p. 306). This is due to the stimulation of the endings in the lungs of the afferent fibres of the vagus which inhibit inspiration.

Apnœa also occurs during deglutition, and lasts for a few seconds; the afferent impulses pass along the glossopharyngeal nerve. The effect of this inhibition is to prevent particles of food being drawn into the lungs by an inspiratory act during the process of swallowing.

Another interesting example of the adaptation of the respiratory mechanism to the needs of the animal is seen in ducks. When a duck plunges its head into water in search of food the respiratory movements

are inhibited; and this form of apnœa can be reproduced experimentally by placing the duck in the vertical position with its head downwards. The afferent impulses which travel to the respiratory centre and inhibit respiration arise in the muscles of the neck and in the labyrinth of the ear; after section of the afferent nerves from these muscles, or destruction of the labyrinth, this form of apnœa can no longer be evoked.

CHEYNE-STOKES BREATHING

This form of breathing (fig. 149), which is not infrequently observed in human beings living at high altitudes or suffering from various diseases, more especially those affecting the circulatory system, has the following characteristics. After an apnœic pause

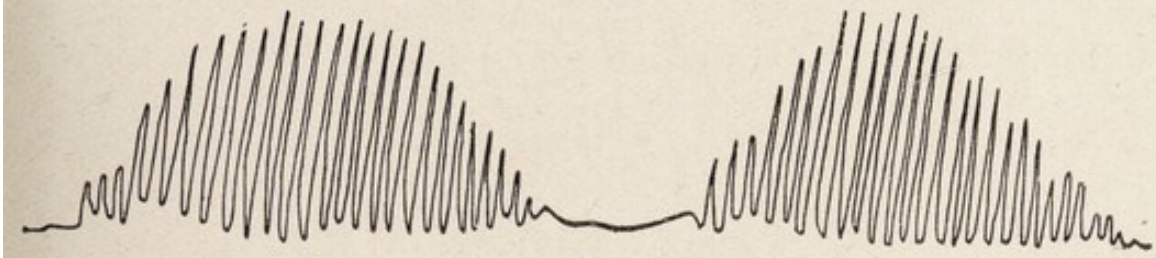


FIG. 149.—Cheyne-Stokes respiration. (Pembrey and Allen.) (From *Practical Physiology*, by Pembrey and others.)

respiration begins, the breaths being shallow at first and gradually increasing in depth till they reach a maximum. They then become smaller, and in a short time cease altogether, being succeeded by a period of apnœa. Cheyne-Stokes breathing can also be produced experimentally in healthy persons as a result of prolonged forced breathing, as is seen in fig. 148; the immediate effect of the forced breathing is a period of apnœa, and, when breathing recommences, it often exhibits the periodic character just described.

The phenomenon is caused by *lack of oxygen* in the blood. During the period of forced breathing, the tension of carbonic acid in the alveolar air falls considerably, leading to prolonged apnœa. During the apnœic period the amount of oxygen in the blood decreases, and the supply of oxygen to the respiratory centre becomes inadequate, the result being that the respiratory centre is rendered more excitable. At the same time the tension of carbonic acid in the blood is slowly rising and eventually reaches a level which, although it is below that normally present in blood,

is sufficient to stimulate the abnormally excitable respiratory centre. Respiration begins again, and the oxygen taken into the lungs and into the blood gradually lowers the excitability of the respiratory centre; at the same time the breathing removes some carbonic acid from the lungs, the result being that the chemical stimulus to respiration disappears, and the breaths become smaller and finally stop. This sequence of events whereby periods of apnœa alternate with periods of respiration may recur many times, until finally the apnœic pauses disappear and normal breathing is resumed.

When this form of breathing occurs in disease, it can be remedied either by allowing the patient to breathe nearly pure oxygen, which improves the nutrition of the respiratory centre, or by the administration of air containing a slight excess of carbonic acid, which, by raising the tension of this gas in the alveolar air and blood, increases the strength of the stimulus to the respiratory centre.

SECTION IV

TISSUE-RESPIRATION

The processes of external respiration, which have been thus far considered, are so adapted that the blood, when it reaches the capillaries, is almost fully saturated with oxygen. Equally important, however, is tissue-respiration, which consists in the transference of oxygen from the blood to the tissues and the passage of carbonic acid from the tissues to the blood.

Oxygen passes from the blood to the tissues by diffusion, and the amount which is available for the tissues depends largely upon the extent to which oxygen is set free in the plasma by the dissociation of oxyhæmoglobin. Since the tissues contain no *free* oxygen, the conditions during the passage of the blood along the capillaries are almost the same as if it were exposed to a vacuum, and, if sufficient time were available, the dissociation of oxyhæmoglobin in the capillaries would be nearly complete. But the time spent by any one portion of the blood in traversing the capillaries is so short that the blood normally gives up only about a third of its oxygen to the tissues, and the venous blood is approximately two-thirds saturated with oxygen.

If the rate at which the blood flows through an organ is increased, less time is available for dissociation of the oxyhæmoglobin in any one portion of the blood, although the *total* amount of oxygen taken up by the tissue may be unchanged. In these circumstances, the blood leaving the organ will be less venous than usual. On the contrary, if the blood-flow is unchanged but

the *rate* at which oxyhæmoglobin can dissociate becomes more rapid, the blood, as it traverses the capillaries, will give up more oxygen than usual. The rate at which oxyhæmoglobin dissociates is increased by the addition to the blood of an excess of carbonic acid or of other acids, such as lactic acid, as it passes along the capillaries.

Greater functional activity of an organ is accompanied not only by a larger blood-flow but also by more rapid dissociation of oxyhæmoglobin as the blood traverses the organ, and the combination of these two processes greatly increases the amount of oxygen available for the needs of the active organ.

Carbonic acid also passes by diffusion from the tissues, in which its tension is high, into the plasma, in which its tension is much lower. The tension of carbonic acid in the tissues has been ascertained indirectly by measuring its tension in bile or urine, and is about 8 to 9 per cent. of an atmosphere, whereas its tension in blood is only 5 to 6 per cent. of an atmosphere.

The Consumption of Oxygen by the Tissues.—The tissues are constantly taking up oxygen, and the amount used by any organ, for example the kidney, can be determined by ascertaining, first, the difference in the quantity of oxygen present in 1 c.c. of the blood entering and leaving the organ respectively; secondly, the amount of blood flowing through the organ in a given time; and, thirdly, the weight of the organ. The degree to which the blood is saturated with oxygen is measured by Barcroft's blood-gas manometer. The rate of blood-flow through the organ is ascertained by observing directly the quantity escaping from its vein in a given time. To take an example, if 1 c.c. of arterial blood contains 0·18 c.c. oxygen, and 1 c.c. of blood from the renal vein contains 0·13 c.c. of oxygen, each c.c. of blood passing through the kidney loses 0·05 c.c. oxygen. Supposing the rate of blood-flow through the kidney to be 50 c.c. per minute, the amount of oxygen taken up by the kidney is 2·5 c.c.; and if the weight of the kidney is 30 grams, 1 gram of kidney uses 0·08 c.c. oxygen per minute. Experiments made in this way show that the amount of oxygen consumed by the different tissues of the body varies greatly; the heart and kidney use (per gram) more oxygen than any other organ.

O_2 Consumed by 1 Gram of Tissue per Minute

Skeletal muscle (resting)	0·003 c.c.
,, ,, (active)	0·03 c.c.
Heart-muscle	0·05–0·2 c.c.
Kidney	0·03–0·06 c.c.
Submaxillary gland (resting)	0·023 c.c.

The amount of oxygen consumed by any organ in a given time is primarily determined by the organ itself, and, provided that the flow of blood to an organ is sufficient to supply the amount of oxygen which it needs, a further increase in the flow of blood through it does not increase its consumption of oxygen. For instance, the rate of blood-flow through the resting submaxillary gland may be increased tenfold without any rise taking place in the oxygen-consumption of the gland. The consumption of oxygen rises, however, whenever the functional activity of a tissue becomes greater, and, in the case of skeletal muscle, it may be increased tenfold during and just after muscular contraction. A similar rise occurs when the heart does more work, or when the secretory activity of the submaxillary or other glands is evoked.

Oxygen Consumed by the Submaxillary Gland

	Oxygen Used by 1 gram of Gland per Minute.	Rate of Blood-Flow through the Gland in c.c. per Minute.
(1) Resting	0·023 c.c.	0·35 c.c.
(2) Resting, with dilated blood-vessels	0·024 ,,	3·5 ,,
(3) During the secretion of saliva .	0·11 ,,	..

The increased consumption of oxygen takes place not only during the period of secretion or of muscular work, but for some time after this is over (fig. 150); and the oxygen is apparently

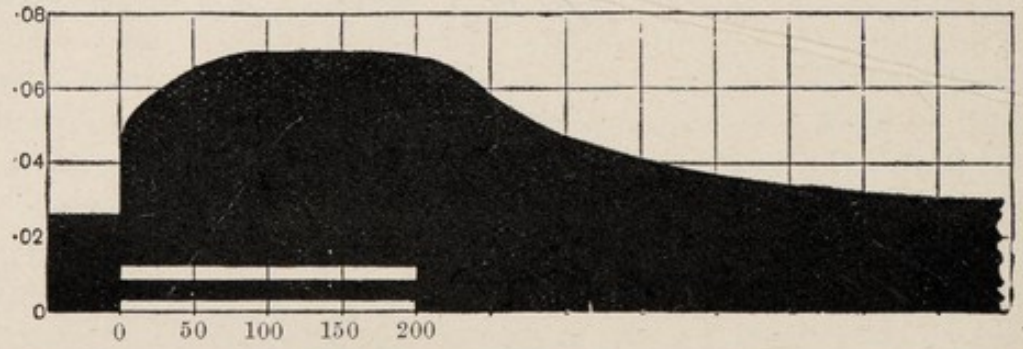


Fig. 150.—Ordinate = volume of oxygen used in c.c. per minute; abscissa = time in seconds; upper signal = duration of flow of saliva; lower signal = duration of chorda stimulation. Blackened area represents the oxygen used by the salivary gland. (From Barcroft, *Respiratory Function of the Blood.*)

used mainly in the carrying out of chemical changes whereby the gland or muscle stores up potential energy and is restored to its previous condition. Every increase in the functional activity of an organ is also accompanied by dilatation of its blood-vessels, which, as already mentioned (p. 266), is brought about by the

action of the metabolic products set free in the tissue upon the vessels of the organ; this increases the supply of blood and, therefore, of oxygen to the active tissues.

The oxidative changes in the body normally take place in the tissue-cells and not in the blood itself. When methylene blue is injected into an animal, and the animal is killed a few minutes later, the blood is coloured blue, whereas the tissues show no change of colour. Although methylene blue is a comparatively stable substance, the avidity of the tissues for oxygen is so great that they are able to reduce it with the formation of a colourless reduction product. On exposing the tissues to the air, methylene blue is re-formed, and the tissues become deeply stained.

Another method of demonstrating the fact that oxidation does not take place in the blood is to allow it to stand for a short time, and to observe whether any of its oxyhæmoglobin is reduced. In normal animals the reduction is almost negligible, and evidently no oxygen is used up in carrying out metabolic changes in the blood itself.

SECTION V

THE EFFECT OF CHANGES IN BAROMETRIC PRESSURE

(1) **The Effect of Lowered Pressure.**—When a person ascends from near sea-level to a height of 5000 to 10,000 feet or more, he is apt to suffer from symptoms which are generally described as *mountain sickness*. These symptoms are headache, mental confusion, blueness of the lips, and nausea or vomiting. They may occur when the individual ascends to this height in a train, and are therefore not due to muscular exercise, although they may become more severe when exercise is taken. They are caused entirely by lack of oxygen. With increasing altitude the barometric pressure, and therefore the partial pressure of oxygen in the atmosphere and in the alveolar air, gradually falls; and when the alveolar pressure of oxygen, which is normally 105 to 110 mm. Hg, falls to about 60 mm. Hg, the symptoms just described make their appearance. Similar symptoms are produced in animals and in man when they are placed in closed chambers and the barometric pressure is gradually reduced. If the individual remains at a high altitude, the symptoms pass off in the course of a few days, and after a time exercise may be taken without their recurrence.

The adaptation of the body to the altered conditions is brought about by changes in both the respiratory and vascular systems.

In the first place, it has been found that, when a man has become acclimatised to residence at a high altitude (*e.g.* 14,000 feet), he breathes more deeply, even when resting, than when he lives at or near sea-level. Owing to the greater ventilation of the lungs, the partial pressure of carbonic acid in the alveoli decreases, and that of oxygen rises. At a high altitude, when the alveolar oxygen-pressure is low, even a small rise in the partial pressure of oxygen appreciably increases the extent to which hæmoglobin can take up oxygen as the blood flows through the lungs. For example, if, as a result of the hyperpnœa, the alveolar pressure of oxygen rises from 36 mm. Hg to 53 mm. Hg, the saturation of the hæmoglobin in the blood leaving the lungs may be increased from 65 per cent. to 85 per cent.

In the second place, in persons who remain at a high altitude for a long period, the number of red corpuscles and the percentage of hæmoglobin in the blood are gradually increased. In one series of observations, made at a level of 14,000 feet, the percentage of hæmoglobin in the blood rose in the course of some weeks from 103 to 127. When the subject returned to a low level, the percentage of hæmoglobin rapidly fell to normal. Hence the deficiency in the amount of oxygen taken up by each red corpuscle in the lungs is made good by the larger number of red cells in the blood, with the result that, at least in the resting man, the *amount* of oxygen carried from the lungs to the tissues is as great at high altitudes as at low levels.

The extent to which adaptation takes place varies in different individuals; in many cases the supply of oxygen to the tissues is barely sufficient during rest, and exercise frequently leads to an inadequate supply of oxygen to the tissues and brings on mountain sickness. This occurs less readily, however, in the trained than in the untrained person, partly because the former uses his muscles more economically, and therefore his demands for oxygen are not so great.

(2) **The Effect of Raised Pressure.**—Men engaged in the building of bridges or tunnels are often compelled to work in caissons, which are filled with compressed air to prevent the inrush of water. They suffer no inconvenience, and the respiratory movements are not affected, while they are in the caisson, even though the pressure may be three or four atmospheres. Under this pressure, however, the blood dissolves an increased amount of oxygen and nitrogen, and, when a man leaves the caisson and the pressure to which the blood and tissue-fluids are exposed is suddenly reduced to one atmosphere, most of the nitrogen, previously in solution, is evolved as bubbles, which may obstruct the flow of blood along the blood-vessels or through

the heart, or, when set free in the tissues, may damage delicate structures such as nerve-cells.

The symptoms caused by this obstruction, and known as *caisson disease*, are very varied, and include paralysis, severe abdominal pain, and collapse. The disease is prevented by allowing the man to pass from the caisson into a special air-chamber (air-lock), in which the pressure is gradually lowered to that of the outer air so as to prevent any sudden evolution of nitrogen.

CARBON MONOXIDE POISONING

The affinity of carbon monoxide for hæmoglobin is about 300 times as great as that of oxygen (p. 179); and, when air containing even a small percentage of carbon monoxide is breathed, the oxyhæmoglobin is replaced by carbon monoxide hæmoglobin, the supply of oxygen to the tissues is cut off, and asphyxia is produced. The fatal effects of breathing air containing coal-gas, in which carbon monoxide is present, are brought about in this way; but death may often be prevented by the administration of pure oxygen, which not only increases the amount of oxygen dissolved in the blood and carried to the tissues, but, by its mass action, gradually displaces the carbon monoxide from its combination with hæmoglobin.

SECTION VI

THE INFLUENCE OF THE RESPIRATORY MOVEMENTS ON THE CIRCULATION

A tracing of the arterial pressure often shows oscillations corresponding with each respiratory movement, the pressure rising a little during inspiration and falling during expiration. Further, the pulse is more frequent during inspiration and less frequent during expiration (fig. 151). The difference in the pulse-rate is due to a slight diminution of the tone of the vagus during inspiration, which allows the heart to beat more rapidly: it is abolished by section of the vagi, but the respiratory oscillations of the blood-pressure are not affected by this procedure.

At the end of expiration, the pressure inside the cavity of the chest is slightly below atmospheric pressure, and the pressure on the walls of the great veins and of the heart is negative, whereas the pressure in the jugular vein in the neck, for example, is slightly higher than that of the atmosphere. Owing to this difference of pressure in the vessels within and outside the chest, blood tends

to be sucked along the great veins and into the heart. With each inspiration the degree of negative pressure is increased, and the flow of blood into the heart becomes more rapid. The thin-walled auricles are also slightly dilated by the negative pressure, and the flow of blood to the heart is thus further assisted, the thick-walled ventricles and arteries being practically unaffected. As the result of the additional blood reaching the heart during inspiration, the amount of blood expelled from the heart at each beat becomes larger, and the arterial pressure rises. Conversely, during expiration the negative pressure diminishes again, less blood flows into the heart, its output is smaller, and the arterial pressure falls.

A second factor which conduces to the inspiratory rise of arterial pressure is the descent of the diaphragm during inspiration; this, by diminishing the size of the abdominal cavity, raises the intra-abdominal pressure and squeezes blood out of the abdomen along the inferior vena cava into the heart.

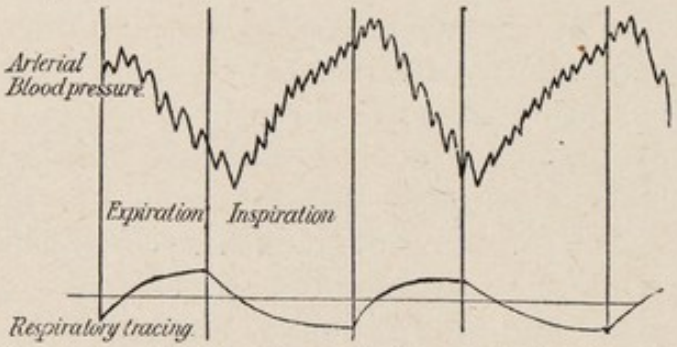


FIG. 151.—Effect of respiratory movements on arterial blood-pressure. (Starling's *Principles of Physiology.*)

According to some observers, a third factor also takes a part in producing the rise of blood-pressure during inspiration, namely, changes in the size of the vessels forming the capillary network in the lungs. The lung is exposed on its inner surface to atmospheric pressure, and on its outer surface to a pressure which is less than atmospheric pressure. An increase in this difference of pressure, such as occurs during inspiration, will dilate the capillaries in the lungs, blood will flow through them more rapidly, and a larger quantity will reach the left ventricle in a given time; the additional blood thus reaching, and expelled from, the left ventricle will raise the arterial pressure. Conversely, during expiration, when the difference of pressure on the two sides of the lung-wall diminishes, the capillaries will shrink, blood will flow less rapidly through them into the left ventricle, and the blood-pressure will fall.

Other writers, however, consider that changes in the calibre of the capillaries of the lung play no part in the variations of blood-pressure which accompany the respiratory movements; they regard these variations as being due entirely to alterations in the amount of blood which is drawn

into the heart by the negative pressure on the walls of the great veins, and is driven out of the abdominal veins by the contraction of the diaphragm.

The negative pressure during inspiration varies with the depth of the inspiration, and, when the breathing is very forcible, the rise and fall of blood-pressure during inspiration and expiration may become very marked. The rise of pressure begins just after the beginning of inspiration, and continues for a short time during expiration, so that the variations in blood-pressure are not quite synchronous with the respiratory movements. The delay in the rise of blood-pressure is due to the fact that, when more blood enters the right auricle at the beginning of inspiration, it has to travel through the lungs before it reaches the left ventricle and is expelled into the aorta. Again, at the beginning of expiration there is, for the same reason, a slight delay in the diminution in the amount of blood sent out by the left ventricle.

In man, the alterations in blood-pressure produced by the respiratory movements are of very complex origin, and the effects are not so constant as those just described for animals; they vary with the type of respiration, a purely costal inspiration causing a fall, and a diaphragmatic inspiration causing a rise, of blood-pressure.

SECTION VII

MUSCULAR EXERCISE

The supply of oxygen to the tissues and the removal of carbonic acid are effected by the conjoint action of the respiratory and circulatory systems; and, in order that the tissues may receive their due supply of oxygen, it is necessary, not only that the blood in its passage through the lungs should become almost fully saturated, but that an adequate amount of blood should be carried through the lungs and to the tissues. We find, therefore, that the demands of the body as a whole for an increased amount of oxygen are met by alterations in both the respiratory and circulatory systems, and that for this purpose the two systems exert a correlated action, which is very clearly illustrated in muscular exercise.

During muscular exercise the active muscles consume a large amount of oxygen and give off much carbonic acid. Their increased demand for oxygen is met in two ways. In the first place, increased ventilation of the lungs allows more oxygen to pass into the blood. In the second place, the blood flows more

rapidly round the body and consequently oxygen is carried more quickly from the lungs to the active muscles.

The Respiratory Changes.—By means of increased respiratory movements sufficient oxygen reaches the alveolar air to replace that which passes into the blood, and sufficient carbonic acid is removed from the lungs to keep its percentage in the alveolar air almost unchanged ; and the blood, during exercise, is probably almost as fully oxygenated as during rest, the hæmoglobin being at least 90 per cent. saturated with oxygen.

The adjustment of the respiratory mechanism to the increased needs of the muscles is brought about, first, by impulses passing from the cerebral cortex to the respiratory centre at the very outset of exercise, which increase the sensitiveness of the centre to the H ion concentration of the blood (p. 308), and secondly, by the chemical stimulus of the altered reaction of the blood. The H ion concentration of the blood is raised not only by the additional carbonic acid passing from the muscles into the blood, but also by lactic acid, the amount of which in the blood increases during muscular exercise, if the latter is at all severe. During rest, the blood in man contains only minute traces of lactic acid, and this is not increased by moderate exercise, such as walking, though running for a few minutes raises the amount of lactic acid in the blood, and lactic acid may then be detected in the urine. Notwithstanding the great increase in the supply of oxygen to the actively contracting skeletal muscles, the latter are unable to oxidise all the lactic acid which is formed in them in these circumstances. The excess of lactic acid passes into the circulation, and not only stimulates the respiratory centre, but also (p. 289) renders the oxyhæmoglobin of the blood flowing through the muscels more readily dissociable, and enables them to obtain oxygen more easily.

The changes in the circulation during exercise are acceleration of the pulse, a larger output of the heart, and a rise in the mean arterial pressure, associated with dilatation of the blood-vessels in the muscles. The greater frequency of the pulse is due primarily to diminution in the tone of the vagus centre and, therefore, of the restraining influence which it normally exerts on the heart. It is seen at the very beginning of exercise, being brought about, in all probability, by impulses passing from the cerebral cortex to the vagus centre. Other factors which contribute later to the acceleration are (1) an increase in tone of the accelerator centre, and (2) the rise of venous pressure which occurs during exercise and reflexly lessens the tone of the vagus centre (p. 249). At the same time, the movements of the skeletal muscles, aided by the more vigorous respiratory movements,

bring about a larger and more rapid return of blood to the heart ; as a result the heart fills more quickly and completely during diastole, and its output becomes larger, and (in man) may reach 15–20 litres per minute. Owing to the greater output of blood from the heart, the velocity of the blood-flow through the lungs, and indeed through the whole body, becomes greater ; and, within a given time, a much larger quantity of oxygen can be taken up by the blood as it passes through the lungs, and can be transported to the tissues, than during rest.

The rise in the arterial blood-pressure is due partly to the increased output of the heart, and partly to constriction of the splanchnic vessels, and, since the blood-vessels to the muscles are dilated, the flow of blood is largely diverted from the abdominal organs to the skeletal muscles. The raised arterial pressure also brings about a more abundant blood-supply to the heart and brain.

During exercise a large amount of heat is evolved in the muscles, and the temperature of the body may rise to 101° F. or even higher ; this rise in temperature tends further to accelerate the heart, and is one of the reasons why the pulse-rate remains rapid for some time after the exercise has come to an end.

Second Wind.—It is a matter of common knowledge that, in a trained person, the respiratory discomfort which occurs soon after the beginning of exercise usually passes off in a few minutes, and the exercise can then be continued for a long period without further inconvenience, the individual being said to have gained his *second wind*. The causation of this has been much discussed, and is not fully understood, though it is probably due in part to the fact that a trained person uses his muscles more economically than an untrained person, and therefore produces less carbonic acid. The observation that the tension of carbonic acid in the alveolar air may fall with the onset of second wind suggests that such is the case. If the muscles are used more economically after a brief period of exercise, the decrease in the production of carbonic acid will lessen the stimulus to the respiratory centre, and will account for the absence of panting and respiratory distress in second wind. It is probable that adjustment also takes place in the circulation, since the process of training consists essentially in the better adaptation of the circulatory system to withstand extra strain.

CHAPTER IX

THE DIGESTIVE SYSTEM

SECTION I

THE NATURE OF DIGESTION

The process of digestion consists essentially in the splitting up of the molecules of the food-stuffs into a large number of much smaller molecules, which, partly because of their smaller size, are easily absorbed through the mucous membrane of the digestive tract. Thus the digestion of fat results in the splitting up of the molecule of neutral fat into one molecule of glycerol and three molecules of fatty acid, a single protein molecule is broken up into a very large number, probably a hundred or more, of molecules of amino-acids, while one molecule of starch is subdivided into about two hundred molecules of glucose. In all cases the process is one of hydrolysis, and, in the case of protein and starch, it takes place in a series of stages. Similar changes can be brought about by chemical means, such as boiling with mineral acids, but the digestive juices achieve their results more rapidly and effectively, at the temperature of the body, by means of certain active agents known as enzymes or ferments.

ENZYMES

Enzymes are widely distributed in the animal body, and many, if not all, of the chemical changes which occur in the tissues are due to the activity of these agents. Some are concerned with the transference of oxygen in tissue-respiration, and are known as oxidases and reductases, others remove the NH_2 group from amino-acids, another series is responsible for the various stages in the production of uric acid, and the digestive enzymes are concerned, as described above, with the hydrolysis of the constituents of the food.

Nature of Enzymes.—No enzyme has yet been isolated and analysed, and therefore nothing definite is known as to the composition and constitution of these bodies. They are

allied to proteins, though they themselves have not protein characteristics, and solutions containing them have colloidal properties, the molecules of the ferment being relatively large.

Source of Enzymes.—Enzymes are products of the activity of cells. Some act intracellularly, as the *zymase* of yeast does. Others are discharged from the cells in which they are formed, to perform their function extracellularly. In the latter case, the discharge of the ferment from the cell usually takes place as the result of a nervous or chemical stimulus, and in the absence of such a stimulus granules of a precursor, or *zymogen*, accumulate in the cell. Generally speaking, this is what occurs in the case of the digestive ferments, the zymogen becoming converted into the enzyme after its discharge from the cell.

Characteristics of the Action of Enzymes.—The action of an enzyme is distinguished by certain definite features.

(1) Each is *specific*; it will act on one particular substance, and on no other. For example, three disaccharides may be found in the digestive tract, sucrose, maltose and lactose, and each of these is split into monosaccharides by its own enzyme, these being *invertase*, *maltase* and *lactase* respectively. Invertase will not act upon maltose or lactose, and similarly maltase and lactase will each act only upon its own particular sugar. A ferment has been compared with a key which will only fit its own lock.

(2) Enzymes act only in the presence of water. The substrate, or substance acted upon, may be undissolved while the enzyme is in solution, or the enzyme may be in the form of a precipitate in a solution of the substrate, or both enzyme and substrate may be in solution, but the action of the ferment cannot occur if enzyme and substrate are mixed in the dry state.

(3) An enzyme will act upon an unlimited quantity of substrate provided the products of the action are continually removed. If the products are not removed, in some cases they tend to destroy the ferment, in other cases they combine with it, so that the rate of its action becomes progressively slower, and finally the action stops.

(4) An enzyme acting upon a limited quantity of substrate, when the products of the action are not being removed, does not effect complete conversion of the substrate, but brings about a certain definite proportion between the latter and the substance into which it is converted. The reason for this is that the action of an enzyme is usually *reversible*. For example, the enzyme maltase, if added to a solution of maltose, will convert most of this sugar into glucose. But if the same ferment is added to a solution of glucose it will convert a certain proportion of

the latter into maltose. The action of maltase is, in fact, to bring about a certain definite proportion between the amount of maltose and glucose in solution, the proportion, or, as it is called, the *equilibrium point*, varying with the concentration of the solution. Thus maltase, acting upon maltose, might convert it entirely into glucose if the latter substance were removed at the same rate as that at which it was produced; or conversely, the same enzyme, acting upon glucose, might convert the latter entirely into maltose, provided the maltose were being simultaneously removed. This reversible action of enzymes is of great importance in the body, where, for example, glucose is at one time converted into glycogen by a synthetic process, while, later, the glycogen is once more turned into glucose by a process of hydrolysis.

(5) The *rate* at which a ferment will convert a given amount of substrate into its end-products is proportional to the amount of ferment present. A small amount of enzyme acting upon a large quantity of substrate will, subject to the conditions already discussed, act upon equal quantities of substrate in equal times, and will thus gradually accomplish what a larger quantity of ferment would bring about in a much shorter time.

(6) Finally, the rate of action of an enzyme is affected by *temperature*. Like chemical reactions, it is accelerated, within limits, by a rise of temperature, and slowed by a fall. The optimal temperature for the action of the enzymes of the body is 37° to 40° C., that is, at, or just over, the temperature of the body. The action of an enzyme is arrested by very low temperatures, but the enzyme itself is not destroyed. At or even below the temperature of boiling water, however, all ferments are destroyed, though there is evidence that some, at least, may be reactivated.

Mode of Action of Enzymes.—It will be seen from what has been said that enzymes resemble inorganic catalysts in that they alter the rate of certain chemical reactions without supplying any energy to the process, without forming part of the final products, and without being themselves used up. They may therefore be described as *organic catalysts*.

Probably the first stage in enzymic action consists in either a physical union by *adsorption* between enzyme and substrate, or an actual chemical combination between the two. When the action is hydrolytic, water is also combined with the substrate. An unstable compound is thus formed, which then splits into simpler molecules, and the enzyme is again set free.

Adsorption by an inorganic catalyst is shown in the case of spongy platinum, which brings about the interaction of hydrogen and oxygen gases to form water at ordinary temperature. The

gases are adsorbed by the platinum and are thus brought into intimate relationship with each other. It is possible that hydrolytic enzymes may act by a similar physical process, bringing about the union of substrate and water.

The chemical union of a catalyst with its substrate may be compared with the action of nitric oxide in the formation of sulphuric acid from sulphur dioxide. The nitric oxide combines with oxygen from the air to form peroxide of nitrogen, and this substance then yields oxygen to oxidise sulphur dioxide, nitric oxide being again set free.

$$2NO + O_2 = 2NO_2$$
$$NO_2 + SO_2 = NO + SO_3.$$

The oxidases of the tissues are believed to act in this way. An organic oxide takes up oxygen from the blood or lymph, and becomes a peroxide. The peroxide yields active oxygen to the tissues, becoming itself reduced to an oxide, and the process is repeated.

THE STAGES OF DIGESTION

The activities of the digestive tract are two in number. First, there is a motor mechanism by means of which the contents of the tract are moved progressively from mouth to œsophagus, stomach, small intestine, and large intestine, and the residues are finally expelled. Secondly, there is a series of secretory glands, which produce the digestive juices met with in the different regions of the tract. The enzymes present in these juices bring about hydrolytic changes in the protein, carbohydrate, and fatty constituents of the various food-stuffs.

Food is mixed with saliva in the mouth, and is then quickly passed on to the stomach, in which it remains for some time. During the early part of its stay in the stomach, the starch of the food undergoes the preliminary stages of digestion through the agency of the saliva. Gastric juice is also secreted, and originates digestive changes in the proteins, while it gradually destroys the salivary enzyme.

The next stage consists in the forwarding of the contents of the stomach into the small intestine, where the pancreatic juice and bile carry the digestive changes in the carbohydrates and proteins a stage further, and bring about the digestion of the fats.

Finally, the intestinal juice effects the concluding stages of carbohydrate and protein digestion, and the hydrolytic products of carbohydrates, proteins, and fats, together with inorganic salts and water, are absorbed through the wall of the small intestine. Undigested substances and certain waste matters reach the large

intestine, where much of the remaining water is absorbed, the residue constituting the fæces. Under normal conditions, such of the constituents of a meal as are not absorbed begin to reach the large intestine four to five hours after the ingestion of the meal, and the residues are finally expelled from twelve to twenty hours later, so that all the processes described above are going on simultaneously, there being as a rule an interval of not more than four or five hours between meals during the day.

SECTION II

CHANGES IN THE FOOD IN THE MOUTH

On entering the mouth the food is masticated, being directed by the muscular movements of the cheeks, lips, and tongue, into position between the opposing teeth, and broken up and formed into a pulpy mass by the vertical, lateral, and antero-posterior movements of the jaws. At the same time, saliva is poured into the mouth in considerable quantity, and is intimately mixed with the food by the same movements. After mastication, the food, mixed with the saliva, is collected into a bolus on the tongue by further movements of the cheeks, lips, and tongue itself, and it is then ready to be swallowed.

Saliva is formed by the salivary glands, which in man and many animals are three in number on each side, namely, the parotid, sublingual, and submaxillary glands. A salivary gland consists of a mass of alveoli or acini bound together by connective tissue; each alveolus is lined by polyhedral cells resting on a basement-membrane, and opens into a duct. The ducts from the alveoli unite to form larger ducts, and eventually end in one main duct which opens on the surface of the mucous membrane of the mouth.

The Composition of Saliva.—The saliva which enters the mouth is the mixed secretion of all the salivary glands, together with that of the small buccal glands which are scattered over the mucous membrane of the mouth. It is a viscid, colourless, slightly turbid fluid, faintly alkaline in reaction, and its specific gravity varies from 1002 to 1008. It contains as a rule just over 99 per cent. of water, and less than one per cent. of solid constituents. The latter consist of coagulable proteins, mucin, a diastatic enzyme called *ptyalin*, and inorganic salts, of which calcium salts form a considerable proportion and are apt to be deposited as tartar on the teeth. Traces of potassium thiocyanate are often present, and, when this is the case, a red colour is produced by the addition of ferric chloride to the saliva. The viscidity of

saliva is due to the mucin which it contains ; the cloudiness is the result of the presence of numerous squamous epithelial cells derived from the mucous membrane of the mouth, and also of the so-called salivary corpuscles. The latter are granular, spherical cells, most of which are probably degenerating leucocytes.

In man it is easy to collect separately the saliva from the parotid or submaxillary glands by inserting a small cannula into the parotid duct or into the submaxillary duct (Wharton's duct). It is then found that the submaxillary saliva contains much mucin and little ptyalin, whereas the parotid saliva is free from mucin but is rich in ptyalin. This difference depends upon the fact that two types of cell are found in the salivary glands, one which secretes mucin and is called a mucous cell, the other which secretes ptyalin and other substances and is called a serous cell. In many animals, including man, the acini of the parotid gland consist entirely of serous cells, and the gland is said to be a serous gland. The submaxillary and sublingual glands in carnivorous animals usually consist almost solely of mucous cells, while in herbivora the cells are mainly, or entirely, serous in character ; in man some of the acini contain mucous, and others serous, cells.

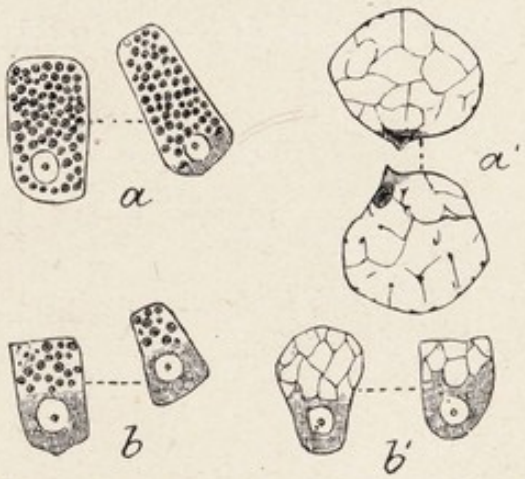


FIG. 152.—Mucous cells from fresh submaxillary gland of the dog. (Langley.) From Sharpey Schafer's *Essentials of Histology*.

a, from a resting or loaded gland ; *b*, from a gland which has been secreting for some time ; *a' b'*, similar cells which have been treated with dilute acid.

If a portion of a *mucous* gland, which is in the resting condition, be teased in 2 per cent. salt solution, the individual cells are seen to be somewhat columnar in shape, and to be filled with large granules which swell up and disintegrate on the addition of acetic acid. If the gland be hardened in alcohol and stained sections be examined, no granules are visible, but the body of the cell is clear, with a delicate network, and the nucleus is flat and lies at the base of the cell. In the case of a gland which has been made to secrete profusely, either by means of electrical stimulation or by the administration of pilocarpine, the granules are fewer in number and are found in the part of the cell which abuts on the lumen of the acinus ; and the cell is smaller than that in the resting condition (fig. 152). The hardened specimen shows a larger proportion of protoplasm, and the nucleus does not lie so close to the base of the cell. In the process of secretion, therefore, there

has been a discharge of the granules contained in the cell. But, from their behaviour to reagents, it is clear that the granules do not represent the final stages of the secretory process, for mucin itself is precipitated by acetic acid. The material contained in the granules must be a precursor of mucin, and it has therefore been called mucinogen.

The cells of the *serous* type, examined in the same way, are more cubical in shape, with a central nucleus, and in the resting state are diffusely filled with fine granules, which, as they are supposed to consist of a precursor of ptyalin, have been called zymogenic. As in the case of the mucous cell, the serous cell becomes smaller during activity and the granules are diminished in number, especially towards the base of the cell (fig. 153). In stained sections of the hardened gland, the cells, even in the resting

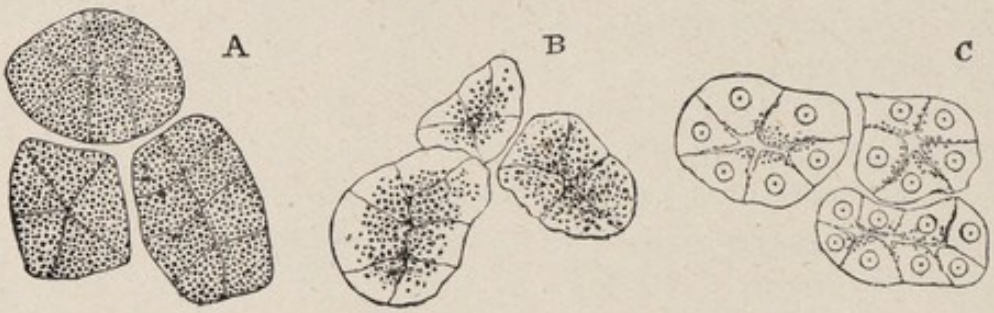


FIG. 153.—Alveoli of a serous gland. (Langley.) From Sharpey Schafer's *Essentials of Histology*.

A, at rest. B, after a short period of activity. C, after a prolonged period of activity. In A and B the nuclei are obscured by the granules of zymogen.

stage, always appear to contain a relatively greater amount of protoplasm than the mucous cells.

In both mucous and serous cells the formation of granules is preceded by the appearance of filaments, basiphile in character, which have received the general name of *ergastoplasm*.

The Functions of Saliva.—The saliva not only assists mastication and deglutition by its admixture with the food, but, by keeping the lips and tongue moist, it is of service in those movements which are essential to the function of speech. Further, it dissolves many substances taken into the mouth, and thereby renders them capable of stimulating the gustatory end-organs, and of giving rise to sensations of taste. In addition to these functions saliva has in many animals, including man, a definite digestive action owing to the presence of ptyalin, which acts upon starch, converting it into dextrin and maltose. Raw starch is not acted upon by saliva, which cannot dissolve the capsules of the starch granules, and, to enable ptyalin to produce its effect upon starchy foods, these must be boiled or otherwise cooked.

When starch granules are heated in the presence of water, they swell, and the capsules are ruptured, so that the starch passes into a pseudo-solution.

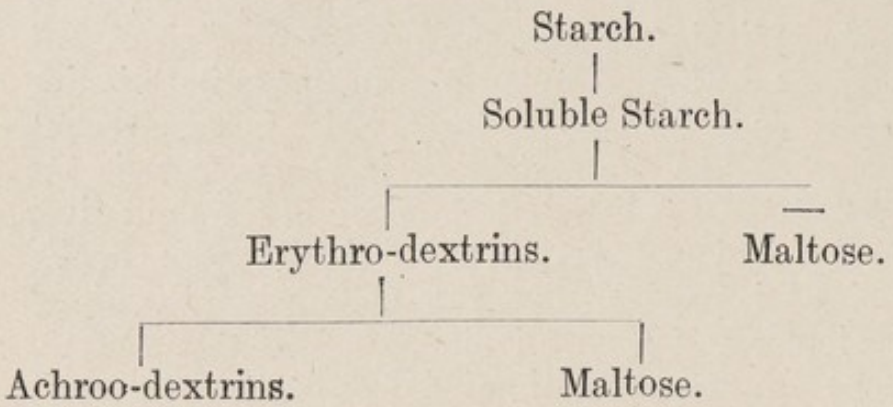
If a little saliva is mixed with some boiled starch-paste in a test-tube and the mixture kept at 40° C., the changes which occur may be conveniently observed. The original starch solution is slightly opalescent. Within a few seconds it becomes clear, but if a drop of the clear solution be added to a drop of dilute iodine a blue colour results, as in the case of starch which has undergone no digestive change. Thus the first stage in the process is the formation of *soluble starch*. A little later, a drop of the fluid gives a purple colour with iodine, later still a reddish brown ; finally an " achromic point " is reached, that is, a stage when the digest does not give a colour reaction with iodine. The digestive power of any particular saliva can be estimated by the time taken to reach the achromic point.

The purple and reddish-brown reactions with iodine indicate the presence of *erythro-dextrin*, at first mixed with a certain amount of unaltered starch, so that the dextrin reaction is complicated by the blue starch reaction, but later without any such admixture. If, at any time after the indications of the presence of dextrin appear, a little of the solution be boiled with an alkaline solution of cupric sulphate, reduction of the latter will take place, a precipitate of yellow cuprous oxide being formed. This reaction indicates the presence of a reducing sugar, the sugar in this case being *maltose*. In the achromic stage the solution is found to contain maltose and a form of dextrin which gives no colour reaction with iodine and is therefore called *achroo-dextrin*. The ultimate result of the digestion usually consists of about 80 per cent. of maltose and 20 per cent. of achroo-dextrin, and, although the proportion of the latter may be reduced in favourable circumstances to 5 per cent., the conversion of starch into maltose by ptyalin is never complete.

Evans' method of determining the amylolytic power of saliva is based upon a calculation of the amount of maltose formed from a given quantity of starch in a definite time. 5 c.c. of mixed saliva are diluted to 50 c.c. with distilled water, and the mixture is filtered. 3 c.c. of the diluted saliva are added to 50 c.c. of a 3 per cent. solution of neutral soluble starch which is at a temperature of 46° C. Digestion is allowed to proceed at 46° C. for ten minutes, and is then stopped by the addition of a little sodium hydrate. The copper-reducing power is then determined, and the amount of maltose formed is calculated.

The salivary digestion of starch consists in the taking up of water by the starch molecule, and for each molecule of water taken up, a molecule of maltose is split off. In this way the

original molecule becomes progressively smaller, and passes through a series of dextrins which are grouped as erythro- and achroo-dextrins according to their reaction with iodine, finally reaching the stage of maltose and achroo-dextrin. The process may be diagrammatically shown thus :—



Or it may be epitomised in the formula—

$$\underset{\text{Starch}}{(C_6H_{10}O_5)_{200}} + 80H_2O = \underset{\text{Maltose}}{80C_{12}H_{22}O_{11}} + \underset{\text{Achroo-dextrin.}}{(C_6H_{10}O_5)_{40}}.$$

The digestive action of ptyalin on starch is most energetic in a faintly acid medium. Hence it is favoured by the addition of a trace of acid to normal alkaline saliva. Like other ferment processes it is arrested by a high temperature, and ptyalin itself is destroyed by the slightest excess of hydrochloric acid, even less than is contained in gastric juice. The optimum temperature for the action of ptyalin is 46° C.

The food does not remain long enough in the mouth for the ptyalin to convert any appreciable amount of starch into sugar, but salivary digestion continues for a considerable time in the stomach. When a meal is taken, the food, mixed with saliva, forms a compact mass in the stomach, and the hydrochloric acid of the gastric juice penetrates comparatively slowly into this mass. As the acid penetrates it destroys the ptyalin, but, in the interval which elapses before this process is complete, the ptyalin has time to convert a considerable amount of starch into dextrin and maltose. The duration of salivary digestion in the stomach is usually from twenty to forty minutes, but it may be prolonged for an hour or more if the animal remains quiescent after the meal, so that the mass of food is not rapidly broken up by bodily movements.

THE SECRETION OF SALIVA

The Nerve-Supply of the Salivary Glands.—Each salivary gland receives a double nerve-supply from the central nervous

system. The submaxillary and sublingual glands are supplied by nerve-fibres which arise from the nucleus of the nervus intermedius and join the facial nerve; they leave this nerve in a branch known as the chorda tympani (fig. 154), and are given off to the glands from the latter after it has joined the lingual branch of the fifth nerve. The fibres supplying the parotid gland also originate in the nucleus of the nervus intermedius, join the trunk of the glossopharyngeal nerve, and, leaving it by its tympanic branch, reach their destination after passing through the tympanic plexus, the small superficial petrosal nerve, the otic ganglion,

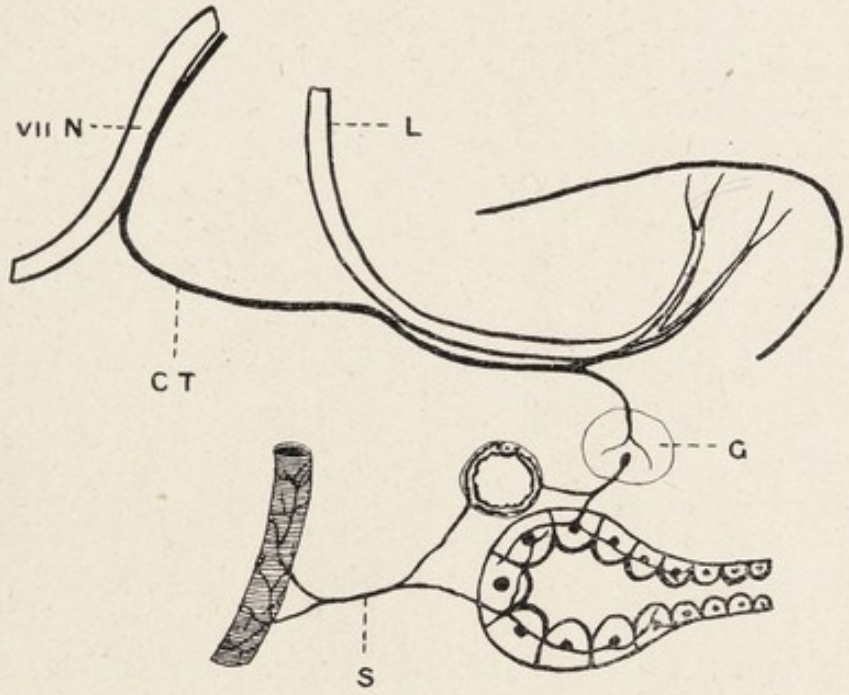


FIG. 154.—Scheme of nerve-supply of submaxillary gland.
VII N, facial nerve; C.T., chorda tympani; L, lingual nerve; G, Langley's ganglion S, sympathetic fibres to the gland.

and the auriculo-temporal nerve. All these fibres belong to the cranial autonomic nervous system (p. 114), and a cell-station is found on the nerve-path in each case. In the dog, the cell-station for the submaxillary gland is a small collection of nerve-cells situated in the hilum of the gland, and known as Langley's ganglion; that for the sublingual gland is the submaxillary ganglion, situated close to the lingual nerve; the station for the parotid gland is the otic ganglion. From these various ganglia post-ganglionic fibres pass to the respective glands.

All the salivary glands also receive a supply from the sympathetic system. In the dog, the pre-ganglionic fibres leave the spinal cord in the white rami communicantes of the first three thoracic nerves, pass through the stellate ganglion, and run in the cervical sympathetic nerve to the superior cervical ganglion, in which they form synapses with nerve-cells. Post-ganglionic

fibres from these cells run in the sympathetic plexus on the external carotid artery to the various glands.

Functions of the Nerves to the Glands.—The function of these nerves may be studied in an anæsthetised animal by placing a cannula in the duct of a salivary gland, and observing the effect of (1) division of the nerve, and (2) stimulation of its peripheral portion. If, for instance, a cannula be placed in the duct of the submaxillary gland, no flow of saliva will be observed either before or after the chorda tympani nerve is divided; but, on stimulation of the peripheral portion of the divided nerve with rapidly repeated induction shocks, an abundant flow of viscid saliva takes place, and continues for a few seconds after the cessation of the stimulus. Stimulation of the peripheral part of the divided cervical sympathetic nerve produces in some animals a scanty flow of saliva, and in others no perceptible flow; but in all animals prolonged stimulation of this nerve leads to definite histological changes in the gland. Similar results are obtained by stimulation of the nerves supplying the parotid gland. All these nerves are therefore said to be secretory. Secretion can be excited, not only by direct stimulation of the secretory nerves, but also by certain drugs, *e.g.* pilocarpine, which stimulate the nerve-endings in the gland.

The Mechanism of Secretion.—The mechanism by which the secretion of saliva is normally evoked can be most easily studied in a dog provided with a salivary fistula. This is made by separating from its attachments the terminal part of the duct of the parotid or submaxillary gland, and sewing the papilla on which the duct ends into the skin of the cheek. If a small tube be fixed by collodion to the skin round the orifice of the duct, the saliva can be collected. In such an animal the most potent stimulus to the secretion of saliva is found to be the presence of food or other substances in the mouth. Apparently the food excites the peripheral endings of the afferent fibres of the fifth and ninth nerves in the mucous membrane of the mouth, giving rise to impulses which pass to a salivary centre in the medulla oblongata, and thence along the efferent nerves to the salivary glands. The secretion is therefore brought about by a reflex mechanism.

All kinds of food are not equally effective in stimulating the reflex mechanism for the production of saliva. It is found, for example, that dry food causes a more copious flow than moist food; again, meat is said to excite secretion from the submaxillary, but not from the parotid, gland in the dog, the fluid from the submaxillary gland forming a better lubricant for meat than that from the parotid, owing to the mucin contained in the former.

The presence of food in the mouth is not the only cause of

salivary secretion, since this can be brought about in the dog by allowing the animal merely to see or smell food ; secretion excited in this way is known as " psychical " secretion. It occurs only when the animal is hungry, and is more readily produced by some kinds of food than by others ; the sight of dry food, for example, evokes a more profuse psychical secretion than that of moist food. Since dry food brings about a more copious flow of saliva than moist food, whether this is merely shown to the animal or is actually placed in its mouth, and since in the former case the stimulus is purely psychical, it is probably also psychical in the latter. It may therefore be concluded that, in ordinary circumstances, the flow of saliva during a meal is of twofold origin, being due (1) partly to the mere presence of any kind of food in the mouth, and (2) partly to psychical factors, which include appetite and are responsible for the varying effect of different kinds of food.

The secretion of saliva is also influenced by emotion, being inhibited, for example, in extreme fear. That the secretion of saliva in the normal animal is entirely reflex in origin is shown by the observation that, after section of the chorda tympani and auriculo-temporal nerves, the taking of food is no longer followed by a flow of saliva. So far as is known, the sympathetic nerves to the glands take no part in the normal reflex secretion of saliva, and their functional significance is obscure.

Division of the chorda tympani is followed, after from one to three days, by a continuous flow of watery saliva (" paralytic secretion ") lasting for five or six weeks, during which time the gland becomes atrophied. When the atrophy is complete, the secretion ceases. The cause of the paralytic secretion is unknown.

Changes in the Blood-Supply during Secretion.—The cranial nerves to the salivary glands contain not only secretory fibres, but also vasodilator fibres ; for example, stimulation of the peripheral portion of the divided chorda tympani causes a flow of saliva and also dilatation of the arterioles of the submaxillary gland, so that the latter becomes flushed and the amount of blood flowing through it in a given time is greatly increased. Indeed, the flow may be so rapid that the blood leaving the gland is almost arterial in appearance. This vasodilatation is an example of a law which holds good throughout the body, that increased functional activity of any organ is accompanied by an increased blood-supply to that organ ; the additional blood-supply provides the organ with the oxygen and nutritive materials which it needs for its activity.

Owing to the relaxation of the arterioles, the blood-pressure in

the capillaries of the active submaxillary gland is raised, and it is conceivable that the saliva might be formed by the filtration of water, salts, and other salivary constituents through the capillary wall as a result of the increased pressure. There is abundant evidence, however, that filtration takes no part in the formation of saliva. In the first place, stimulation of the chorda tympani nerve, after the injection of a small dose of atropine, produces as marked vasodilatation as is observed in the normal animal, but causes absolutely no flow of saliva. In the second place, if one mercury manometer is connected with the duct of the submaxillary gland (Wharton's duct), and another with the carotid artery so as to measure the arterial blood-pressure, and if the chorda tympani is stimulated, the pressure of the saliva which is formed may raise the level of the mercury in the manometer connected with the duct higher than that in the manometer attached to the artery. In these circumstances, the pressure exerted by the saliva is greater than that in the carotid artery, and must exceed considerably the pressure in the capillaries of the gland.

These experiments make it clear that the formation of saliva is not brought about by filtration from the capillaries, and it must therefore be due to the vital activity of the gland-cells; the process is termed *secretion*.

The Secretory Process.—The distinguishing features of the secretory process are (1) that the gland-cells manufacture, and discharge into the lumen of the gland, substances which are not present in the blood, and (2) that in forming the secretion the cells carry out work. The process is normally aroused by impulses passing along the nerves to the gland (or, in the case of the pancreas and some other glands, by a chemical messenger or hormone), but the work involved in the act of secretion is effected by the cells themselves, and is determined by them. This fact is confirmed by the histological examination of the cells at various stages of their activity. The cells of the submaxillary gland, for example, during the periods when they are not secreting, form a store of mucinogen granules; when the gland becomes active, these granules are converted into mucin, and the latter is discharged into the duct, together with water and salts, to form saliva.

The amount of material thus discharged from the cells when the secretion is rapid may be so great that the gland actually shrinks, notwithstanding the increased amount of blood contained in its dilated blood-vessels (fig. 155). Not only the discharge of the secretory granules, but also the transference of water and inorganic salts from the lymph through the gland-cells into the

saliva, is effected by the vital activity of these cells. The percentage of inorganic salts in the saliva is much less than that in the blood-plasma, and consequently the osmotic pressure of the saliva is found to be lower than that of the plasma. If the gland-cells behaved as a semi-permeable membrane, this difference of osmotic pressure would cause fluid to pass from the saliva into the lymph

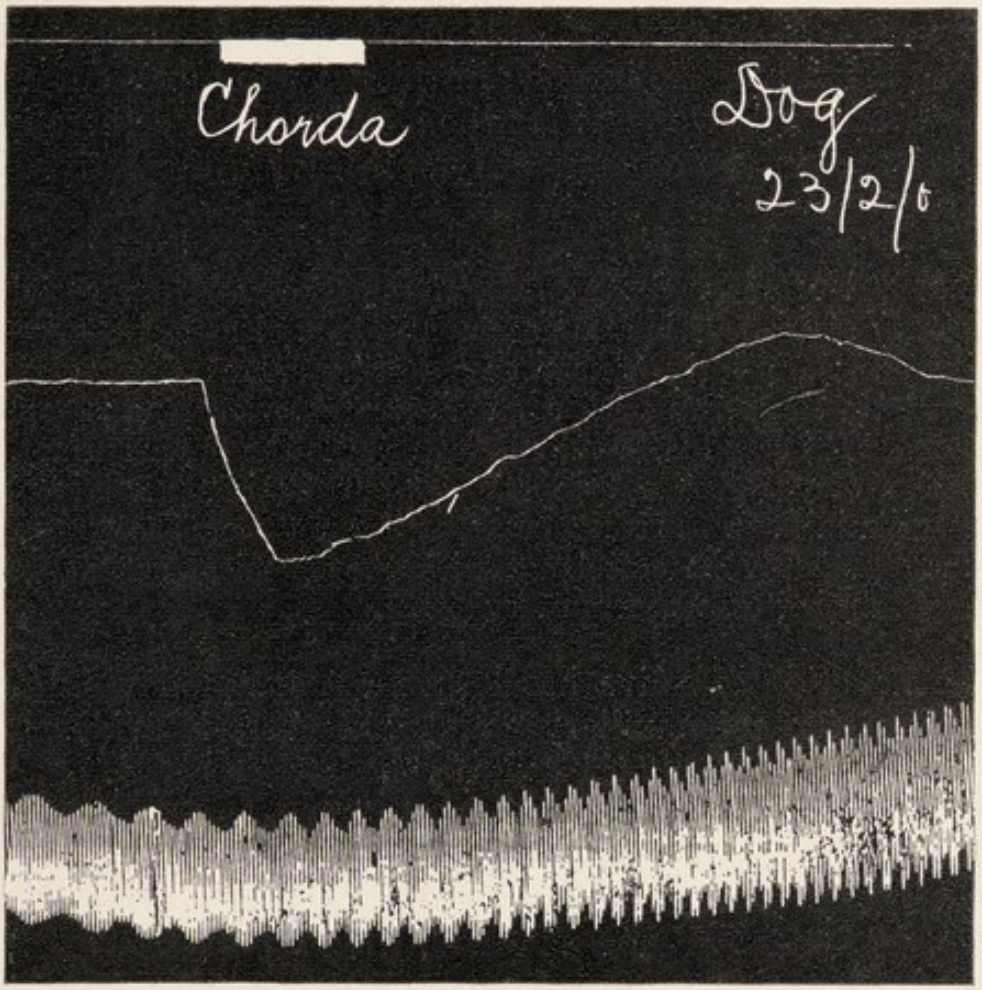


FIG. 155.—Effect of stimulation of the chorda tympani on the volume of the submaxillary gland. (Bunch.

a, volume of gland; *b*, blood-pressure.

and blood; and the fact that the gland-cells form saliva in opposition to this osmotic pressure implies the carrying out of much work by them during secretion. The cells derive the energy required for this purpose from the oxidation of the nutritive materials within them, and therefore use up during their activity more oxygen than during rest. It is found that the amount of oxygen taken up by the submaxillary gland from the blood is enormously increased when the gland is actively secreting (p. 314).

Changes in the Flow of Lymph.—Although secretion is a vital act, the water and salts of the saliva must be ultimately derived from the blood, since a salivary gland may secrete its own weight of saliva in a few minutes. As the gland-cells take

up water and salts from the lymph which bathes them, and as the percentage of salts in the saliva is less than that in the normal lymph, the latter tends to become more concentrated. This concentration is still further increased by the escape into the lymph of substances of small molecular weight, formed as waste products of the activity of the cells. As a consequence of its increased concentration, the osmotic pressure of the lymph becomes higher than that of the blood, and water passes by osmosis from the blood into the lymph ; in this way an abundant supply of lymph becomes available for the gland-cells, and there is also some increase in the amount of lymph leaving the active gland along the lymphatics.

Electrical Changes during Secretion.—The secretory activity of the salivary gland-cells is also accompanied by electrical changes. If the hilum and the outer surface of a resting submaxillary gland are connected by electrodes with a galvanometer, a current is found to flow through the gland from the hilum towards the outer surface. On stimulation of the chorda tympani this current is at first increased, and later diminished. It is not easy to interpret these changes, though they may probably be correlated with the chemical activity of the gland-cells during the process of secretion.

The secretion of saliva has been most completely studied in the case of the submaxillary gland, but there is evidence that the process is essentially the same in the parotid gland.

Summary.—The changes which accompany the secretion of saliva are therefore (1) histological changes in the gland-cells, (2) dilatation of blood-vessels, (3) increased consumption of oxygen, (4) increased flow of lymph, and (5) electrical changes. Although these changes may be regarded as evidence of the vital activity of the cells, the real nature of the secretory process is quite unknown ; and it is impossible at present to form any clear conception, either of the means by which the secretory granules are formed in the cells, or of the manner in which the actual discharge of saliva is effected.

SECTION III

DEGLUTITION

Food is transferred from the mouth to the stomach by the act of deglutition or swallowing. In this process the bolus formed in the mouth is first projected past the anterior pillars of the fauces into the pharynx, then through the pharynx into the œsophagus, and finally along the latter tube into the stomach.

It is therefore customary to speak of three stages of deglutition, but it must be remembered that there is no pause between the stages, and that the act of swallowing, once begun, is a continuous one. The first stage of the process, the passage of the food from the mouth into the pharynx, is a voluntary act, the second and third are involuntary.

In the first stage, the jaws are closed and the tongue is raised so as to press against the palate, the latter movement being due to contraction of the mylohyoid muscle, aided by the intrinsic muscles of the tongue itself. At the same time the base of the

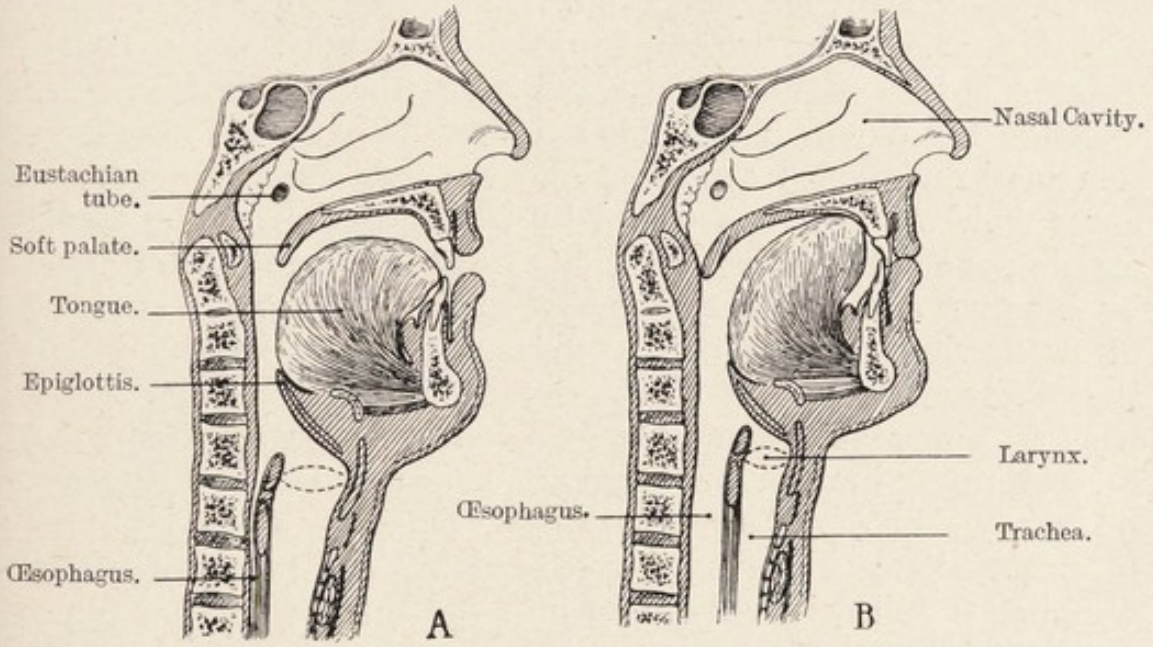


FIG. 156.—A diagram to show the position of the tongue, soft palate and larynx, A, during quiet breathing; B, in deglutition.

tongue is drawn slightly backwards by the contraction of the styloglossi and palatoglossi.

While the bolus is in the pharynx, the soft palate is raised so as to form an inclined plane and prevent the passage of food into the nares. The opening into the respiratory tract is guarded in the following manner. The arytenoid cartilages are rotated inwards by contraction of the lateral crico-arytenoid muscles, and approximated by contraction of the arytenoideus. They are at the same time drawn forward by contraction of the thyro-arytenoids, so that the glottis takes the form of a T-shaped slit. Further, the opening of the larynx is diminished in size by contraction of the ary-epiglottidean muscle-fibres; and, by the elevation of the larynx and the drawing back of the tongue, the opening is further guarded by the lower part of the epiglottis (fig. 156).

By these means the risk of food passing into the back of the

nasal cavity or into the larynx is rendered very slight, and it is still further diminished in two ways. In the first place, the passage of food through the pharynx is carried out extremely rapidly ; and, in the second place, during swallowing the respiratory movements are inhibited for a few seconds. Even then, it occasionally happens that particles of food " go the wrong way," that is to say, they enter the larynx and have to be expelled by coughing.

The passage of the swallowed material can be observed by means of X-rays if the food has been mixed with an insoluble salt of barium or bismuth. In the case of solid food the bolus is carried along the œsophagus by a wave of contraction, immediately preceded by a wave of relaxation. In man the wave travels more rapidly in the upper two-thirds of the œsophagus, which contain striated muscle, than in the lower third, the muscle of which is unstriated. When liquid food is swallowed the œsophagus remains in a relaxed condition and the fluid rapidly reaches its lower end, where it is arrested by a constriction at the cardiac opening of the stomach ; it is then slowly forced into the stomach by a wave of contraction. Owing to this difference in the mode of swallowing of liquids and solids, liquid food usually reaches the stomach in from 4 to 6 seconds after leaving the mouth, whereas solids take from 10 to 18 seconds. If liquid is swallowed several times in rapid succession, it accumulates in the œsophagus, which remains relaxed until the last of the series of acts of deglutition ; a wave of contraction then passes down the œsophagus and drives the fluid into the stomach.

The Nervous Mechanism.—The second and third stages of swallowing are purely reflex, and are initiated by the contact of food with certain sensitive spots near the base of the tongue and in the pharynx. This is shown by the observation that swallowing may take place in an unconscious person, and that it can be evoked in an animal whose cerebral hemispheres have been removed. It is usually started voluntarily by forcing food from the back of the tongue on to the sensitive area, but the movements of the larynx, pharynx, and œsophagus cannot be brought about voluntarily, and only occur as a reflex act in response to mechanical stimulation of the sensitive spots in that area. If, for example, one swallows repeatedly until the mouth is free from saliva, further swallowing becomes impossible for a short time.

Sherrington has shown that, in the decerebrate animal, some kinds of liquid are more effective than others in producing swallowing. Thus, while a few drops of water placed on the back of the pharynx evoke a single act of deglutition, a few drops of dilute alcohol call forth repeated acts of deglutition, and castor oil is not swallowed at all.

It seems clear that the stimulus to deglutition cannot be merely mechanical, but that obscure physical or chemical factors must also be involved.

The afferent impulse passes along the glossopharyngeal nerve to a centre in the medulla oblongata, and gives rise to the complicated series of movements just described, each stage of the process apparently initiating the succeeding stage.

The efferent nerves chiefly concerned are (1), for the voluntary stage, the fifth cerebral nerve to the mylohyoid muscle, and the twelfth nerve to the tongue ; (2), for the involuntary stages, the glossopharyngeal and vagus nerves to the muscles of the pharynx, and the vagus nerves to the entire length of the œsophagus.

The centre in the medulla oblongata controls each step of the process in the pharynx and œsophagus, and even the wave of contraction in the œsophagus is due to impulses passing from the central nervous system to its successive segments ; for, when the œsophagus is cut across, it is observed that during deglutition an orderly wave of contraction travels along its whole length just as in the intact gullet. It has been shown, however, that waves of contraction take place in the lower part of the œsophagus, where the muscular coat consists of unstriped muscle, even when all connection with the central nervous system has been severed. Presumably they are brought about by a local reflex mechanism.

The inhibition of respiration which accompanies swallowing is brought about by impulses passing along the glossopharyngeal nerve to the respiratory centre ; if this nerve is divided, electrical stimulation of its central portion arrests respiration for a period corresponding with that of a normal act of deglutition, namely, 5 or 6 seconds.

SECTION IV

THE STOMACH AND ITS FUNCTIONS

The stomach forms a dilated portion of the digestive tube capable of storing considerable quantities of nutritive material, and it thus obviates the necessity of taking food at inconveniently frequent intervals. The food remains in the stomach for some hours, and during this period it is acted upon by the gastric juice, so that, when it afterwards comes under the influence of the more potent digestive juices found in the small intestine, the hydrolysis of the protein constituents is already well advanced, and, as has already been described, the saliva has effected a conversion of much of the starch into dextrin and maltose.

The Composition of Gastric Juice.—Gastric juice may be

obtained for analysis by producing a permanent gastric fistula in an animal. Pawlow's method is to make an incision in the stomach, separating it into a larger and a smaller portion. The larger portion is stitched up and remains in continuity with the digestive tract. The smaller portion is kept separate from the larger by a layer of mucous membrane, and is made to open on the surface of the body (fig. 157).[1] It is found by experiment that the juice secreted by the small stomach has the same composition as that produced by the large stomach, and also that it is secreted in the same proportional amount when the available extent of mucous membrane is taken into consideration; more-

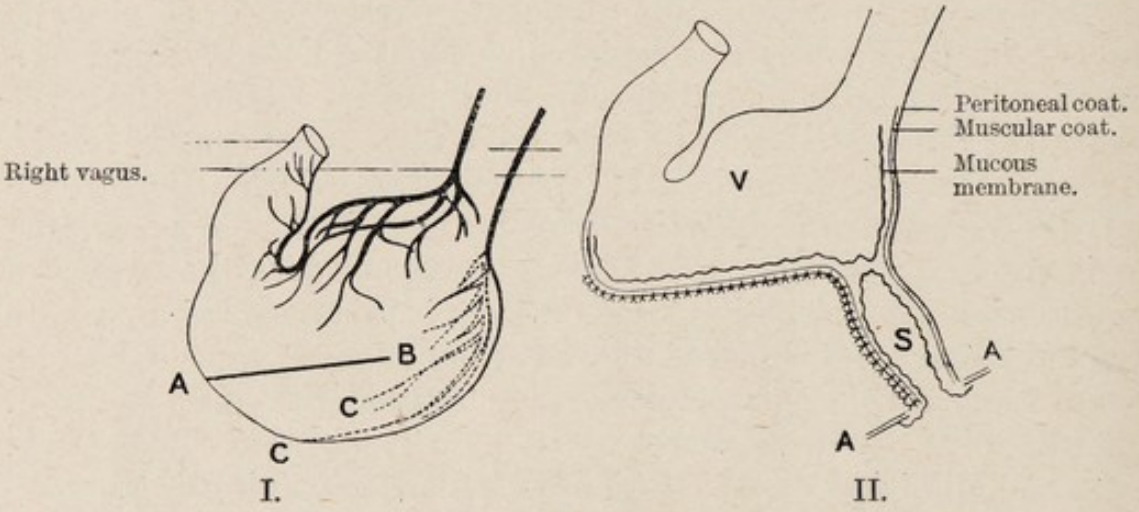


FIG. 157.—Pawlow's method of forming a subsidiary stomach. (From Pawlow's *Work of the Digestive Glands.*)

I., first stage: A—B, incision. II., lesser stomach completed; S, lesser stomach; A, abdominal wall.

over, it has the advantage of being free from admixture with food.

The juice thus obtained is a clear fluid having a specific gravity of 1003 to 1005, and an acid reaction. It consists of about 99 per cent. of water and 1 per cent. of solids, the latter including mucin, proteins, enzymes, and inorganic salts. The juice also contains free hydrochloric acid in the proportion of about 0·2 per cent. in man; the percentage is rather higher in the dog and other carnivorous animals. The salts are chiefly chlorides and phosphates of potassium, sodium, calcium, and magnesium, the most abundant base being potassium.

The presence of free hydrochloric acid may be proved by two tests: (1) A solution of Congo red added to gastric juice gives a blue colour, showing the presence of free mineral acid. (2) If a drop of

[1] We are indebted to the kindness of Messrs. C. Griffin & Co., Ltd., for permission to use these diagrams.

Gunzberg's reagent (phloroglucin-vanillin) be evaporated to dryness, and a drop of gastric juice be added to the residue and gently heated, as drying takes place a bright red colour is developed, proving that the acid is hydrochloric. Lactic acid and other organic acids do not give this reaction.

THE FUNCTIONS OF THE GASTRIC JUICE

It has already been pointed out that the acid of the gastric juice destroys the ptyalin of the saliva, but the hydrolysis of the carbohydrates of the food may be continued, to some extent at least, by the hydrochloric acid in the stomach. This chemical hydrolysis, however, if it occurs, is of less importance than the action of the gastric enzymes upon proteins and milk.

The digestive action of gastric juice can be studied, like that of saliva, by means of experiments in test-tubes. Fresh gastric juice obtained from a fistula may be used, but it is generally more convenient to make an artificial extract. For this purpose the mucous membrane of a pig's stomach is cut in small pieces and extracted with glycerol. By adding some of the glycerol extract to 0·2 per cent. hydrochloric acid an artificial gastric juice is obtained.

(1) If a few flakes of fibrin be placed in a test-tube containing such an artificial juice, and the tube be kept at a temperature of 37° C., it will be observed that the fibrin gradually swells up and then dissolves. If the solution is neutralised, a precipitate of metaprotein is formed. If this is removed by filtration, the solution gives a pink colour on the addition of dilute copper sulphate and caustic soda (biuret reaction), owing to the presence of proteoses and peptones.

Further analysis of this filtrate shows that several varieties of proteose and at least two kinds of peptone are present. The proteoses are classified as primary and secondary, the primary group being precipitated by the addition of an equal volume of a saturated solution of ammonium sulphate; when this precipitate has been removed by filtration, the secondary varieties are precipitated by full saturation with the same salt. When the latter precipitate is removed, the solution contains peptones only.

The changes produced in the fibrin are due to the activity of an enzyme, *pepsin*, which, in the presence of dilute hydrochloric acid, brings about hydrolysis of the protein molecule, and breaks it up into smaller and more soluble molecules. The first change produced is the solution of the fibrin; this is then changed into acid metaprotein, and, by successive hydrolytic stages, the

various proteoses, and finally peptones, are formed. In normal gastric digestion, the conversion of protein into peptone is not complete when the contents of the stomach are passed on into the small intestine.

The stages of peptic digestion of protein may be represented in tabular form thus :—

Protein
↓
Acid metaprotein
↓
Primary proteoses
↓
Secondary proteoses
↓
Peptones

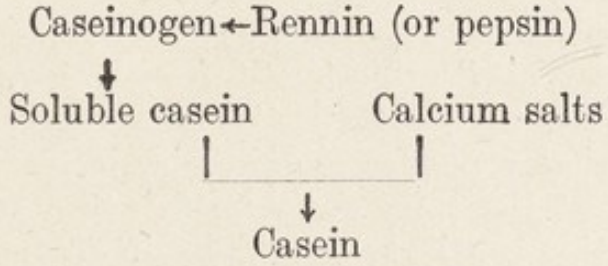
Some proteins which occur in food do not undergo these changes. Thus *elastin* is unaffected by peptic digestion in the time available in the stomach. The *collagen* of connective tissue is probably converted first into gelatin and then into gelatoses and gelatin peptones. The protein constituent of the conjugated proteins is usually converted into proteose and peptone, the prosthetic group being set free. Thus, in the digestion of *nucleo-protein* by gastric juice, an insoluble residue of nuclein is formed ; in the digestion of *mucin* (gluco-protein), glucosamine is found among the products.

(2) The effect of gastric juice upon *caseinogen*, the phospho-protein of milk, is peculiar in that there is a conversion of the caseinogen into a comparatively insoluble substance, casein. This action of gastric juice has been for many years ascribed to a separate ferment called *rennin*, but latterly evidence has been brought forward which suggests that the formation of casein from caseinogen is due to pepsin itself. The matter has not been conclusively settled, and it will be convenient to retain the term rennin in the meantime when describing the effect of gastric juice on caseinogen.

The action of rennin can be demonstrated by adding a little neutralised gastric juice to a quantity of milk, and allowing the mixture to stand for a time at a temperature of 37° C. In a few minutes the milk becomes clotted, and after a time the clot shrinks, squeezing out a clear fluid, whey, which contains all the constituents of milk except caseinogen and fat. It can be shown that the fat is entangled in the clot in an unaltered form, so that the coagulation is brought about by the action of the rennin on the caseinogen. If a little potassium oxalate is added to milk,

the addition of rennin does not cause the formation of a clot, though if calcium chloride is subsequently added clotting occurs.

Three factors are therefore necessary for the formation of the clot, namely, caseinogen, rennin, and lime salts. If rennin is added to a solution of pure caseinogen, and the mixture is kept for a short time at a temperature of 37° C., and then boiled to kill the enzyme, the addition of calcium chloride will bring about the formation of casein. Obviously the enzyme has produced some change in the caseinogen, and the only factor required to complete the conversion into casein is the addition of lime salts. There is in the first place, therefore, a conversion of caseinogen into " soluble casein " by the action of the enzyme, and, secondly, soluble casein combines with lime salts with the production of insoluble casein. The process may be represented thus :—



(3) It has been stated that gastric juice also acts upon neutral fats, which are in the form of a fine emulsion, such as those of yolk of egg or milk, and splits them into glycerol and fatty acids by the agency of an enzyme, *lipase*. The lipase which is occasionally found in the stomach is, in all probability, however, a constituent of pancreatic juice which has entered the stomach by regurgitation from the duodenum. Pepsin indirectly assists the digestion of fat by dissolving the cell-envelopes of the fat-cells of adipose tissue contained in food. In this way fat is set free and prepared for the subsequent digestive action of pancreatic lipase.

THE SECRETION OF GASTRIC JUICE

The mechanism of the secretion of gastric juice may be studied in an animal provided with a gastric fistula which has been made in the manner already described (p. 340). In such an animal the secretion of gastric juice from the lesser stomach has been shown to take place simultaneously with that in the main stomach and to furnish an index of the amount and character of the secretion occurring in the latter. When the animal takes a meal, the flow of gastric juice starts five minutes after the beginning of the meal, and continues throughout the period of digestion of the contents of the stomach.

Nervous Mechanism.—It might be supposed that the secretion

is brought about by the entrance of food into the stomach, but the following experiment of Pawlow shows that this is not the case. The œsophagus of a dog is cut across, and the open, cut ends are sewn to the skin of the neck; a gastric fistula is also made. Food taken by the animal escapes by the upper aperture in the neck, and does not reach the stomach; this is spoken of as "sham feeding," and it is accompanied by a copious flow of gastric juice, showing that the presence of food in the stomach is not necessary in order to excite secretion. Nor is the presence of food in the mouth essential to the production of gastric juice, since, in a hungry animal, the sight or smell of food, or a sound indicating the approach of food, evokes a flow which is quite as abundant as that brought about by a "sham" meal. In these circumstances the stimulus must be a psychical one, the predominant factor in the dog being what, in the absence of a more precise term, is known as appetite; and the secretion thus induced is known as "psychic" or "appetite" secretion.

It is probable, therefore, that the presence of food in the mouth only excites a flow of gastric juice in so far as it arouses appetite, and that the value of palatable and attractive foods as an aid to digestion can be thus explained. Indeed, the effective carrying out, not only of gastric, but also of intestinal digestion, is in large measure dependent on the presence of appetite.

The efferent path for the secretory impulses to the gastric glands is the vagus nerve, and after section of both vagi neither the presence of food in the mouth, nor the sight or smell of food, causes a flow of gastric juice. Further, it is possible to evoke a flow of gastric juice by stimulating the peripheral portion of the divided vagus nerve. One vagus is divided in the neck, and two or three days later the peripheral end of the nerve is gently drawn to the surface and stimulated with a tetanising current. The heart is unaffected, because the cardiac inhibitory fibres have degenerated, but a flow of gastric juice occurs after a latent period of five minutes. The cause of the long latent period is unknown, though possibly it represents the time occupied by preparatory changes in the gland-cells.

The primary secretion of gastric juice, when a meal is taken, must therefore be regarded as purely reflex in origin, the afferent impulses being caused by the sight, smell, or taste of food, provided that this gives rise to appetite, and the efferent path being the vagus. The secretion is influenced by emotional conditions, pain or depressing emotions tending to inhibit the flow of juice, whereas agreeable emotions favour secretion and thereby assist digestion.

Chemical Mechanism.—The nervous mechanism just described

is not the only factor concerned in the secretion of gastric juice. It was observed by Pawlow that the introduction of food into a dog's stomach was followed, after an interval of from fifteen to forty minutes, by a flow of gastric juice, even after the nervous mechanism had been put out of action by division of the vagus nerves. It was further noticed, under these conditions, that secretion was excited only by certain kinds of food, such as meat, or meat extracts, dextrin or partially digested bread ; starch or white of egg produced no secretion. The fact that secretion is brought about by some, and not by all, kinds of food makes it clear that it does not depend upon mere mechanical stimulation of the gastric mucous membrane, and its occurrence after section of all the nerves supplying the stomach shows that it cannot be nervous in origin.

Some light has been thrown upon the means by which the secretion is produced by the experiments of Edkins. This observer has found that, if the pyloric mucous membrane is boiled with water or dilute hydrochloric acid, a decoction is obtained which, when neutralised, filtered, and injected into the blood-stream of another animal, excites a secretion of gastric juice ; similar extracts of the mucous membrane of the body of the stomach do not excite gastric secretion. The conclusion drawn from these experiments is that the presence of partially digested food, or of dextrin or extract of meat, in the stomach, leads to the formation of a hormone by the pyloric mucous membrane. The hormone, which has been called *gastrin*, is believed to be absorbed into the blood-stream, and to be carried by the circulation to the gastric glands, which are thereby stimulated to produce their secretion.

The term " hormone " is applied to a group of substances which have certain definite characteristics. In the first place, they have a relatively small molecular weight, and are easily diffusible. Secondly, each hormone exercises a specific function in exciting or inhibiting the activity of a particular organ or tissue, and, when its function has been performed, it is rapidly destroyed in the body. Thirdly, a hormone does not act as an antigen, that is, it does not excite the production of an antibody which would interfere with the performance of its function. Fourthly, the hormones of the digestive tract are not destroyed by boiling.

The Gastric Juice Produced by a Normal Meal.—When a meal is taken by a normal animal, the secretion of gastric juice is brought about partly by nervous and partly by chemical means. At first the flow of juice is purely nervous in origin, but, as the food is gradually digested, the products of digestion, more especially dextrin, furnish a chemical stimulus, and the secretion thus

excited continues until the stomach is empty. The following table from Pawlow illustrates the relative quantity and digestive power of the juice secreted (1) after a normal meal, (2) as a result of the chemical stimulus alone, and (3) after a sham meal, *i.e.* by the nervous secretion alone. The figures indicate the amount of juice secreted by the subsidiary stomach. The digestive power is measured by filling short lengths of narrow glass tube with egg-white, coagulating the latter by heat, and placing the tubes, the ends of which are open, for a given time in the juice to be tested. The digestive power is estimated by the length of the column of coagulated protein which has undergone solution.

Hours.	Normal Meal. 200 gm. Meat into Stomach.		150 gm. Meat into Stomach.		Sham Meal.		Sum of two last Expts.
	Quantity c.c.	Strength mm. dig.	Quantity c.c.	Strength mm. dig.	Quantity c.c.	Strength mm. dig.	Quantity c.c.
1	12·4	5·43	5·0	2·5	7·7	6·4	12·7
2	13·5	3·63	7·8	2·75	4·5	5·3	12·3
3	7·5	3·5	6·4	3·75	0·6	5·75	7·0
4	4·2	3·12	5·0	3·75	0·0	0·0	5·0

It will be observed that the amount of juice secreted as the result of a normal meal, shown in the first column, corresponds with the totals given in the last column for the nervous and chemical secretions obtained separately.

The secretion of gastric juice by chemical means is therefore to a large extent dependent on the initial nervous secretion whereby the food is partially digested, though it will still take place, even in the absence of the nervous secretion, provided the food includes dextrin, meat, or meat-extracts. Fat, on the contrary, inhibits gastric secretion.

The effect of different kinds of food upon the amount of juice secreted is also considerably influenced by the psychic factor of appetite; in the dog, for example, meat, which is appetising to that animal, gives rise to a greater flow than bread.

The Origin of the Chief Constituents of the Gastric Juice.—The mucous membrane of the stomach is lined by glands which are of two types, one type being found in the fundus and body, and the other in the pyloric portion, of the organ. The glands of the fundus and body are comparatively straight tubes opening by short ducts on to the inner surface of the stomach. Each gland is lined by cubical, granular cells, which are called *chief* or *peptic* cells; between these cells and the basement-membrane there occur at intervals large, ovoid cells, staining readily with eosin. These

are known as *oxyntic* cells, because they are believed to secrete the acid of gastric juice.

The glands in the pyloric region are more twisted, and have longer ducts than the glands of the body of the stomach ; they are lined by cells resembling the chief cells, but contain no oxyntic cells.

The cells lining the general surface of the stomach and the ducts secrete the mucin of the gastric juice. The enzymes of the juice are contained in the secretion of the body of the stomach and also in that of the pyloric portion, and are derived from the chief cells of the glands of the body and from the cells lining the pyloric glands. Pepsin, however, does not exist in the secretory cells as such, because extracts of the mucous membrane do not possess marked peptic activity until they have been treated with acid. It is therefore a precursor of pepsin, known as *pepsinogen*, which is found in the secretory cells, and this is converted into pepsin, after its discharge from the cells, by the hydrochloric acid of the gastric juice.

The facts from which it is concluded that the acid itself is derived from the ovoid cells are (1) that it is most abundant in the middle of the stomach, where these cells are most numerous, and (2) that it is absent from the secretion of the pyloric portion of the stomach, where ovoid cells are wanting.

Various explanations have been offered as to the method of production of the free acid in the gastric juice. The most probable of these suggestions is that the acid is derived from the interaction of chlorides with di-sodium hydrogen phosphate, according to the formula

$$2Na_2HPO_4 + 3CaCl_2 = Ca_3(PO_4)_2 + 4NaCl + 2HCl.$$

During the early stages of secretion the cells of the gastric glands become enlarged, the chief cells, and those lining the pyloric glands, are crowded with secretory granules, and the ovoid cells are distended and clear. As secretion proceeds, all the cells become diminished in size, as in the case of the salivary glands. The granules are probably zymogenic in nature and consist chiefly of pepsinogen.

THE MOVEMENTS OF THE STOMACH

The movements of the stomach are most conveniently studied by direct observation with the aid of X-rays after the administration of a meal mixed with a quantity of oxychloride of bismuth. In these circumstances the organ is seen to consist of two parts, the axis of the larger portion being nearly vertical and forming an angle with the smaller pyloric portion, which is again subdivided

by a constriction into two parts, the *pyloric vestibule*, or *antrum*, and the *pyloric canal* (fig. 158). The junction of the pyloric canal with the duodenum is marked by the presence of a thickening of the circular layer of the muscular coat, the *pyloric sphincter*. The pyloric canal is about 3 cm. in length, while the pyloric vestibule is less constant in size.

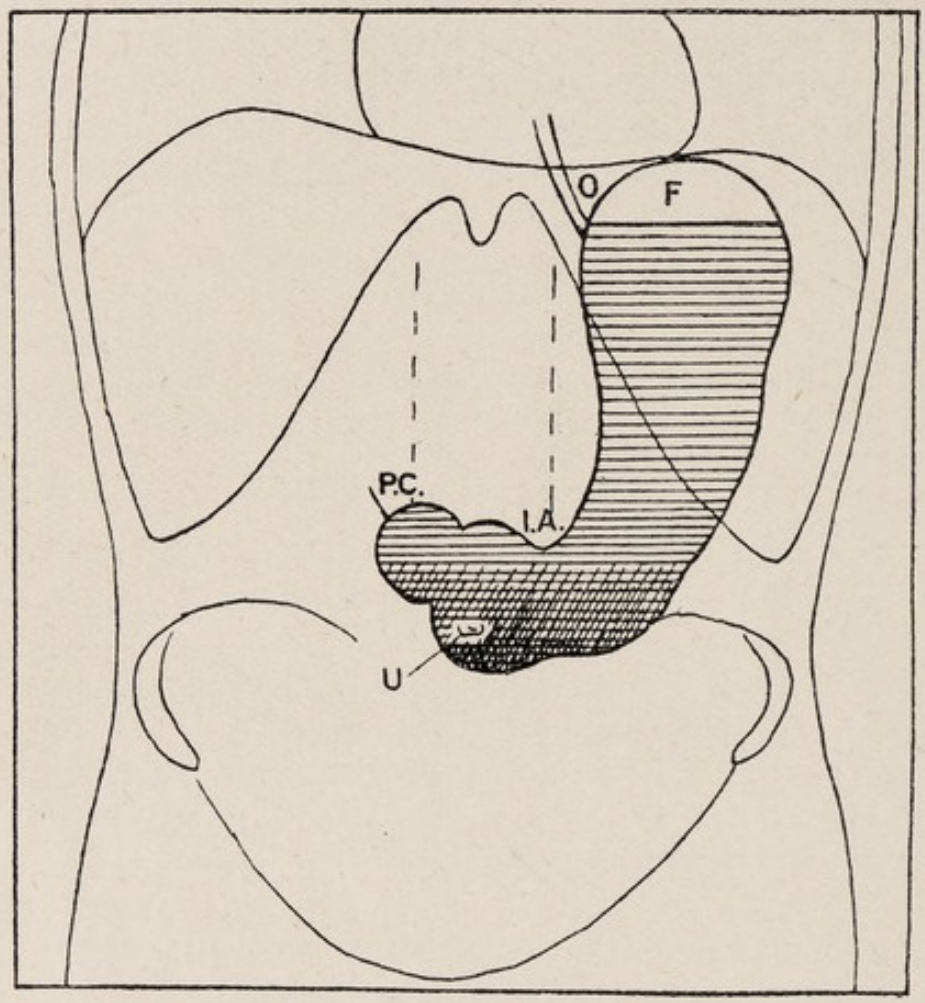


FIG. 158.—Shape of human stomach, in vertical position, shortly after a bismuth meal. (Hertz.)

U, position of umbilicus; O, œsophagus; F, fundus; P.C., pyloric canal; I.A., incisura angularis.

After the ingestion of a meal the muscular walls of the fundus and body of the stomach contract in a tonic manner, and exert a steady pressure upon the contents of the organ. At the same time, rhythmic waves of contraction begin about the middle of the stomach, and travel towards the pyloric sphincter; the waves occur three or four times a minute, and travel so slowly that two or more of them are often visible at the same moment as rings of constriction. The contents of the pyloric vestibule are propelled by these waves towards the pyloric sphincter, and, if this remains closed, they return in an axial stream towards the body of the stomach. The food in the pyloric end of the stomach is in this

way thoroughly mixed with gastric juice. As digestion proceeds, the pyloric sphincter opens from time to time to allow the passage of liquid or semi-liquid digested material, known as *chyme*, into the duodenum, and fresh food and gastric juice are forced into the pyloric mill by the steady tonic contraction of the fundus and body. As the contents of the stomach gradually diminish in amount, the organ becomes more tubular in shape (fig. 159), and it is usually completely emptied in from three to five hours after a meal.

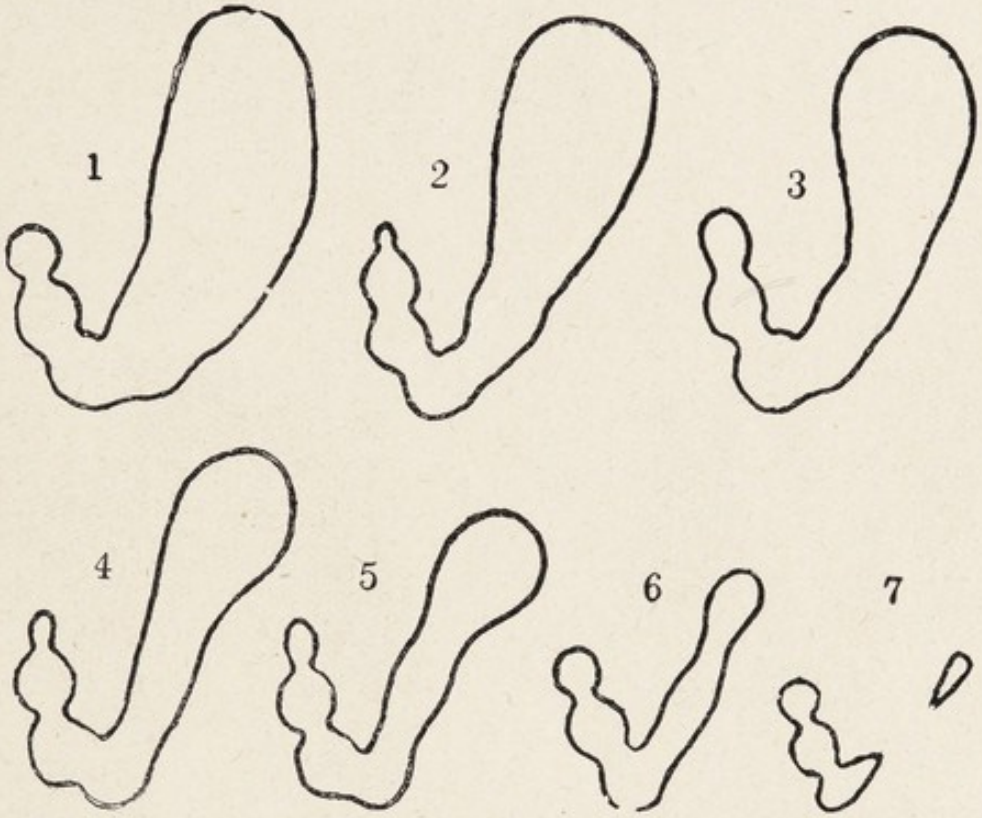


FIG. 159.—Showing the changes in shape of a cat's stomach after a meal containing a bismuth salt. The numbers indicate the period in hours after the meal was taken. (Edward Arnold.) (From Cannon's *Mechanical Factors of Digestion.*)

The movements of the stomach are therefore of two kinds, namely, (1) tonic contraction of the fundus and body, and (2) rhythmic waves of contraction in the pyloric portion. The fundus and body thus serve chiefly as a reservoir, in which comparatively little mixing of the food or gastric digestion takes place, although, as already pointed out (p. 330), salivary digestion may continue for some time. At the pyloric end of the stomach the food is thoroughly mixed with gastric juice, and is digested to a considerable extent before being passed on into the duodenum.

In the normal animal the emptying of the stomach is controlled by the pyloric sphincter, and the tone of the sphincter depends upon the reaction of the contents of the pyloric part of the stomach and of the duodenum respectively. When the

duodenal contents are acid in reaction, the sphincter remains firmly contracted whatever may be the reaction of the gastric contents; if, however, the reaction in the duodenum is neutral or alkaline, the presence of acid in the pyloric canal causes the sphincter to relax. Immediately after a meal the sphincter is tightly closed, but, as soon as the pyloric contents become acid, it relaxes, and the rhythmic contractions of the stomach wall drive some acid chyme into the duodenum. The presence of acid in the duodenum causes the sphincter to close, and it remains closed until the duodenal contents have been neutralised by the alkaline pancreatic juice and bile. When this has been completed, the presence of acid in the pyloric canal once more brings about relaxation of the sphincter, and a further quantity of gastric contents enters the duodenum. It is for this reason that the gastric contents do not pass into the duodenum continuously, but escape from the stomach in gushes from time to time until the stomach is empty.

Since each gush of acid chyme into the duodenum is followed by an interval during which the duodenal contents are being neutralised, it is clear that, after a meal which evokes an abundant secretion of acid gastric juice, a considerable period must elapse before the stomach is completely emptied. On the contrary, when a quantity of water is drunk, it does not immediately excite the secretion of gastric juice, the pyloric sphincter is not stimulated to contract, and, if the stomach is free from food, the fluid passes into the duodenum very rapidly. Fat is anomalous in that, although it does not cause a secretion of gastric juice, it leaves the stomach very slowly.

The gradual character of the emptying of the stomach not only allows time for gastric digestion to take place, but also protects the upper part of the small intestine from being suddenly filled with a mass of undigested food. In this way the pyloric sphincter is of importance for the effective carrying out of both gastric and intestinal digestion.

The Nervous Supply.—Lying between the circular and longitudinal layers of the muscular coat of the stomach is a plexus of nerve-fibres with which are associated many nerve-cells (Auerbach's plexus); fibres pass from the plexus to end in relation with the muscle-fibres of the stomach wall. Branches of the vagi and of the splanchnic nerves are distributed to the stomach, the vagus fibres probably ending in synapses in association with the cells of Auerbach's plexus, whereas the sympathetic fibres run directly to the muscle.

Division of the vagus nerves is followed by temporary cessation of gastric movements, and for some time afterwards the

movements are defective, with the result that food accumulates and stagnates in the stomach. Stimulation of the peripheral portion of the divided vagus causes brief inhibition followed by increased muscular tone and more vigorous rhythmic contractions (fig. 160). Conversely, stimulation of the splanchnic nerve

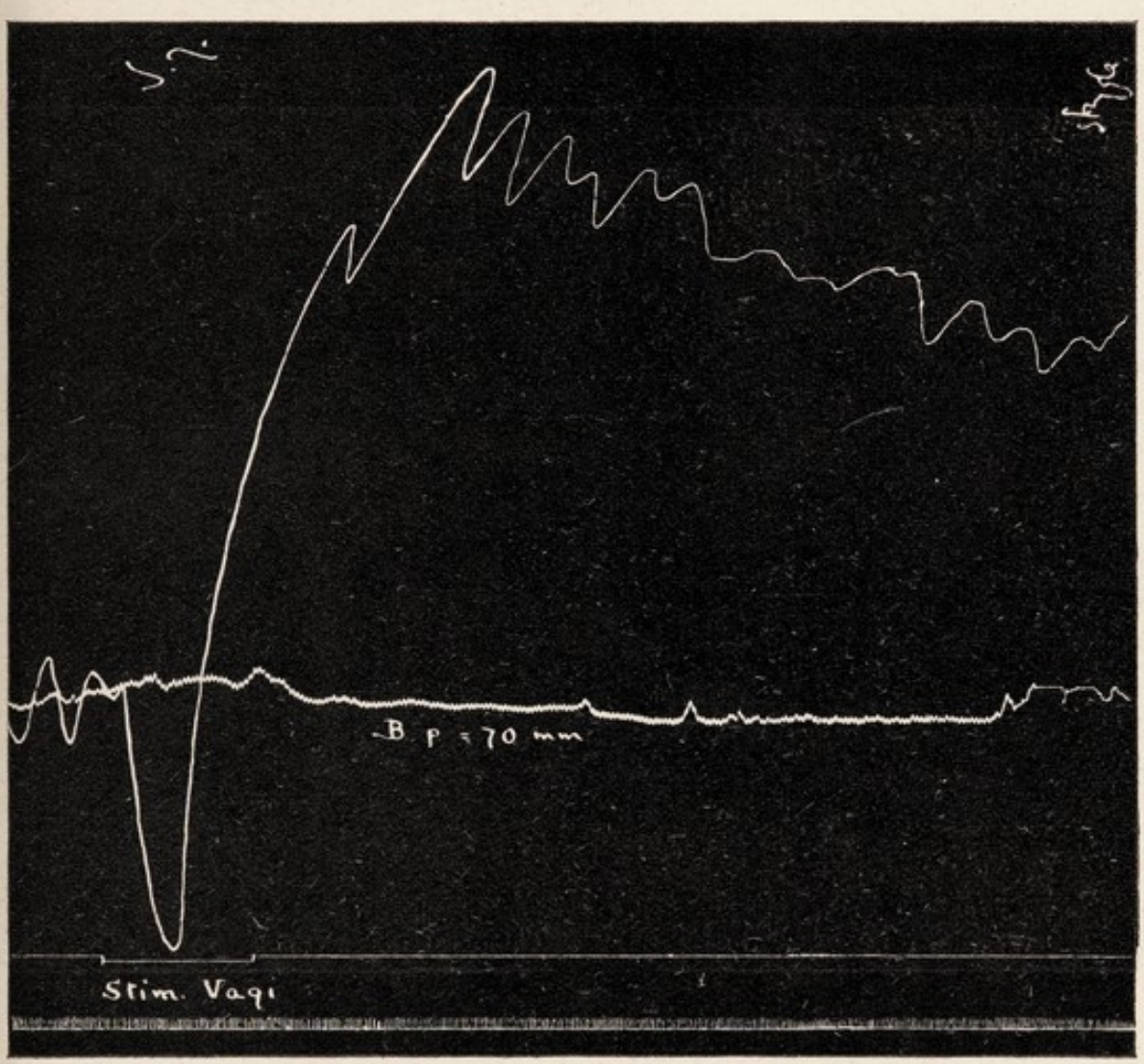


FIG. 160.—Tracing showing initial relaxation followed by contraction of the muscular wall of the stomach on stimulation of vagus nerves. (Elliott.)

lessens the tone of the fundus and body of the stomach, and abolishes the rhythmic movements of the pyloric part (fig. 161).

It has also been observed by means of X-rays that, in the normal animal, emotional disturbances, such as anger or fear, may produce immediate cessation of the movements of the stomach, and that it remains quiescent until the emotion has passed off. After section of the splanchnic and vagus nerves, emotion does not modify the movements of the organ. It is clear, not only that the movements of the stomach can be affected by impulses from the central nervous system, but also that

psychical disturbances, particularly those of a depressing character, may affect these movements and thereby interfere with the normal progress of gastric digestion.

The movements of the stomach, although they are influenced by the central nervous system, are not dependent upon it, since they may continue in a normal manner when the organ is excised and placed in warm oxygenated Ringer's solution. They are

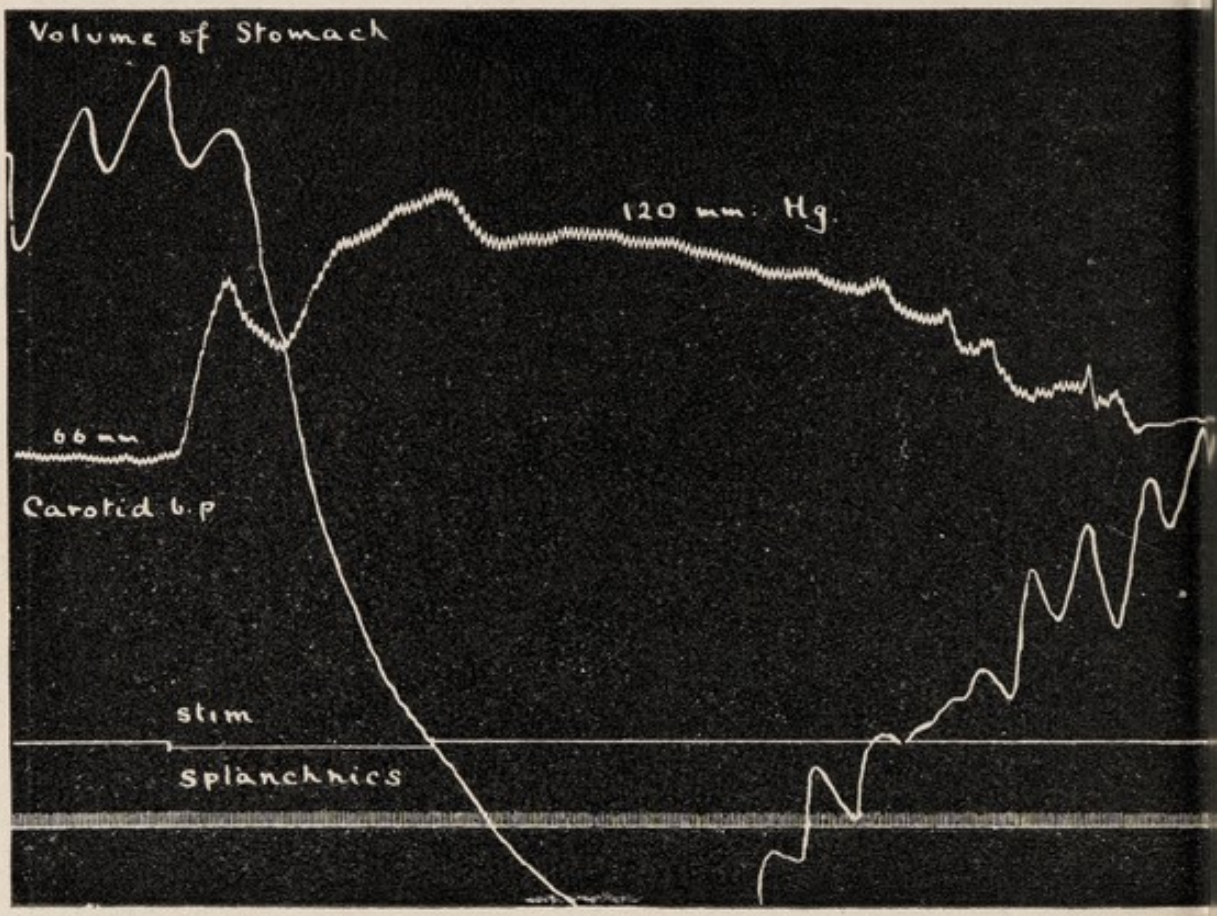


FIG. 161.—Tracing showing relaxation of the muscular wall of the stomach of a cat on stimulation of splanchnic nerves. (Elliott.)

probably brought about by a local reflex through Auerbach's plexus, and are aroused by the distension of the stomach by food. The response of the pyloric sphincter to the reaction of the gastric and duodenal contents is also due to a local reflex mechanism situated in this plexus.

SECTION V

DIGESTION IN THE SMALL INTESTINE

If an experimental meal is given to an animal in which a fistula has been made just beyond the pylorus, it is found that food begins to pass from the stomach into the intestine eight to

twelve minutes after the meal is taken. The rate of escape of the food from the stomach is indicated in the following table :—

1st hour	32·6 per cent.
2nd ,, ...	17·9 ,,
3rd ,, ...	29·5 ,,
4th ,, ...	1·87 ,,
5th ,, ...	6·66 ,,
6th ,, ...	4·21 ,,

If the material collected in this way is analysed, it is found that 67 per cent. of the nitrogen is in the form of proteose and peptone, and that, of the starch of the meal, 21 per cent. has been converted into dextrin and 4 per cent. into sugar. The whole of the protein and carbohydrate of the meal is accounted for, no absorption of these substances, or of fat, having taken place in the stomach. The mixture of semi-digested substances which enters the intestine has a yellowish colour and a semi-fluid consistence, and is immediately subjected to the action of the pancreatic juice and bile. The secretion of Brunner's glands and the intestinal juice are also mixed with the duodenal contents, but the digestive action of the former is not known to have any importance, and that of the latter has its chief value in the later stages of the digestive process. The action of the pancreatic juice and bile must therefore be considered in the first place.

THE COMPOSITION OF PANCREATIC JUICE

Pure pancreatic juice may be obtained from an animal either by means of a temporary fistula, made by introducing a cannula into the pancreatic duct, or by a permanent fistula. In the dog there are two ducts, the larger of which opens into the duodenum about an inch below the entry of the bile duct. Pawlow's method of making a permanent fistula is to cut out a patch of the duodenal wall with the opening of the duct in its centre, stitch up the gap in the duodenum, and suture the patch with the opening of the duct into the abdominal wall.

The pancreatic juice obtained in this way is a clear, limpid fluid, having a strongly alkaline reaction. The degree of alkalinity is such that equal volumes of gastric juice and pancreatic juice neutralise each other. The concentration of pancreatic juice varies considerably, but it contains on an average about 3 to 4 per cent. of solids. These consist of nucleo-protein, enzymes or their precursors, and inorganic salts ; the chief salts are sodium carbonate and sodium chloride.

THE FUNCTIONS OF THE PANCREATIC JUICE

The action of the pancreatic juice on the constituents of the food may be studied in test-tubes, using either the secretion obtained from a fistula, or an artificial juice made by adding a glycerol extract of the fresh gland to a solution of sodium carbonate of such a strength that the mixture contains 0·5 per cent. of the carbonate.

The Action of Pancreatic Juice on Proteins.—Pure pancreatic juice, obtained directly from the pancreatic duct without contact with the intestinal mucous membrane, has no action on proteins. If, however, the juice has flowed over the duodenal mucous membrane, or has been mixed with intestinal juice, it is strongly proteolytic. The active proteolytic ferment is called *trypsin*, and is derived from an inactive precursor present in pure pancreatic juice and known as *trypsinogen*. Since a mere trace of intestinal juice is capable of activating an unlimited amount of pancreatic juice, the activation of trypsinogen is believed to be effected by a ferment, *enterokinase*, present in intestinal juice and formed by the mucous membrane of the small intestine. Trypsinogen may also be converted into trypsin by other means, for example by the action of lime salts; or the activation will take place spontaneously, but slowly, if the juice is allowed to stand. But enterokinase brings about the formation of trypsin from trypsinogen in the course of a few minutes, whereas many hours are required for the activation of pancreatic juice by means of calcium salts.

If a few flakes of fibrin are placed in a solution containing trypsin and 0·5 per cent. sodium carbonate in a test-tube, and kept at a temperature of 37° C., the fibrin will begin to be eroded in a few minutes, and gradually it will become dissolved. The products in solution will vary according to the time during which digestion has been allowed to proceed, but, generally speaking, the course of hydrolysis is the same as in peptic digestion, except that, as the process takes place in an alkaline medium, the meta-protein formed is the alkaline, and not the acid, variety. A second point of difference is that the intermediate stages are passed through more rapidly in pancreatic than in gastric digestion; and, thirdly, amino-acids are separated in tryptic but not in peptic digestion.

In the normal course of digestion in the intestine, the final conversion of peptone into amino-acids is largely effected by the ferment, *erepsin*, which is contained in the intestinal juice; but almost complete hydrolysis into amino-acids can be obtained

in vitro by means of trypsin, if the digestion is allowed to proceed for three or four days. The splitting is not quite complete, for, even if the digestion has been allowed to go on for some weeks, some amino-acids remain united in groups of two or more, known as *polypeptides*. These latter substances have much smaller molecules than peptones and do not give the biuret reaction, that is, they do not give a pink colour with copper sulphate and caustic soda.

If tryptic digestion of fibrin or casein has been allowed to proceed for some days, the solution contains the amino-acids derived from these substances (p. 15). One of these, namely tryptophane, is split off comparatively early in tryptic digestion; its presence may be detected by the appearance of a red colour when bromine water is added to the tryptic digest. Leucine and tyrosine are also easily demonstrated in the digest, and crystallise out readily if the fluid is concentrated. Tyrosine appears as sheaves of colourless needles, and leucine, which is the more soluble of the two, occurs in the form of yellowish balls, which sometimes show concentric and radial striation (fig. 162). Solutions of tyrosine, when boiled with Millon's reagent, give a red colour.

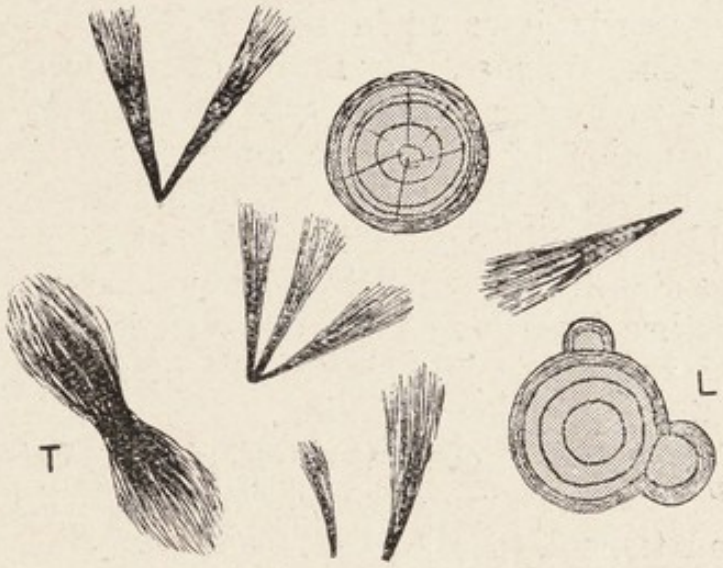


FIG. 162.
L, crystals of leucine. T, crystals of tyrosine.

The stages of tryptic digestion may be represented in tabular form thus :—

Protein
↓
Alkali metaprotein
↓
Primary proteoses
↓
Secondary proteoses
↓
Peptones
↓
Polypeptides and Amino-acids

The earlier stages of tryptic digestion of protein are most

efficiently carried out in a slightly alkaline medium, but the ferment is active in either an alkaline or a neutral solution. Under natural conditions, the alkaline pancreatic juice and bile are nearly neutralised by the acid contents from the stomach, and the contents of the small intestine throughout its length are almost neutral. The activity of trypsin diminishes during the course of normal digestion, since the ferment enters into combination with the products of its own activity, that is, with amino-acids and peptones, and in this way it becomes inactive. The intestinal contents taken from the lower end of the ileum show very little tryptic activity.

The Action of Pancreatic Juice on Starch.—The action of pancreatic juice upon starch depends on the presence of an enzyme, *amylase*. By means of this ferment starch is converted into maltose, as in the case of salivary digestion (p. 329), but the action of pancreatic amylase is more rapid and powerful than that of the ptyalin of saliva. If some pancreatic extract is added to dilute starch paste kept at a temperature of 37° C., the starch is converted into soluble starch in a few seconds, and erythro-dextrin may be detected in half a minute. Moreover, the pancreatic juice is capable of digesting unboiled starch, on which saliva has no action.

The Action of Pancreatic Juice on Fats.—If perfectly neutral fat, such as pure olive oil, be shaken up with pancreatic juice, and the mixture be kept at a temperature of 37° C., the fatty ester will be hydrolysed, yielding fatty acid and glycerol, and the reaction of the fluid will become acid. The agent which brings about this change is an enzyme, *lipase*, which is a constituent of the pancreatic juice. Lipase may be extracted from the fresh pancreas by glycerol, but not by water. The fat-splitting action of lipase is greatly facilitated by the presence of bile, taking place four or five times as rapidly when assisted by bile as in its absence. This acceleration is due to the bile-salts, which not only reduce surface tension and so promote the admixture of the enzyme and the fats, but also have the property of bringing fatty acids and soaps into solution.

The digestion of the fats is further assisted mechanically by the formation of soaps. Some of the fatty acid which is set free combines with the alkalies of the intestinal contents to form soap. Segmental contractions of the intestine lead to the mechanical subdivision of the fats with the formation of an emulsion. Each droplet of fat becomes coated with a fine film of soap, which prevents it from coalescing with others, and in this way the formation of a still finer emulsion is favoured, and the fat is made more accessible to the enzyme.

The Action of Pancreatic Juice on Milk.—A milk-curdling ferment has been described as occurring in the pancreatic juice, and it is a fact that clotting of milk takes place when the juice is mixed with milk at the temperature of the body. It is doubtful, however, whether a separate rennet ferment is present in the pancreatic secretion, and the milk-curdling function has been ascribed by some authorities to trypsin ; moreover, the presence of rennin in the pancreatic juice would seem to be unnecessary in view of the active milk-curdling property of gastric juice.

THE SECRETION OF THE PANCREATIC JUICE

In an animal with a permanent pancreatic fistula, a flow of juice is seen to begin within five to twenty minutes after the ingestion of a meal. The secretion is largely increased two or three hours later, when the contents of the stomach are passing into the duodenum in largest amount, and it comes to an end in about five hours. The following record of two of Pawlow's experiments shows the rate of flow :—

Pancreatic Secretion after a Meal of 600 c.c. of Milk

Hour after Feeding.	Quantity of Juice in c.c.	
1st . . .	8·75	8·25
2nd . . .	7·5	6·0
3rd . . .	22·5	23·3
4th . . .	9·0	6·25
5th . . .	2·0	1·5
Total . .	49·75	45·3

The formation of pancreatic juice, therefore, coincides with, and is normally brought about by, the passage of the acid gastric contents into the duodenum. A flow of pancreatic juice can also be evoked by the introduction of weak (0·4 per cent.) hydrochloric acid into the duodenum or into a loop of small intestine.

Bayliss and Starling have shown that the flow of juice which occurs under these conditions cannot be due to a nervous reflex, since the introduction of acid into a loop of small intestine is followed by a flow of pancreatic juice, even when all the nervous connections of the loop of gut with the rest of the body have been destroyed. Hence the stimulus must be a chemical one, some substance being formed by the action of the acid on the intestinal epithelium and carried in the blood-stream to the pancreas. This substance is *secretin*, and it may be prepared

by grinding up the duodenal mucous membrane with sand, and boiling it with 0·4 per cent. hydrochloric acid. If alkali be added to the boiling fluid till it is almost neutral, the proteins are precipitated, and a protein-free filtrate may be obtained. Injection of the filtrate into a blood-vessel of another animal excites the production of pancreatic juice (fig. 163). From this experiment it is obvious that secretin is not destroyed by acid or by boiling; it is, however, readily destroyed by alkalies. It belongs to the group of hormones or "chemical messengers," the chief characteristics of which have already been described (p. 345).

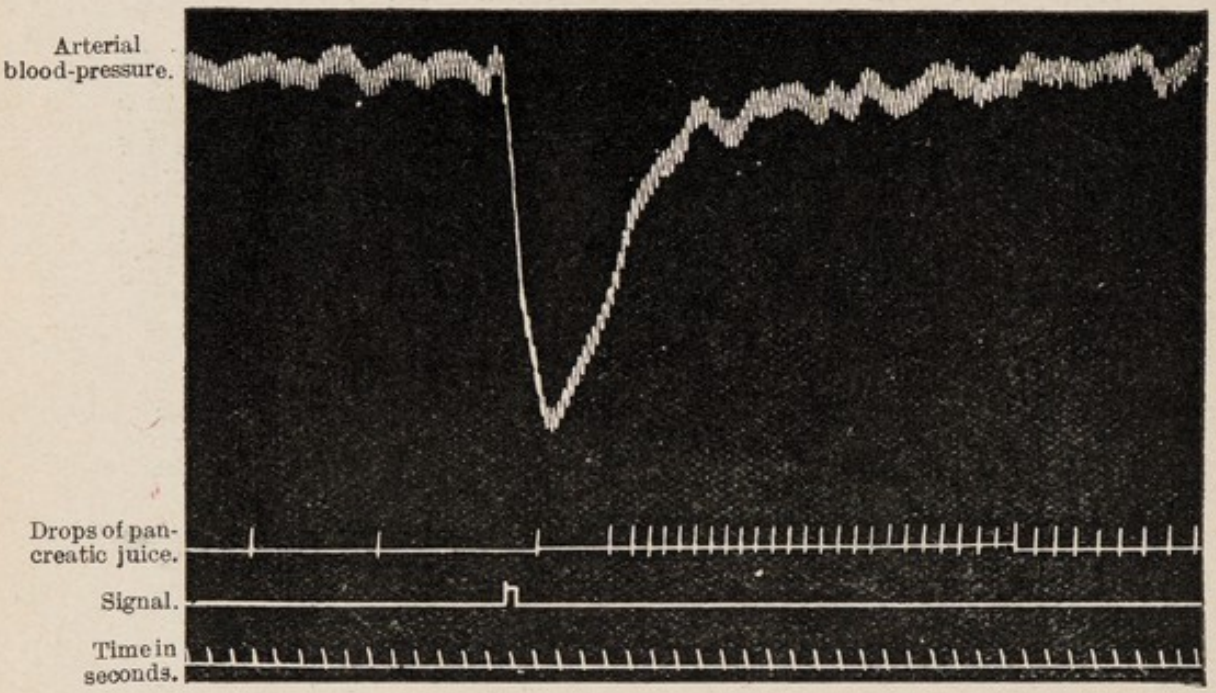


FIG. 163.—Effect on blood-pressure, and on the secretion of pancreatic juice, of the injection of a solution containing secretin. (Bayliss and Starling.)

(From *The Endocrine Organs*, Sharpey Schafer.)

Secretin is absorbed directly into the blood and does not normally reach the lumen of the intestine; and its introduction into the duodenum does not lead to a flow of pancreatic juice.

Secretin itself is freely soluble in water and alcohol, but an extract of intestinal mucous membrane made with either of these fluids contains no secretin, and a watery extract of duodenal mucous membrane does not excite a flow of pancreatic juice. Secretin must, therefore, be formed by the action of acid on some precursor: this precursor is called *prosecretin*, and is present in the intestinal epithelium.

Prosecretin is most abundant in the duodenum, and occurs also to a considerable extent in the jejunum, and to a less degree in the ileum; but near the junction of the small and large intestines it is present in very small amount.

The secretion of pancreatic juice after a meal is almost entirely due to secretin, and the amount of secretin formed in the body, as shown by the volume of pancreatic juice produced, varies with the nature of the food. After a meal of bread or meat the flow of juice is more abundant, and reaches its maximum more rapidly, than after a meal of milk. The reason for this difference is that meat, or semi-digested bread, stimulates the production of gastrin and thus causes a large flow of gastric juice, whereas milk is a less efficient stimulus to gastric secretion. As a result, more acid reaches the duodenum after a meal of bread or meat than after the ingestion of milk, and therefore more secretin is produced

FIG. 164.—A section of the pancreas of a dog. × 300.

in the former case than in the latter. Soaps also stimulate the production of secretin, and the delayed maximal production of pancreatic juice after a meal of milk may be explained by an additional formation of secretin in this way.

Much work has been done with a view to determining whether a nervous factor is also concerned in the production of pancreatic juice, comparable with the reflex which brings about the first secretion of gastric juice ; and Pawlow has shown that stimulation of the vagus will excite a small flow of pancreatic juice, even when the pylorus of the stomach is ligatured so as to prevent the passage of the acid contents of the stomach into the duodenum. The amount secreted as the result of vagus stimulation is, however, so small that the nervous factor is obviously of subsidiary importance in the case of the pancreas. It is possible that the first few c.c. of juice secreted may be nervous in origin, because the juice first formed appears a few minutes after a meal is taken,

and, further, it differs in character from that formed later, being more viscid, richer in ferments and in protein constituents, and poorer in alkali than the latter.

The Changes in the Pancreas which accompany Secretion.—The pancreas is a compound tubular gland, and it contains, in addition to the ordinary secretory tubules, clumps of cells which do not stain deeply with the ordinary dyes, and which are known as cell-islets. These islets are supposed to be concerned with the formation of an internal secretion, and their function will be discussed in connection with metabolism. The secretory tubules of the pancreas are lined by a single layer of columnar cells, each of which shows two zones—an outer, which stains with basic dyes such as hæmatoxylin or toluidin blue, and an inner, filled, in the resting stage of the gland, with secretory granules (fig. 164). The granules stain well with osmic acid, eosin, or neutral gentian.

After a prolonged period of secretory activity the granules are greatly diminished in number, and the inner zone of the cell is relatively and absolutely smaller as compared with the outer zone. Under normal conditions this diminution of the inner zone does not occur, because the formation of new granules keeps pace with the extrusion of those previously formed, so that the appearance of the cells is little altered by the secretion required for an ordinary meal. The secretory granules are in all probability zymogenic, and represent the precursors of the enzymes found in the juice. In the case of trypsinogen, the precursor has received the name of *protrypsinogen*.

THE BILE

The bile is not a digestive juice in the same sense in which saliva and the gastric and pancreatic juices belong to that category. It is to be looked upon as being mainly an excretion, which incidentally assists the digestive action of the pancreatic juice. The production of bile is always taking place, although its rate of formation varies with the period of the day and other circumstances, and, as it is formed, the secretion is stored in the gall-bladder. This reservoir discharges the accumulated bile into the intestine simultaneously with the great flow of pancreatic juice which takes place during the third hour of digestion of a meal.

THE COMPOSITION OF THE BILE

Bile may be obtained for analysis from the gall-bladder of a recently killed animal, or it may be collected from a gall-bladder fistula during life. Its composition, however, is not the same in

the two cases, fistula bile being more dilute than bile which has been stored for a time in the gall-bladder. The difference is shown in the following two analyses of human bile by different observers :—

Fistula Bile.		Gall-Bladder Bile.	
Mucin and pigments	0·148	Mucin	1·29
Sodium taurocholate	0·055	Sodium taurocholate	0·87
Sodium glycocholate	0·165	Sodium glycocholate	3·03
Cholesterol	—	Cholesterol	0·35
Lecithin	0·038	Lecithin	0·53
Fats	—	Fats	0·73
Inorganic salts	0·840	Soaps	1·39
Water	98·7		

Bile thus becomes more concentrated by the absorption of water during the time it remains in the gall-bladder. It is a viscid fluid, golden brown in carnivora, green in herbivora, and possesses a bitter taste. The viscidity is due to the presence of mucin in human bile, and of a nucleo-protein in that of the ox and some other animals. The colour depends upon the presence of the bile-pigments, bilirubin and biliverdin. The former is more abundant in the bile of carnivora, the latter in the bile of herbivora. The proportion appears to vary in human bile according to the nature of the diet, the brown tint of bilirubin predominating when a flesh diet is taken, and the green of biliverdin when the diet is largely vegetarian. The bitter taste of bile is due to the bile-salts, glycocholate and taurocholate of sodium. In dog's bile only the latter is present.

The Properties, Source, and Fate of the Chief Constituents of the Bile.—The *mucin* of human bile gives a stringy precipitate on the addition of acetic acid, the precipitate being insoluble in excess of the acid. The nucleo-protein of ox-bile gives a similar precipitate with acetic acid, but, as in the case of nucleo-proteins generally, the precipitate is dissolved by excess of the acid. The mucin or nucleo-protein of the bile is derived from the mucus-secreting cells which line the bile-ducts and gall-bladder.

The *bile-salts* are compounds of sodium with glycocholic and taurocholic acid respectively. These acids may be split up by hydrolysis, glycocholic into glycine (amino-acetic acid) and cholic acid, and taurocholic into taurine (amino-ethylsulphonic acid) and cholic acid.

$$\underset{\text{Glycocholic acid.}}{C_{26}H_{43}NO_6} + H_2O = \underset{\text{Glycine.}}{CH_2 . NH_2 . COOH} + \underset{\text{Cholic acid.}}{C_{24}H_{40}O_5}$$

$$\underset{\text{Taurocholic acid.}}{C_{26}H_{45}NO_7S} + H_2O = \underset{\text{Taurine.}}{C_2H_4 . NH_2 . HSO_3} + \underset{\text{Cholic acid.}}{C_{24}H_{40}O_5}$$

If a little syrup of cane-sugar be added to a solution of bile-salts in a test-tube, and strong sulphuric acid be poured down the side of the tube so as to lie below the solution, a cherry-red colour appears at the junction of the two fluids (Pettenkofer's test). The colour is due to a reaction between cholic acid and furfuraldehyde, the latter being formed by the action of the sulphuric acid on the cane-sugar. The bile-salts have the property of reducing the surface tension of the fluid in which they are dissolved. This can be shown by comparing the effect of scattering flowers of sulphur on water and on a solution of bile-salts. The sulphur floats on the water, but sinks immediately in the bile-salt solution (Hay's test). Further, watery solutions of bile-salts readily dissolve fatty acids. Bile-acids are derived from protein sources and are formed in the liver.

The larger proportion of the bile-salts which pass into the intestine is reabsorbed into the portal vein, and returns to the liver to be secreted again in the bile. This is spoken of as the circulation of the bile-salts, and not only do these substances enter once more into the formation of bile, but they also stimulate the liver to further secretion, that is, they act as cholagogues. A small proportion of the bile-salts is excreted in the fæces in the form of *dyslysin*, a substance formed from them by bacterial decomposition. Part of the excretion of sulphur from the body takes place in this way, since this element forms part of the taurine molecule.

Cholesterol (p. 9) and *lecithin* (p. 9) are probably largely derived from the stroma of the red blood-corpuscles which are broken down in the liver. Gall-stones, which are of fairly common occurrence in the gall-bladder, are usually composed chiefly of cholesterol. Normally the latter substance is excreted in the fæces.

The *bile-pigments* are characterised by their colour and by the fact that they are easily oxidised by nitrous acid, yielding a series of coloured products (Gmelin's test). If nitric acid containing nitrous acid is added to bile in which the pigment present is bilirubin, the colour changes to green (biliverdin), then to blue, violet, red, and finally to yellow, the final product being called *choletelin*. Bilirubin and biliverdin show no absorption-bands with the spectroscope. Bilirubin ($C_{16}H_{18}N_2O_3$) is identical with hæmatoidin, a substance formed by the decomposition of hæmoglobin in old blood-clots in the body. The composition of its molecule is almost identical with that of iron-free hæmatin (hæmatoporphyrin), formed by the action of strong mineral acids on hæmoglobin.

Bile-pigments are derived from the pigment of the blood by

the breaking down of the latter in the liver. The facts upon which this statement is based are (1) the identity of bilirubin with hæmatoidin, (2) histological observations on the liver, (3) observations on the proportion which exists between the rate of destruction of the red blood-corpuscles and the amount of bile-pigments formed, and (4) the effect of injection of hæmoglobin into the blood-stream. Histological observations show that the walls of the sinusoids in the liver are incomplete, so that red blood-corpuscles can pass through them; and red corpuscles, broken up to a greater or less degree, have been seen within the liver-cells. Moreover, the presence of iron in the liver-cells can be demonstrated by the blue colour produced by treatment of sections with ferrocyanide of potassium and hydrochloric acid. Again, when the destruction of red blood-corpuscles is increased, as in the disease known as pernicious anæmia, or in poisoning by the injection of pyrogallic acid or toluylene diamine, the amount of bile-pigment produced is excessive and the iron in the liver-cells is increased. Finally, when a solution of hæmoglobin is injected into the blood-stream, there is an increased production of bile-pigment.

The bile-pigments undergo bacterial decomposition in the large intestine with the formation of *stercobilin*, the pigment of the fæces. Some of the latter is reabsorbed, and appears in the urine as a chromogenic substance, *urobilinogen*, from which *urobilin* is formed by oxidation. Urobilin itself is identical with stercobilin, and it occurs in the urine in pernicious anæmia and other diseases in which destruction of red blood-corpuscles is excessive.

THE FUNCTIONS OF THE BILE

It has already been pointed out that bile is not a digestive juice in the proper sense of the term. It is said to contain a weak amylolytic enzyme, but the action of this ferment is quite insignificant. Nevertheless the bile exercises important functions in connection with the process of digestion. (1) The acid metaprotein and the proteoses resulting from the gastric digestion of proteins are precipitated by the bile-salts in the duodenum. This conversion of a fluid or semi-fluid material into the solid condition will retard its progress along the intestine and allow more time for the action of the pancreatic juice. (2) The bile-salts act as a "co-enzyme" to each of the principal ferments of the pancreatic juice, that is, they increase the rate of the digestive process without themselves taking any active part in it. In the presence of bile-salts the power of the pancreatic

amylase to hydrolyse starch is doubled, and the proteolytic power of trypsin is similarly increased, while the action of lipase upon fats is quadrupled. The adjuvant action of bile in digestion is due to the property which the bile-salts possess of reducing surface tension, as well as to their power of dissolving fatty acids and soaps. By the reduction of surface tension the contact of enzyme with substrate is promoted, and this is of especial value in facilitating the access of lipase to oily fluids. (3) Bile promotes the absorption of the products of digestion, this property also being due to the bile-salts. Free fatty acids are brought into solution, and in this form are more adapted for passing through the epithelial cells of the intestinal villi. Moreover, these cells have their surface tension lowered, and are thus made more permeable by all the products of digestion. Lecithin and cholesterol, which are held in solution in the bile, also play a part in promoting absorption, though the precise way in which they act is not understood. The importance of the presence of bile for the digestion and absorption of fat is shown by the fact that, when bile is prevented from entering the intestine, 60 per cent. of the fat of a meal passes into the fæces, as compared with about 5 per cent. under normal conditions. (4) Bile is said to stimulate the peristaltic movements of the intestine, and (5), as already pointed out, the reabsorbed bile-salts stimulate the liver to further secretion.

THE SECRETION OF BILE

The secretion of bile is a continuous process, and, in periods when digestion is not taking place, bile accumulates in the gall-bladder. The rate of production of bile has been studied in animals with experimental fistulæ, and also in man when fistulæ have formed in the course of disease. It is found in man that something less than a litre of bile can be collected from a fistula in twenty-four hours, an amount equal to that of the juice secreted by the pancreas in the same time.

So far as is known, the secretion of bile is independent of nervous action, and is excited (1) by the reabsorbed bile-salts, and (2) by secretin. The flow from a fistula is fairly continuous, though it varies in rate with the period of the day and with other conditions. The rate of flow in such a case is, of course, unaffected by reabsorption of bile-salts. It is doubled by the introduction of dilute hydrochloric acid into the duodenum, or by the injection of secretin into the blood-stream. The rate of secretion of bile, like that of the pancreatic juice, varies with the nature of the food, and for the same reason (p. 359),

being greatest when a meat diet is taken, and least when the food consists mainly of carbohydrates. Fatty food, which inhibits the secretion of gastric juice, excites the secretory activity of the pancreas and liver, though not to the same extent as does meat. The influence of fat in this respect is due to the formation of soap in the duodenum, the latter substance acting as a stimulus to the production of secretin. The flow of bile into the duodenum normally begins shortly after the ingestion of a meal and continues for five hours or longer. As in the case of pancreatic juice, the flow of bile is most abundant during the third hour after a meal, and it is during this period that the gall-bladder discharges its contents into the lumen of the duodenum; the emptying of the gall-bladder is probably brought about reflexly, but the nature of the processes involved is not definitely known. Owing to the simultaneous secretion of the bile and pancreatic juice in response to the stimulus of secretin, these two fluids co-operate to the greatest advantage in intestinal digestion.

THE FINAL STAGES OF THE DIGESTIVE PROCESS

Saliva, gastric and pancreatic juice in turn carry the digestion of the food-stuffs up to a certain point. The pancreatic juice completes the digestion of the fats; it converts proteins into peptones and amino-acids; it converts starch into maltose, but has no action upon cane-sugar or lactose, and little or no action upon maltose. The completion of the digestive process is the function of the intestinal juice.

THE COMPOSITION OF THE INTESTINAL JUICE

Intestinal juice is obtained, like the other digestive secretions, by means of a fistula. A segment of intestine of sufficient length is separated by incisions; one end of the separated portion is closed by sutures, and the open extremity is sutured into the abdominal wall, the continuity of the remainder of the bowel being restored by stitching the free ends together. The detached segment retains its normal blood-supply. In another method, both ends of the segment are left open, and each is sutured separately into the abdominal wall (fig. 165).

The juice obtained from such a fistulæ has a specific gravity of about 1010, and is alkaline. It contains 1 to 2 per cent. of solids, half of which are organic and half inorganic. The organic solids consists mainly of serum-albumin, serum-globulin, and enzymes. The chief inorganic substances are sodium chloride and sodium carbonate.

THE FUNCTIONS OF THE INTESTINAL JUICE

It has already been pointed out that the intestinal juice converts trypsinogen into trypsin by virtue of the enzyme, *enterokinase*, which it contains, and also that another of its enzymes, *maltase*, completes the digestion of starch by converting maltose into glucose. Each molecule of maltose takes up a molecule of water, and is split into two molecules of glucose.

$$C_{12}H_{22}O_{11}+H_2O=2C_6H_{12}O_6.$$

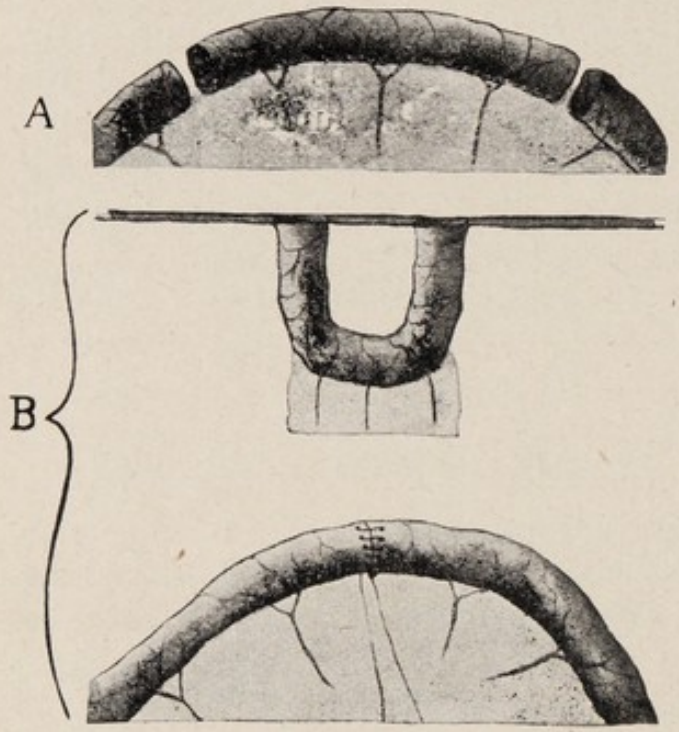


FIG. 165.—Scheme of intestinal fistula.
A, first stage of operation; B, fistula completed.

The intestinal juice also contains two enzymes which convert the disaccharides, cane-sugar and lactose, into monosaccharides. One of these ferments, *invertase*, converts a molecule of cane-sugar into one molecule of glucose and one molecule of fructose. The other, *lactase*, hydrolyses lactose in a similiar way with the formation of glucose and galactose. Lactase is most abundant in young animals, at the period of life when lactose is an important constituent of the dietary. The terminal stages of the hydrolysis of protein are effected by a ferment, *erepsin*, existing in the intestinal juice. Erepsin acts upon proteoses and peptones, splitting them up into amino-acids. Erepsin is also contained in the epithelial cells covering the villi, and it is possible that the final stages of hydrolysis may occur to some extent in these cells.

The chief amino-acids resulting from the digestion of proteins are leucine, tyrosine, aspartic acid, glutamic acid, tryptophane, cystine, and the hexone bases, lysine, arginine, and histidine.

THE SECRETION OF THE INTESTINAL JUICE

The intestinal juice is produced by the crypts of Lieberkühn, which are tubular glands lined by columnar epithelium, occurring

in the mucous membrane of the small intestine, and opening between the bases of the villi. There is no evidence that the secretion is influenced by a nervous factor. The normal stimulus for the secretion of the intestinal juice is undoubtedly secretin, and possibly also other hormones. This possibility is supported by the fact that intestinal juice is produced in the dog about ten minutes after the ingestion of a meal of meat, and that the flow is increased in the third hour after the food has been taken. The secretion of intestinal juice can also be brought about by mechanical stimulation of the intestinal mucous membrane.

THE PROGRESS OF DIGESTION IN THE SMALL INTESTINE

Experiments have been made in which the intestinal contents of dogs were withdrawn, by means of appropriate fistulæ, at different stages of their passage along the bowel. It has been found that, after a test-meal, 77 per cent. of the protein is converted into proteose and peptone, and one-half to three-fifths of the starch into dextrin and sugar, as a result of gastric and duodenal digestion, and that, when the intestinal contents reach the lower end of the ileum, the digestion of all the food-stuffs is complete.

The final result of the action of the digestive juices on the food-stuffs is, therefore, their conversion into amino-acids, monosaccharides, fatty acids, soap, and glycerol; and consideration of the process whereby this is effected shows that it possesses two striking features. One is the extent to which each stage of the process is correlated with, and dependent on, the preceding stage. For example, the dextrin formed during salivary digestion gives rise to the formation of gastrin, and this causes a secretion of gastric juice. Again, the secretion of bile, pancreatic juice, and succus entericus is dependent on the formation of secretin by means of the acid of gastric juice; and, if the secretion of gastric juice is deficient, intestinal digestion is less effectively carried out.

The other feature is the gradual replacement of nervous by chemical control of the secretions in successive stages of digestion. The production of saliva is purely reflex in origin, that of gastric juice partly nervous and partly chemical, and that of bile, pancreatic juice, and succus entericus entirely, or almost entirely, due to chemical stimuli (hormones).

THE MOVEMENTS OF THE SMALL INTESTINE

The intestinal contents are slowly propelled along the gut towards the colon, and at the same time they are subjected to

a continuous mixing process. The onward movement is effected by waves of contraction which travel along the muscular coat of the bowel, and constitute what is known as *peristalsis*. The mixing of the material in the intestine is brought about by ring-like or *segmental contractions*, which are not progressive in character. These movements may be observed in the living animal or person by the aid of X-rays after the administration of a bismuth meal. They can also be observed directly, if the abdomen is opened in an anæsthetised animal, the intestines being protected from drying by partially immersing the animal in warm saline solution. The movements may then be recorded by means of a balloon inserted in the lumen of the bowel and connected with a tambour and writing lever; contraction of the intestinal wall compresses the balloon and air is forced into the tambour, thereby raising the lever.

Peristalsis.—Peristalsis can be produced experimentally by introducing into a loop of intestine a bolus of cotton wool smeared with vaseline. Immediately above the bolus a narrow ring of constriction is formed by the contraction of both muscular coats, whereas below the bolus the muscular wall is relaxed for a distance of 20 to 30 centimetres. The ring of constriction travels slowly along the intestine as a wave, pushing the bolus before it towards the colon, and always preceded by the zone of relaxation. A similar wave of peristalsis can be set up by pinching the gut. These experiments demonstrate the chief features of peristalsis, namely, (1) that a stimulus applied at any point of the small intestine produces contraction above, and relaxation below, the point of stimulation, and (2) that both the contraction and the relaxation travel as a wave at the rate of 1 to 2 centimetres a minute, and always in the aboral direction. The normal stimulus to peristalsis is the presence of a bolus of food, and the character of the movement is such that the wave of contraction drives the food into a region of the intestine which is already relaxed, and thereby prepared to receive it.

Occasionally a more rapid peristaltic wave travels along the bowel. This is known as "peristaltic rush," and is seen, for example, when purgation occurs.

Peristalsis continues in a normal fashion when all the nerves passing from the central nervous system to the intestine have been divided, but it is abolished by painting the wall of the intestine with cocaine or nicotine, which puts the myenteric plexus out of action. It is concluded, therefore, that peristalsis is brought about by a local reflex mechanism, situated in Auerbach's plexus (the myenteric plexus), the afferent impulse being evoked either by distension of the intestinal wall, or by the

action of irritant substances upon the nerve-endings in the mucous membrane.

Segmentation.—The segmental contractions are most readily observed in a normal animal after the administration of a bismuth meal. The process consists in the sudden appearance of narrow rings of constriction in a previously quiescent loop of intestine. The constrictions divide the loop into a number of segments, and give it the appearance of a string of sausages. These constrictions, represented by *a*, *a*, *a* (fig. 166), rapidly disappear, and are succeeded by fresh constrictions, *b*, *b*, *b* (fig. 166), starting at the centres of the segments just formed ; as a result the original

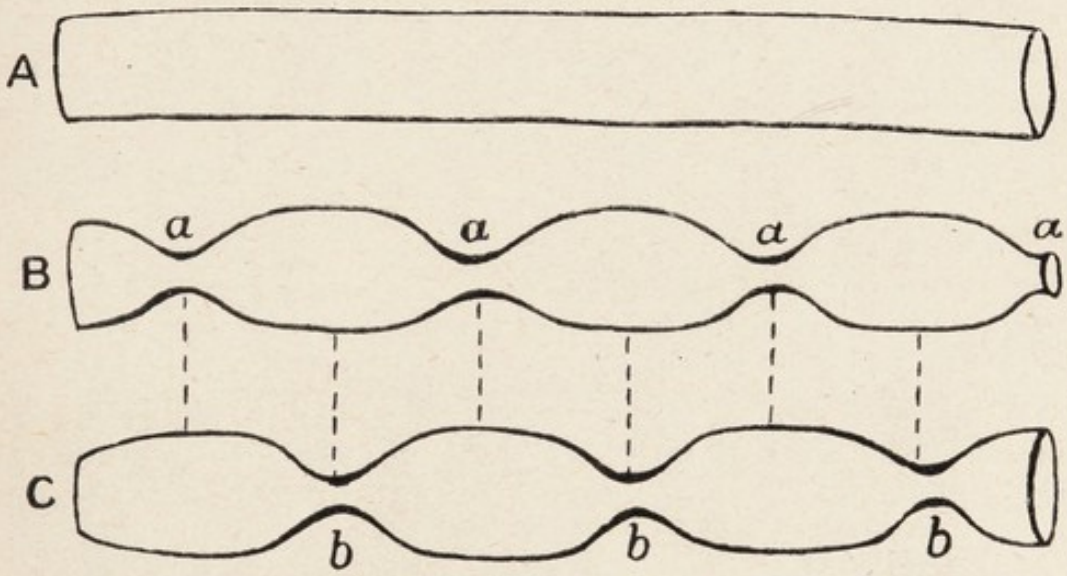


FIG. 166.—Diagram showing segmental contractions of small intestine. A. Intestine at rest. B. Segmental contractions at *a*, *a*, *a*, *a*. C. Later stage, contractions at *b*, *b*, *b*.

segments are divided in half, and the halves of adjacent segments reunite to form fresh segments. This process of segmentation is repeated seven or eight times a minute in man, and may continue for half an hour or more in the same loop of intestine. It has a twofold effect. In the first place, it ensures thorough mixture of the food with the digestive juices and thereby assists digestion, and, in the second place, by continually bringing fresh portions of the intestinal contents in contact with the mucous membrane, it facilitates the absorption of the products of digestion. Both layers of the muscular coat take part in these contractions, as well as in the peristaltic waves, but the segmental contractions do not cause any onward movement of the intestinal contents towards the colon. The rhythmic character of these movements is well shown by inserting a balloon into a loop of intestine, and connecting it with a piston-recorder in order to obtain a graphic record.

The normal stimulus to rhythmic segmental contractions is probably distension of the intestinal wall by a bolus of food, and, since they take place in loops of intestine after removal from the body, these contractions cannot be dependent upon impulses proceeding from the central nervous system. Since they are unaffected by nicotine or cocaine, which put the myenteric plexus out of action, the segmental contractions are probably purely myogenic in origin, and due to a direct response of the muscle to increased tension. This view is supported by the observation that rhythmic contraction can take place in isolated strips of intestinal muscle from which the myenteric plexus has been removed.

When the exposed intestines are observed directly, a swaying movement of coils of intestine is sometimes seen, and is known as *pendular movement*; this appears to be due to the combined effect of segmental and peristaltic movements. It is probable, however, that pendular movement only occurs under experimental conditions, since it has not been observed with the X-rays in the normal, intact animal.

It must not be imagined that segmentation and peristalsis are taking place simultaneously throughout the whole length of the small intestine. Observation shows that at any given moment some coils of intestine are quiescent, while others are undergoing segmentation, and in others again peristalsis is taking place.

The Nerves of the Small Intestine.—The small intestine is supplied by the vagus and the splanchnic nerves, and although, as has been pointed out, the intestinal movements are independent of the central nervous system, it can be shown that these nerves exert a controlling influence. Stimulation of the vagus is followed by contraction of the muscle of the intestinal wall after a preliminary relaxation, but has no effect on the ileo-colic sphincter. Stimulation of the splanchnic nerve results in a cessation of both segmentation and peristalsis (fig. 167), but in contraction of the ileo-colic sphincter. The vagus and sympathetic fibres to the small intestine are distributed to the myenteric nerve-plexus lying between the layers of the muscular coat. The influence of the central nervous system on the intestinal movements is shown in their inhibition as a result of pain, anger, or anxiety and also in their exaggeration in consequence of emotional excitement.

The movements of the intestinal wall are increased by pilocarpine, which stimulates the nerve-endings of the vagus. The nerve-endings are paralysed by atropine, the effect of which is antagonistic to that of pilocarpine.

A segment of intestine immersed in oxygenated Ringer's fluid at

the temperature of the body shows segmental contractions, which can be recorded by means of a lever connected with the piece of intestine. If adrenalin is added to the Ringer's fluid, the contractions cease.

The Passage of the Intestinal Contents from the Ileum into the Cæcum.—The ileo-colic sphincter is usually closed, and observations with the aid of X-rays show that the material in the small bowel tends to accumulate behind it. From time to time the sphincter relaxes, and a considerable quantity of the contents of the lower part of the ileum passes into the cæcum and

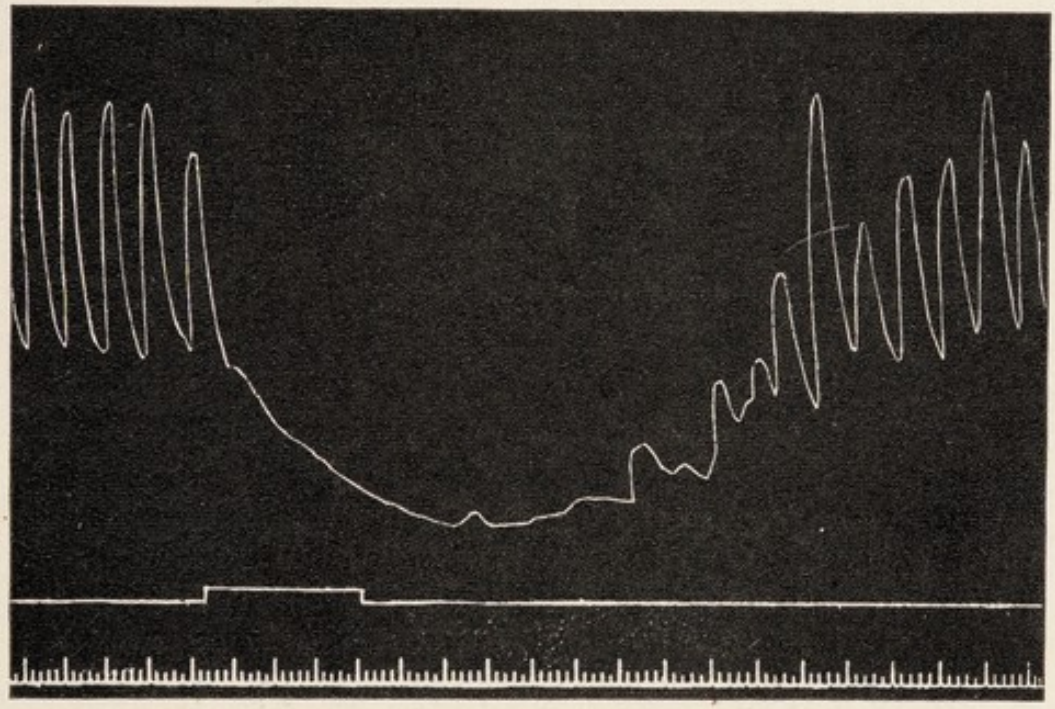


FIG. 167.—Tracing showing cessation of rhythmic segmental contractions and relaxation of the intestinal wall on stimulation of the splanchnic nerve (balloon method). (Bayliss and Starling.)

Fall of lever = relaxation.

ascending colon. The immediate cause of the relaxation of the sphincter appears to be a nervous reflex (gastro-ileac reflex), which follows the entrance of a fresh meal into the stomach. The delay in the ileum will obviously favour the absorption of the last traces of nutritive substances.

SECTION VI

ABSORPTION IN THE SMALL INTESTINE

The absorption of the food-stuffs is almost entirely limited to the small intestine. It has been proved that no water is absorbed in the stomach, and, although some experiments have seemed to indicate that there may possibly be some absorption of

peptone, sugar, and more especially alcohol in that organ the quantities concerned are, at the most, so small as to be negligible. It will be shown later that a large amount of water is absorbed in the large intestine, and that there is a possibility of the absorption of a small amount of glucose there also, but, in normal circumstances, the material which reaches the large bowel is free from sugar, and almost free from other nutritive digestive products.

The progress of absorption can be investigated by the method, already referred to, of collecting the intestinal contents by means of fistulæ after the ingestion of a weighed meal, and analysing them. For example, after a meal of 200 grams of bread given to a dog, the following results were obtained :—

Fistula.	Absorbed per cent.
Pyloric	0
Duodenum	17·45
Jejunum	37·77
Ileum	67·65
Cæcum	94·34

It is evident that the food material is practically completely absorbed by the time the lower end of the ileum is reached. The absorption takes place through the villi of the small intestine, partly directly into the blood-stream, and partly by way of the lymphatic system, the food material in the latter case reaching the blood-vessels along the thoracic duct.

A *villus* (fig. 168) is a finger-like projection of the mucous membrane, covered by columnar epithelium, each cell having a refractive, striated border on its free end, and resting by its deep extremity on a basement-membrane. In the centre of the villus is a lymphatic vessel, the central lacteal, commencing by a blind extremity and communicating with the plexus of lymphatic vessels in the submucosa. Between the lacteal and the basement-membrane are retiform tissue with scattered leucocytes and strands of smooth muscle, the latter extending from the muscularis mucosæ and being attached to both basement-membrane and lacteal. A tiny artery is supplied to each villus and breaks up into a plexus of capillaries, lying immediately under the basement-membrane and reuniting to form a small vein.

THE PROCESS OF ABSORPTION

The absorption of the products of digestion is effected by what, in the absence of a more precise definition, is called the

vital activity of the epithelial cells of the intestinal mucous membrane. Experiments show that the process cannot be accounted for by filtration, diffusion, and osmosis. Filtration cannot take place into the blood-capillaries of the mucous membrane, because the pressure in them is higher than the pressure in the lumen of the intestine. Again, a solution which is isotonic

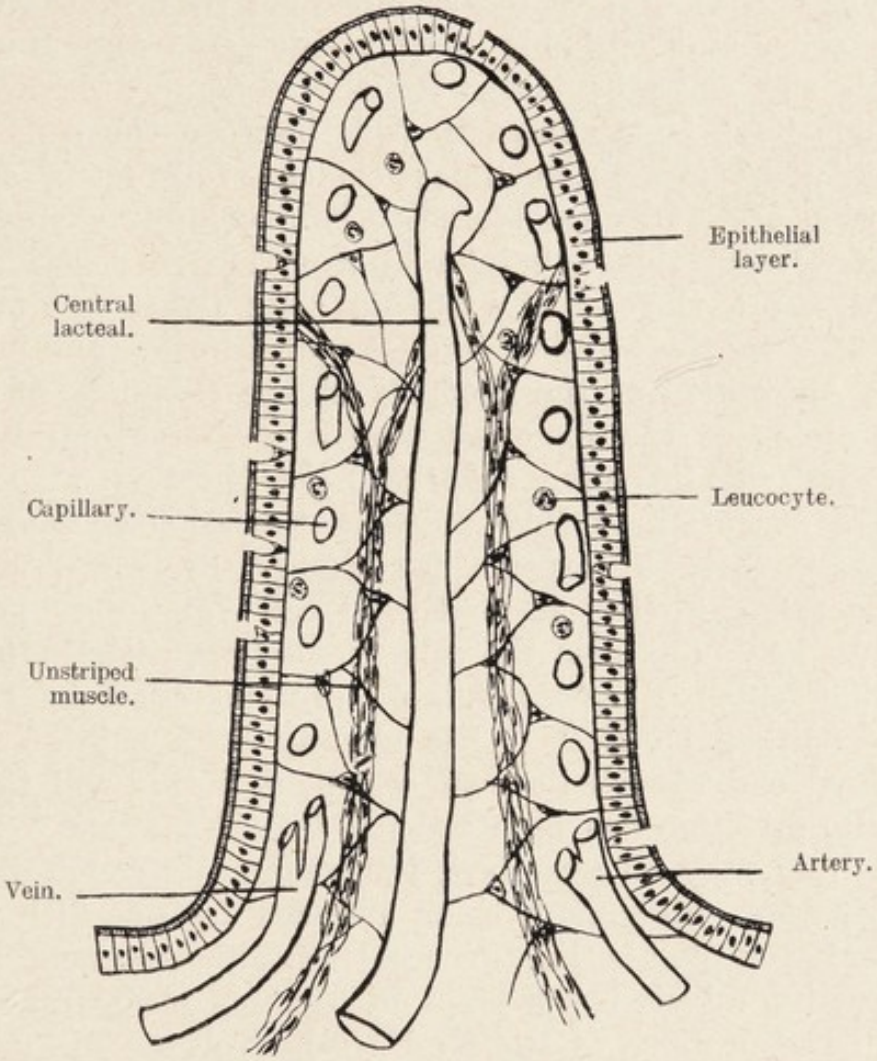


FIG. 168.—Diagram of a villus.

with the blood-serum undergoes absorption, and an animal will even absorb its own blood-serum, so that diffusion and osmosis do not provide a complete explanation.

Although these physical processes alone do not account for absorption, they nevertheless occur in the intestine. Thus, if the bowel contains a hypertonic solution of salt, water passes from the mucous membrane into the solution until the latter becomes isotonic with the blood, after which it is steadily absorbed. Osmosis may, therefore, retard, or, on the contrary, it may assist, absorption, but the passage of material from the lumen of the intestine into the villi must be regarded as due to the activity

of the epithelial cells. If, however, the epithelial cells are injured, for instance by means of sodium fluoride, absorption is entirely regulated by the processes of diffusion and osmosis, and is therefore incomplete. Histological evidence as regards the absorption of fats shows that they pass through the epithelial cells, and experiments with dyes soluble in lipoids show that these enter the cells themselves. The absorption of the products of protein digestion is also said to be accompanied by structural changes in the cells, and probably both amino-acids and glucose pass through the cell-substance. On the contrary, dyes insoluble in lipoids have been shown to pass between the cells, and the possibility of the intercellular cement forming a route for absorption cannot be considered to be absolutely excluded.

Generally speaking, therefore, absorption is an active or vital process, even in the case of water and salts, but it may be assisted or retarded by the physical processes of diffusion and osmosis.

The Absorption of the Products of the Digestion of Proteins. The proteins of the food are almost entirely hydrolysed into amino-acids before being absorbed, but the final stages of the digestive process may take place in the mucous membrane of the intestine after absorption has begun. Proteose and peptone may be taken up by the epithelial cells, and may be further hydrolysed by erepsin in the cells themselves, with the formation of amino-acids. Even coagulable proteins may be taken up by the epithelial cells. It has already been pointed out that an animal can absorb its own serum, and this will take place when the intestine has been washed free of enzymes. Similarly egg-albumin may be absorbed, the amount introduced into the bowel in one experiment being reduced by one-fifth in three hours. It is probable that, even in these circumstances, complete digestive hydrolysis takes place in the mucous membrane, and that all the proteins of the food are hydrolysed to amino-acids before they enter the blood-stream.

There is no direct evidence that the products of the digestion of protein are synthesised into protein in the walls of the villi. On the contrary, there is no doubt that the amino-acids enter the blood-stream as such, and their presence in the circulating blood can be demonstrated by the following means.

An artery of an anæsthetised animal is connected with one end of a series of tubes, the walls of which consist of a thin collodion membrane, the other end of the series being attached to a vein. The system of tubes (fig. 169) is filled with saline solution, and hirudin is injected into the animal; the blood is then allowed to flow from the artery through the tubes and back to the vein, a continuous circulation of the animal's blood being thus main-

tained through the tubes. The tubes are surrounded by normal saline solution at the temperature of the body, and, as the blood flows through them, its diffusible constituents, including sugar and amino-acids, pass through the collodion wall into the saline solution, and can be subsequently examined. Since amino-acids diffuse into the salt solution, they must have been previously present in the circulating blood.

Further, the percentage of amino-acids in the circulating blood has been estimated by chemical methods, and has been found to increase after a protein meal.

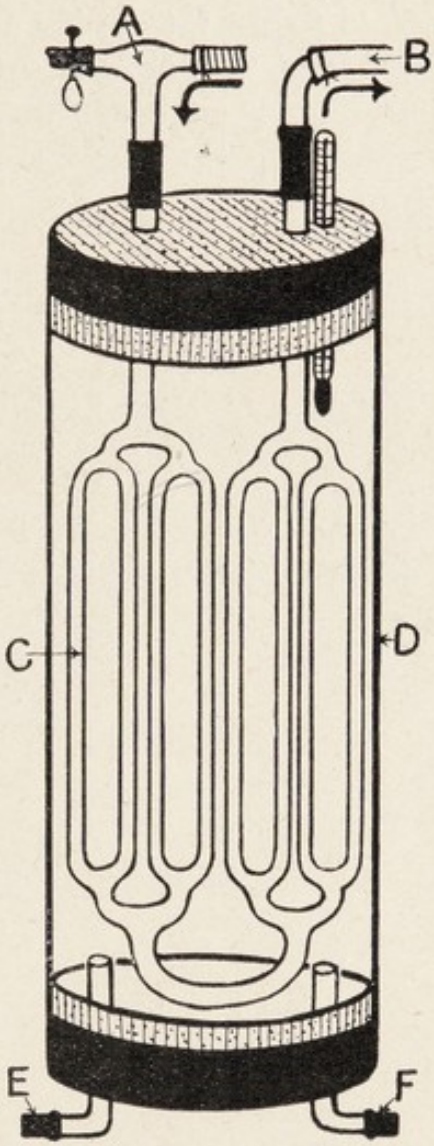


FIG. 169.—Diffusion apparatus (semi-diagrammatic).

A, arterial cannula; B, vein; C, collodion tube; D, outer vessel containing saline solution; E, F, tubes for admitting or removing saline solution.

The Absorption of the Monosaccharides.—The products of carbohydrate digestion all belong to the group of monosaccharides and are easily diffusible substances. The chief of these is glucose, but some fructose is formed by the hydrolysis of cane-sugar, and some galactose by that of the sugar of milk. All three varieties are absorbed directly into the blood-stream. During absorption of a carbohydrate meal more sugar is found in the portal vein than in the hepatic vein. Moreover, the absorption of sugar is not accompanied by an increase of that substance in the lymph of the thoracic duct, and it is not interfered with by ligature of that structure. Disaccharides are not absorbed from the intestine.

The Absorption of Fat.—The products of digestion of fat are fatty acid, held in solution by the bile-salts, glycerol, and a little soap. The absorption of fat differs from that of amino-acids and glucose in that it takes place for the most part into the lymphatic system. During the absorption of a fatty meal the lymphatics of the mesentery become filled with a milky fluid called *chyle*, so that they are easily visible to the naked eye. Chyle collected from the thoracic duct may contain over 6 per cent. of fat. The absorbed fat reaches the blood-stream by the thoracic duct, and, if an animal

be bled during absorption of fat, the plasma will be found to be milky from the quantity of minute fat-globules present in it. A few hours later the plasma is again clear, because the small quantity of fat still present in it is held adsorbed by the serum-proteins, the remainder having either been oxidised or transferred to the fat-depôts of the body.

About 98 per cent. of the fat taken as food is absorbed, but only 60 per cent. can be recovered in the chyle. The fate of the remaining 40 per cent. is unknown. It cannot be recovered either from the blood or from the thoracic duct, nor does it appear in the fæces.

The bile-salts have an important influence on the absorption of fat, partly because of their property of holding fatty acids in solution, and partly because they reduce surface tension and so facilitate the passage of the fatty material into the epithelial cells. In the absence of bile 60 per cent. of the fat of a meal remains unabsorbed. The absence of pancreatic juice also prevents the absorption of much of the fat, because fat is not absorbed unless it is acted on by lipase.

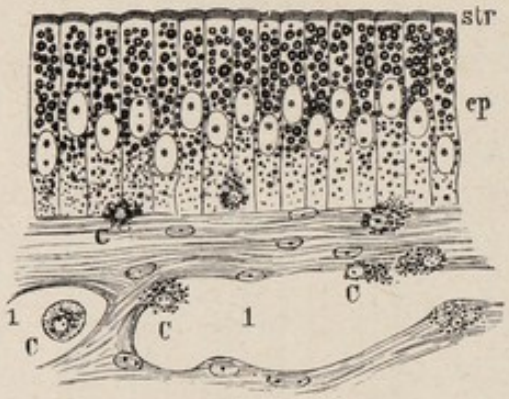


FIG. 170.—Mucous membrane of frog's intestine during absorption of fat. (From Sharpey Schafer's *Essentials of Histology*.)

ep, epithelium; *str*, striated border; *c*, leucocytes; *l*, lacteal.

The soaps formed in the intestine are split up by the intestinal epithelial cells into fatty acids and alkali. The fatty acids are absorbed, and recombined with glycerol in the cells to form neutral fats.

The absorption of fat may be studied histologically. During its occurrence the epithelial cells covering the villi become filled with droplets of fat, which may be stained black with osmic acid (fig. 170), red with Scharlach R or Sudan III., or pink by means of Nile-blue. The reaction with Nile-blue shows that the droplets consist of neutral fat, so that a re-synthesis takes place in the epithelial cell. The fat may be traced through the cell into the core of the villus, where the droplets are finely emulsified by the lymph in the tissue-spaces, and are carried into the central lacteal. The wandering leucocytes in the villus take up fat-droplets, and this may account to some extent for the 40 per cent. of absorbed fat which cannot be recovered from the thoracic duct.

Alternate contraction and relaxation of the muscular fibres

in the villus tend to propel the contents of the central lacteal towards the larger lymphatic vessels in the intestinal submucosa.

It has been demonstrated that hydrocarbons such as paraffin and petroleum are not absorbed in the intestine.

SECTION VII

THE LARGE INTESTINE

Four or five hours after each meal the contents of the small intestine begin to pass through the ileo-colic junction into the large intestine. An important factor in promoting the transference of material from ileum to colon is the gastro-ileac reflex. The entrance of the succeeding meal into the stomach excites the production of peristaltic waves in the lower part of the ileum, and, as each wave reaches the ileo-colic junction, the sphincter is relaxed. In this way the contents of the ileum are propelled into the colon in successive portions, and, if they contain bismuth, the level which they attain in the ascending portion of the large intestine can be observed by means of X-rays to rise towards the hepatic flexure in an intermittent manner.

The material which passes into the bowel is in the form of a jelly, coloured by the presence of bile-pigment. It normally contains hardly any nutritive substances, the derivatives of the digestion of protein, fat, and carbohydrate having been almost completely absorbed in the small intestine. Indigestible substances contained in the food are present, especially cellulose, together with cast-off epithelial cells and the unabsorbed portions of the various digestive juices. The chief secretory waste products are the pigment of the bile, unabsorbed glycocholate and taurocholate of sodium, and cholesterol.

THE FUNCTIONS OF THE LARGE INTESTINE

In carnivorous animals the large intestine is relatively short, and its function is almost entirely limited to the absorption of water and the consequent reduction in bulk of the fæces. In herbivora, on the contrary, the large intestine is of considerable length, and not only absorbs water but serves an additional purpose. A large proportion of vegetable food-stuffs consists of cellulose, which is not affected by the digestive enzymes. Cellulose is decomposed in the large intestine of the herbivora by bacterial action, being converted into fatty acids, which are absorbed and utilised in the body. Further, in all the higher animals, the cells lining the simple tubular glands of the large

intestine are for the most part of the mucus-secreting type, and are of service in producing mucin, which acts as a lubricant and facilitates the passage of the fæces along the bowel.

In man the functions of the large intestine include secretion, excretion, and absorption, and in addition some bacterial decomposition takes place in its contents. (1) The *secreted* material, as in the higher animals generally, is mucin, derived from the tubular glands of the mucous membrane. (2) The substances *excreted* by the large intestine are calcium, magnesium, and iron, chiefly in the form of phosphates. The amount of calcium excreted by the bowel varies inversely with the amount contained in the urine. Acid urine, such as occurs normally in carnivora, and in man when the diet contains a due proportion of protein, holds calcium phosphates in solution, and in such a case the proportion of calcium excreted by the large intestine is small. When the urine is alkaline, as in herbivora, and in man when the diet is largely vegetable, the amount of calcium excreted by the bowel is greater. Other chemical substances taken as drugs, for example, mercury, may also be excreted by the large intestine.

(3) The only substance *absorbed* in any quantity in the large bowel is water. The contents of the ascending colon contain no nutritive substances, but their bulk is fairly large owing to the amount of fluid which they contain. During their stay in the large intestine the bulk is greatly reduced, chiefly by the absorption of water; it is said that 400 c.c. of water are absorbed from the contents of the colon in twenty-four hours. The possibility of the absorption of nutritive substances in the large intestine is of importance, because attempts are frequently made to introduce food-stuffs into the body by means of rectal injections. Experiments prove, however, that nutritive material is not absorbed by the large intestine, with the exception of glucose, and this only in amounts too minute to be of real practical value. But some injected material may find its way through the ileo-cæcal opening into the small intestine, and be absorbed there.

(4) The *bacteria* in the human large intestine act upon cellulose with the production of lower fatty acids, marsh gas (CH_4), carbonic acid, and hydrogen. Undigested protein residues also undergo bacterial decomposition, with the production of certain amines and the aromatic bodies, indol (C_8H_7N), skatol (methyl-indol), and phenol; indol and skatol are derived from tryptophane. There is evidence that absorption of indol, skatol, and phenol takes place to some extent, inasmuch as compounds of these substances with sulphuric acid, the ethereal sulphates, are found in the urine.

THE FÆCES

The residues which finally reach the rectum constitute the fæces, and form a solid or semi-solid mass, coloured by the pigment stercobilin, which is derived from bilirubin. The composition of the fæces has already been indicated. They contain about 65 per cent. of water, with organic material and inorganic salts. The organic substances are partly nitrogenous and partly of a fatty nature, and soluble in ether. The nitrogenous constituents include cholic acid, dyslysin, indol and skatol, purin bodies, epithelial cells, and dead bacteria. The lipoids are fatty acids, lecithin, and coprosterol, a body allied to cholesterol. There may be a small quantity of neutral fat. When vegetable food has been taken, the fæcal matter will include undecomposed cellulose, but, for the most part, the fæces consist of substances derived from the digestive tract itself.

THE MOVEMENTS OF THE LARGE INTESTINE

The movements of the large intestine have been most satisfactorily studied with the aid of X-rays (fig. 171).[1] The cæcum and ascending colon are filled, in the manner which has already beed described (p. 371), by the peristaltic contractions of the ileum, and are entirely passive during the process. A little later, rings of constriction appear near the junction of the ascending and transverse colon, and pass backwards along the ascending colon to the cæcum ; regurgitation of the contents of the colon into the ileum is prevented by closure of the ileo-colic sphincter. These movements, which are known as *antiperistalsis*, serve to churn up the contents of the colon and to assist the absorption of water. They are not preceded by relaxation of the intestinal wall. It is not yet certain whether antiperistalsis occurs in man.

The transference of their contents from the cæcum and ascending colon to the transverse and descending colon takes place at long intervals, usually three or four times in twenty-four hours, by means of rapid peristaltic contractions. These movements generally follow the entry of food into the stomach, and are ascribed to a gastro-colic reflex. Scattered masses may remain in the transverse colon for a time, and these are gradually transferred to the descending colon by a slow peristaltic wave.

The fæces remain for a time in the sigmoid flexure, until, usually after a meal, a certain amount passes into the rectum

[1] We are indebted for this diagram to the kindness of the Oxford University Press.

and gives rise to the desire for defæcation. By relaxation of the sphincter ani, accompanied by contraction of the walls of the sigmoid flexure and rectum, and assisted by voluntary contraction of the muscles of the abdominal wall and pelvic floor,

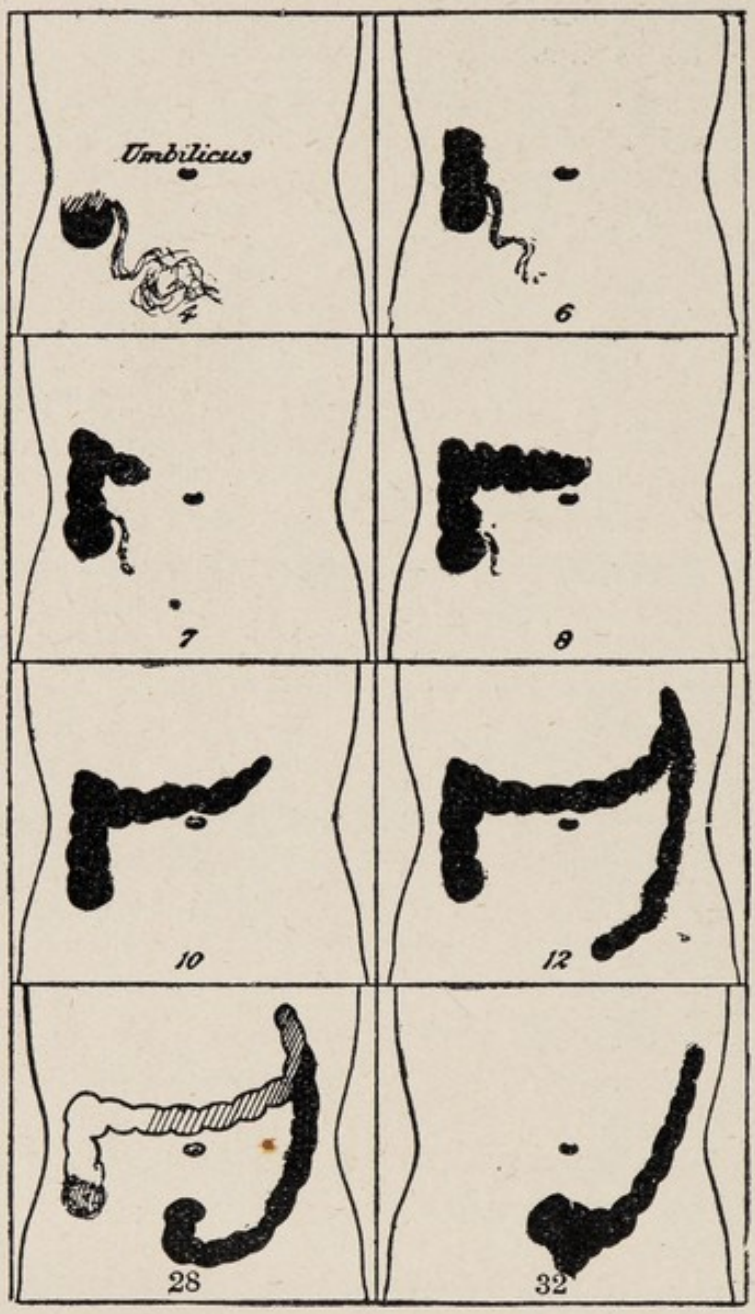


Fig. 171.—Passage of food along the large intestine after a bismuth meal, as seen by means of X-rays. The numbers refer to the hours after the meal was taken. (Hertz.)

the lower end of the bowel is evacuated. The act is a reflex one, but in the adult it is under the control of the higher centres.

The Nerve-Supply of the Large Intestine.—The large intestine receives its nerve-supply from the sympathetic system and from the pelvic visceral nerves or *nervi erigentes* (fig. 5). The sympathetic fibres form the inferior mesenteric nerves, running

from the inferior mesenteric ganglion to the ascending, middle, and transverse colon, and the hypogastric nerves pass from the same ganglion to the rectum. The preganglionic fibres emerge from the spinal cord by the first, second, and third anterior lumbar nerve-roots.

The pelvic visceral nerves emerge from the cord by the second and third sacral nerve-roots, and are distributed to the whole length of the large intestine. Stimulation of the sympathetic nerves causes inhibition of the tone of the intestinal wall and cessation of its movements. Stimulation of the pelvic nerves causes contraction of the whole length of the colon. The sympathetic is therefore inhibitory, and the pelvic visceral nerves are motor in function.

As in the small intestine, there are ganglionated plexuses in the wall of the large intestine, of which the myenteric, lying between the layers of the muscular coat, is associated with the local reflex mechanism controlling the movements of the bowel.

THE VERMIFORM APPENDIX (VERMIFORM PROCESS)

In man the cæcum is very short and has attached to it a worm-like process, the vermiform appendix. This has a thin muscular coat and a thicker mucous coat, the latter composed almost entirely of lymphoid tissue containing scattered tubular glands. The human appendix is regarded as a vestigial remnant of no functional importance. It is homologous with the long and capacious cæcum of herbivora, which serves the useful purpose of retaining food material while the cellulose undergoes bacterial decomposition.

CHAPTER X

METABOLISM

SECTION I

METHODS OF INVESTIGATION

In carrying out its functions the body expends energy, and every movement of the body, every heart-beat, every secretory act demands the expenditure of energy. The normal source of this energy is the food-stuffs which, after being digested and absorbed, are carried to the tissues, where they undergo a complex series of chemical transformations, the end-products thereby formed being removed from the body by the lungs and kidneys. This series of chemical changes constitutes *metabolism*, and the metabolic activities of the tissues are of two kinds. On the one hand, the living tissues are constantly undergoing changes whereby a portion of their substance is broken down and removed from the body ; on the other hand, this loss is replaced by the building up of fresh tissue from the nutritive materials supplied in the blood. The former of these processes is called *katabolism*, and the latter *anabolism*.

Our knowledge of these changes is still very imperfect and their nature is to a large extent hidden from us. But their main outcome is the conversion of the potential energy of the food-stuffs into kinetic energy, which is utilised either for the performance of external muscular work or for the maintenance of the temperature of the body. During this process fats and carbohydrates are completely oxidised to carbonic acid and water, whereas the proteins are converted partly into carbonic acid and water, and partly into urea and other incompletely oxidised nitrogenous substances, which are excreted in the urine. The carbonic acid is removed from the body almost entirely through the lungs, and the water by the respiratory tract, kidneys, and skin. Further, it is evident that, in carrying out these oxidative changes, the tissues must use oxygen and that the amount of oxygen taken up by the body in a given time furnishes a rough index of its metabolic activity.

The metabolic (chemical) activities of the body may therefore be studied in three ways, namely, (1) by measuring the total

amount of energy expended as work or heat by the body in a given time, (2) by determining the amount of oxygen required for the carrying out of the oxidative processes which provide this energy, and (3) by measuring the amount of the end-products which are formed. Although these methods measure the total metabolic activity of the body they throw but little light on the nature of the processes involved; and for this purpose they must be supplemented by the study of the actual changes undergone by the individual food-stuffs within the tissues themselves.

THE PRODUCTION OF HEAT

The heat evolved by the complete oxidation of a food-stuff can be ascertained by means of the bomb-calorimeter (fig. 172), which consists of a metal bomb, A, through the top of which pass two wires, *h* and *h'*, connected below by a strip of soft iron wire, B; one gram of the substance, *e.g.* glucose, which is to undergo combustion, is placed in contact with the iron wire. The bomb is filled with oxygen from an oxygen cylinder under a pressure of 7 to 8 atmospheres, and is enclosed in a bath, C, containing a known volume of water, and surrounded by an air-jacket, E, and a water-jacket, D. When a current is passed through the wires, the soft iron fuses and ignites the sugar, which is rapidly oxidised to carbonic acid and water. The heat evolved in this process raises the temperature of the water in which the bomb is placed; and, if the temperature of the water before and after the combustion is observed, the amount of heat evolved can be calculated, and is expressed in *calories*. A large calorie is the amount of heat required to raise 1000 grams of water 1° C. (A small calorie is the amount of heat necessary to raise the temperature of 1 gram of water 1° C.; this measurement is now seldom used.) If the volume of water in such an experiment is 1 litre and the rise of

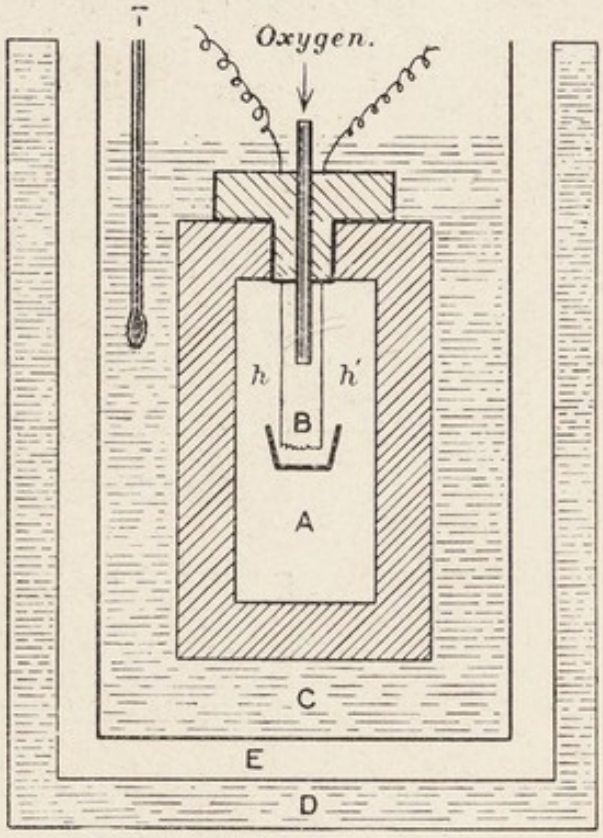


FIG. 172.—Bomb-calorimeter.
T, thermometer; E, air-jacket; B, strip of iron wire.

temperature is 4·1° C., 1 gram of sugar when fully oxidised gives out 4·1 calories; and this amount, which is spoken of as the calorie-value of glucose, is constant. The average calorie-value of fat, carbohydrate, and protein is shown in the following table :—

Fat, 1 gram = 9·3 calories.
Carbohydrate, 1 gram = 4·1 calories.
Protein, 1 gram = 4·1 calories.

The calorie-value of protein when completely oxidised in the calorimeter is 5·6; but protein is not fully oxidised in the body, its nitrogen being excreted in the urine largely as urea, and to a

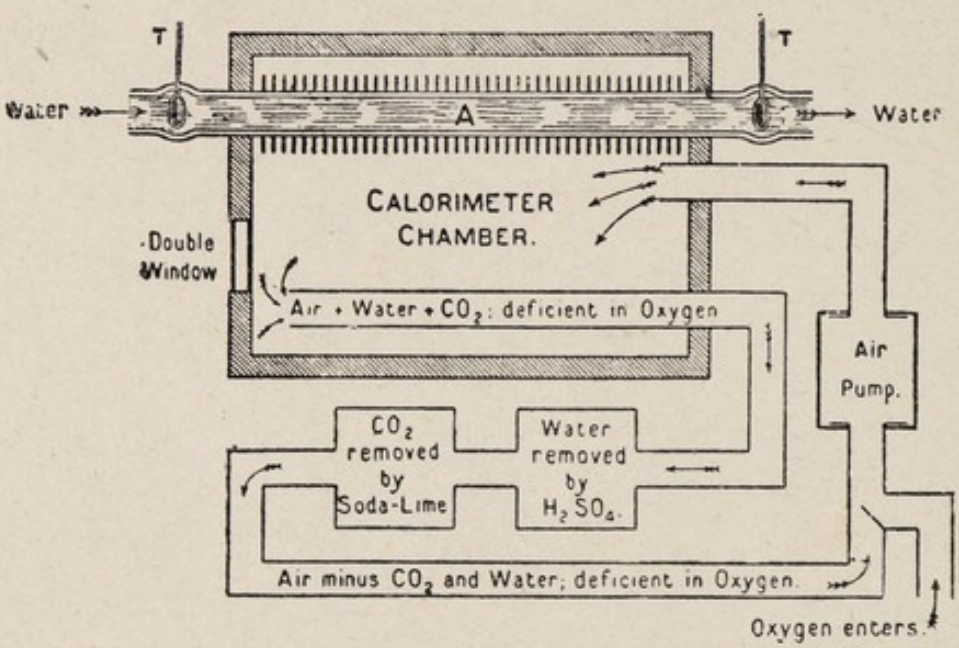


FIG. 173.—Diagram to show the principle of the Atwater-Benedict calorimeter. (After Halliburton.) Starling's *Principles of Physiology*.

less extent as other substances, each of which has a calorie-value of its own. In determining the physiological calorie-value of protein, the heat-value of urea and other nitrogenous products must be deducted from the figure 5·6. When this is done, the heat-value of protein is reduced to 4·1, which represents its calorie-value in the body.

The energy set free in the body by the oxidation of the food-stuffs appears partly as heat and partly as muscular work. The energy set free as muscular work may be calculated as heat according to the following equation :—

425 kilogram-metres of work = 1 large calorie.

The heat formed in the body is determined by placing the animal in a suitable calorimeter. Large calorimeters such as that of Atwater and Benedict have been constructed, in which a man can live for two or three days or longer, and can carry out muscular

work. The Atwater-Benedict calorimeter consists of a room, with double, non-conducting walls, containing a series of pipes through which cooled water is flowing at such a rate that the temperature of the room remains constant (fig. 173). The heat given off by the man warms the water passing through the pipes, and is thus carried off. By measuring the amount of water flowing along the pipes and the rise in its temperature as it passes through the calorimeter, the total heat lost by the individual can be estimated ; and, since his temperature remains steady, this is equivalent to the heat produced by him in a given time.

By means of these methods it is possible to determine, on the one hand, the energy supplied to the body in the food, and, on the other hand, the energy lost from the body as heat and muscular work. It is found that these two balance one another within the limits of experimental error, and that the energy lost from the body has its origin entirely in the potential energy taken into the body in the food. Thus the principle of the conservation of energy is as true for living beings as it is in the rest of the organic and the inorganic world.

The following table summarises an experiment in which the calorie-value of the food consumed is compared with the actual heat given out by the body :—

Day of Experiment.	Calorie-Value of Material Oxidised in the Body.	Calories Lost from the Body.
1	2349	2414
2	2345	2386
3	2391	2413

THE RESPIRATORY QUOTIENT AND EXCHANGE

The *respiratory exchange* is the total quantity of oxygen taken into the body and of carbonic acid discharged from the body in a given time.

The respiratory quotient, as already mentioned (p. 280), is the *ratio* of the amount of carbonic acid discharged from the body to the amount of oxygen taken in during a given time.

In man the amount of oxygen used, and of carbonic acid evolved, in the metabolic changes taking place in the body under varying conditions, such as rest or muscular exercise, can be determined by means of the calorimeter just described. A continuous circulation of air through the chamber is maintained by a small pump. The air leaving the calorimeter passes through vessels containing soda-lime, which absorbs carbonic acid, and

others containing sulphuric acid, which absorbs water, the increase in weight of these vessels giving the weight of carbonic acid and water vapour respectively exhaled in a given time. The oxygen used by the individual is replaced from a cylinder, the amount supplied being measured.

The respiratory quotient and exchange may also be determined approximately by finding with the aid of a spirometer the average volume of air breathed in a minute, and by analysing a sample of expired air. Thus, if a man breathes 500 c.c. of air at each breath and his respirations are 12 per minute, he breathes 6 litres per minute. Assuming that the expired air contains 16 per cent. oxygen, he must have absorbed 5 c.c. oxygen from each 100 c.c. of air breathed, namely 300 c.c.; similarly, if the expired air contains 4·04 per cent. of carbonic acid he must have breathed out 240 c.c. carbonic acid, and the respiratory quotient is $\frac{240}{300} = 0 \cdot 8$.

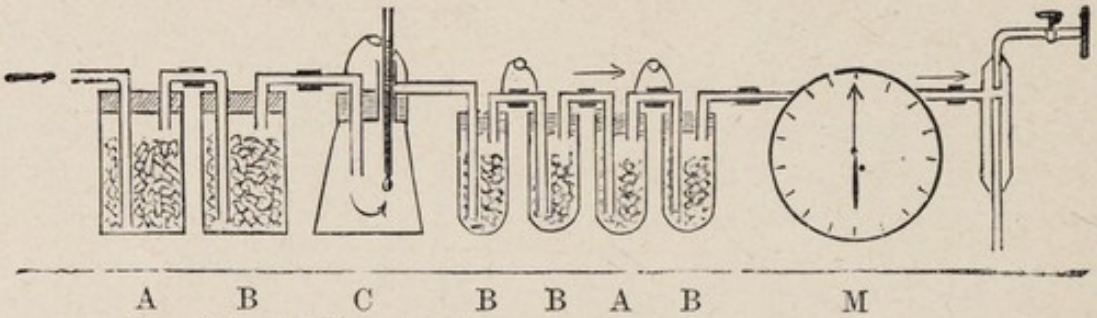


FIG. 174.—Haldane-Pembrey respiration apparatus for mouse. (From *Practical Physiology*, by Pembrey and others.)
A, soda-lime; B, H_2SO_4; C, chamber for animal; M, gas-meter.

For small animals the apparatus devised by Haldane and Pembrey, and shown in fig. 174, may be employed. The animal, *e.g.* a mouse or a guinea-pig, is placed in a vessel C, through which is drawn a current of air, freed from carbonic acid and water by passing it through soda-lime and sulphuric acid. The water in the air leaving the chamber is absorbed by pumice saturated with sulphuric acid in the tubes B B; these are weighed before and after the experiment, the increase in weight representing the water given off by the animal. The carbonic acid evolved is absorbed in the tube A, which contains soda-lime, and the water taken up from the soda-lime is absorbed by sulphuric acid in the tube B; these two tubes are weighed before and after the experiment. During the experiment the animal loses weight, because the weight of carbonic acid and water given off exceeds the weight of oxygen taken into its tissues. The amount of oxygen taken up by the animal can be determined indirectly by subtracting the loss in weight of the animal during the experiment from the total weight of carbonic acid and water given

off. To calculate the respiratory quotient and exchange, the weights of oxygen and carbonic acid are converted into volumes.

The respiratory exchange serves as an index of the total oxidative processes taking place in the body, just as the amounts of oxygen used, and of carbonic acid evolved, by a single organ indicate the functional activities of that organ. It is not influenced by the nature of the food which is consumed, but is very greatly modified by the functional activity of the animal. A resting man consumes on an average 200–250 c.c. of oxygen per minute. During muscular activity the chemical changes taking place in the muscles are increased, heat is evolved, and more oxygen is used by the muscles; and, as the muscles form about 40 per cent. of the total weight of the body, the respiratory exchange during muscular exercise may be eight to ten times greater than during rest.

Respiratory Exchange in Man. (Benedict and Cathcart.)

	Oxygen Absorbed in c.c. per Minute.	Carbonic Acid Discharged in c.c. per Minute.
Resting . . .	242	218
Moderate work . .	1490	1224
Severe work . .	1850	1789

Further, the respiratory exchange varies with the size of the animal. The smaller the animal the greater is its surface relatively to its weight, and, since the body loses heat chiefly from its surface, the relative loss of heat must be greater in a small than in a large animal. In order to make up for this loss the smaller animal must produce a relatively larger amount of heat, and must use up in this process relatively more oxygen, than a bigger animal. It is found, in fact, that metabolism is more active and the respiratory exchange is greater, weight for weight, in small animals than in large ones. The following table shows the relationship of heat production to the weight and surface-area respectively of various animals :—

	Weight in Kg.	Calories produced per Diem.	
		Per Kg. of Weight.	Per Square Metre of Surface.
Pig	128·0	19·1	1078
Man	64·3	32·1	1042
Dog	15·2	51·5	1039
Mouse . . .	0·01	654·0	1188

Apart from the question of size, the consumption of oxygen is also relatively greater in growing than in adult animals, since oxygen is being used not only in the chemical changes necessary to maintain the weight of the animal, but also in the metabolic processes associated with growth.

The Respiratory Quotient. — The size of the respiratory quotient is determined almost entirely by the nature of the food-stuffs which are being oxidised in the tissues, and this normally depends upon the character of the food consumed by an animal. If an animal were living solely upon carbohydrate food, all the oxygen taken into the body would reappear as carbonic acid, and the quotient would be 1, in accordance with the following equation :—

$$C_6H_{12}O_6 + 6O_2 = 6CO_2 + 6H_2O. \quad \frac{6CO_2}{6O_2} = 1.$$

If the diet consisted entirely of fat, the oxygen taken into the body would not all reappear as carbonic acid ; some of it would be used in converting hydrogen into water, and the quotient would be less than 1, the oxidation being represented thus :—

$$\underset{\text{Olein.}}{C_3H_5(C_{18}H_{33}O_2)_3} + 80\,O_2 = 57\,CO_2 + 52\,H_2O. \quad \frac{57\,CO_2}{80\,O_2} = 0{\cdot}71.$$

On a purely protein diet part of the oxygen would be combined with nitrogen and sulphur, as well as with hydrogen, and the respiratory quotient would be approximately 0·8. In man living on a mixed diet the quotient is usually about 0·85 ; it can be lowered by the exclusion of carbohydrate from the diet, and is raised when the diet consists mainly or exclusively of carbohydrate food. The respiratory quotient is thus of great value, in that it gives an indication of the nature and relative amount of the food-stuffs which are being oxidised in the body under various conditions.

END-PRODUCTS OF METABOLISM

The whole of the carbon in fat and carbohydrate, and a large proportion of that in protein, is removed from the body in a completely oxidised form as carbonic acid, while the nitrogen of protein leaves the body in the form of urea, uric acid, and other substances, which are excreted in the urine. Since protein contains about 16 per cent. nitrogen, it is possible, by determining the total amount of nitrogen in the urine, to calculate the amount of protein from which it has been derived ; each gram of nitrogen in the urine represents the breaking down in the body of 6·25

grams of protein. By measuring the output of nitrogen in the urine and the amount of carbonic acid discharged from the lungs daily, the total amount of protein, fat, and carbohydrate which has been oxidised in the body can be calculated, if the respiratory quotient is known. In health the amount of carbon and nitrogen thus removed from the body is equivalent to the amount taken in with the food, provided that the weight of the individual remains steady. If the individual is putting on weight, some of the carbon taken in the food is retained in the body as fat or carbohydrate, and there may possibly be some retention of nitrogen; when weight is being lost, more carbon, and possibly more nitrogen, will be discharged than are taken in with the food.

We may now consider the changes taking place in the various food-stuffs after their absorption from the digestive tract.

SECTION II

THE METABOLISM OF FAT

The fats taken by the mouth, after being hydrolysed in the digestive tract and re-synthesised in the walls of the villi, enter the thoracic duct as neutral fats and pass into the blood-stream. For a short time after a fatty meal the fats circulate in the blood-stream, and may give the blood a slightly milky appearance. The fats are, for the most part, rapidly taken up from the blood and stored in the subcutaneous tissues and omentum, which serve as depôts in which the fat not immediately required by the body can be kept. The composition of the subcutaneous fat thus reflects that of the fat in the food; and, if abnormal and easily recognisable fats are given by the mouth, they can be identified shortly afterwards in the fat in the subcutaneous tissue. For this purpose, erucic acid or fats containing iodine may be used. In man the greater part of the fat deposited in the body is derived from the fat in food, but it can be formed, and in herbivora is mainly formed, from carbohydrates. This was demonstrated in the classical experiment of Lawes and Gilbert. These observers took two young pigs from the same litter. One was killed, and the amount of fat and protein in its body was determined; the other was fed on a diet containing known quantities of protein, fat, and carbohydrate, and after some weeks it was killed and the amount of fat in its body was ascertained. After deducting the amount of fat taken in the food from that present in the animal's body when it was killed, a large residue remained, which must have been formed from either the protein or carbohydrate

of the food. It could not have been formed from protein, since the amount of fat in the animal was larger than the amount of protein food consumed. The greater part of the fat must, therefore, have been formed from carbohydrate; and there is no doubt that in herbivora, whose diet consists mainly of carbohydrate, the bulk of the fat is formed in this way. There is no evidence that fat can be formed from protein, and animals, *e.g.* dogs, fed on a purely protein diet do not put on any fat.

The process by which carbohydrate is converted into fat in the body is not known, but it is probable that the carbohydrate is first broken down into pyruvic acid ($CH_3 . CO . COOH$), which, by decarboxylation, yields acetic aldehyde ($CH_3 . CHO$), and that, by the linking up of molecules of the latter, the fatty acids are synthesised.

Their possible formation from aldol is thus shown :—

(1) $CH_3 . CHO + CH_3 . CHO = CH_3 . CHOH . CH_2 . CHO$ (aldol)

(2) $$CH_3 . CHOH . CH_2 . CHO + \begin{matrix} H \\ H \end{matrix}\!\!\rangle O$$
$$= \underset{\text{Butyric acid.}}{CH_3 . CH_2 . CH_2 . COOH} + H_2O$$

The fat formed from carbohydrate contains a larger proportion of stearin and palmitin, and has a higher melting-point than that usually deposited in the tissues from the food. For this reason the fat of cattle is much firmer than that of omnivorous animals, which may be practically fluid at the temperature of the body.

The fat in the fat-depôts cannot be used directly by the muscles or other tissues, but has first to undergo certain changes in the liver; these consist in the conversion of saturated into unsaturated fats by the removal of hydrogen. A saturated fat, *e.g.* stearin, is one in which the affinities of all the carbon atoms are satisfied, whereas an unsaturated fat, such as olein, is one in which the affinities of two or more of the carbon atoms are unsatisfied and the carbon atoms are united by a double bond. Thus oleic acid has the formula, $C_8H_{17} . CH : CH . C_7H_{14} . COOH$, and has one double bond.

The fatty acids present in the liver contain two, three, or even four double bonds, each of which represents a weak spot in the long chain of carbon atoms; and an unsaturated fatty acid tends to split at these points with the formation of smaller molecules. The unstable fatty acids formed by the liver are carried to the muscles and other tissues, in which they enter the complex protoplasm of the living cells, and are finally oxidised to carbonic acid and water.

During starvation the fat in the body is used by the tissues as their chief source of energy, and the liver is called upon to desaturate fat in larger amount and thus render it available for use by the tissues. The liver takes up more fat from the blood and, at the same time, fat passes in larger amount from the fat-depôts into the blood. The fat passes to the liver from the fat-depôts more rapidly than it can be desaturated, and an accumulation of saturated fat takes place in the liver ; this accumulation, which is termed *fatty infiltration*, readily occurs in starvation, and equally readily passes off again when food is given. It takes place, not only in starvation, but whenever the tissues need a larger supply of fat, for example in diabetes, and usually occurs only when the liver-cells are free or almost free from glycogen.

The nature of the process whereby the subcutaneous tissues and omentum take up fat after a meal and give it off to the blood again in times of need is not known, though it has been supposed to be due to the reversible action of an enzyme (lipase) in the fat-cells.

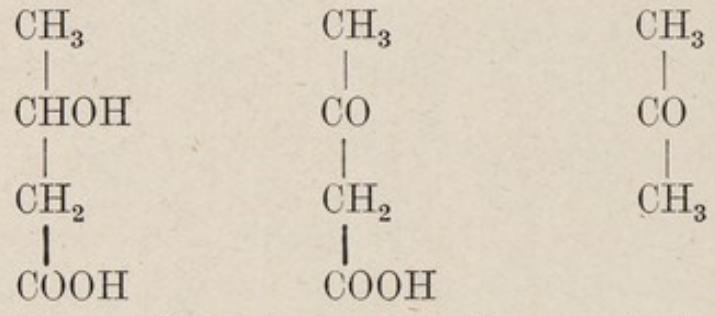
In a man whose weight remains steady the fat taken in the food is rapidly used in supplying energy in the body, and little or none of it is permanently stored in the fat-depôts. When weight is being put on, a certain proportion of fat in the food is stored up instead of being oxidised, and fat also may be formed from carbohydrate. On the contrary, loss of weight during starvation, or produced by some other means, involves depletion of the store of fat in the body. The fat normally stored represents a reserve of potential energy which can be increased, or which, in time of need, can be drawn upon for the use of the muscles and other tissues ; and the calorie-value of fat is so high that the energy which may be thus kept in reserve is very considerable.

The fats in the tissues are combined in such a way that they can no longer be recognised histologically, although their presence is made manifest by chemical analysis of the tissue. A healthy kidney, for instance, when stained with Sudan III, may show only a few specks of fat here and there, although, when analysed, it is found that 18 to 20 per cent. of its dried substance is fat. Under the influence of certain poisons (*e.g.* phosphorus), and in some diseases, the combination of fat with the rest of the protoplasm is broken, and the fat is set free in such a form that it can be stained and recognised under the microscope. This change, which is called *fatty degeneration*, was formerly believed to be the result of the formation of fat from protein. Chemical analysis of such an organ shows, however, that it contains no more fat than would be found in a healthy organ. Hence fatty degeneration implies, not the formation of fat from protein, but

merely the setting free, in a visible form, of previously combined fat.

When fat is oxidised in the tissues, the final products are carbonic acid and water; in all probability the long chain of carbon atoms constituting a fatty acid is broken down in stages, two carbon atoms being split off at each stage, and converted into carbonic acid. The complete oxidation of fat, however, is dependent upon the presence of carbohydrate in the tissue-cells.

When the tissues are deprived of carbohydrate, for example during starvation or on a diet free from carbohydrate, the oxidation of fat is incomplete, and intermediate metabolic products are formed in the tissues and pass into the blood and urine. These products are β-oxybutyric acid, aceto-acetic (diacetic) acid, and acetone, their chemical relationship being shown as follows :—



β-oxybutyric acid. Aceto-acetic acid. Acetone

In all probability β-oxybutyric acid and aceto-acetic acid are normally formed in the body during the metabolism of fat, but are fully oxidised. In the absence of carbohydrate they pass into the blood-stream, and aceto-acetic acid, instead of undergoing oxidation, is converted into acetone. The origin of these bodies from fat is clearly shown by the observation that, when the diet consists solely of fat, their amount in the urine may become very large. Further, there is evidence that aceto-acetic acid can also be formed from amino-acids, notably from leucine and tyrosine. β-oxybutyric acid and its products are formed to some extent at least in the liver. The presence of these substances in the urine is an indication that the supply of carbohydrate to the tissues is inadequate.

Acidosis.—When β-oxybutyric acid and aceto-acetic acid are present in the blood in appreciable amount, they combine with ammonia which would otherwise be converted into urea. They also react with sodium bicarbonate in the blood-plasma, thereby reducing the "alkali-reserve." The acids are neutralised by the ammonium and sodium, and the reaction of the blood remains almost or quite unchanged; the amount of ammonia excreted in the urine serves as a rough index of the extent to which these

acids are being formed in the body. These (and other) effects, produced by the passage of fixed acids from the tissues into the blood, constitute the condition known as *acidosis*. Acidosis may also arise as a result of the injection of acids into the circulation.

Test for Acetone in Urine.—A few c.c. of urine are saturated with ammonium sulphate, and a few drops of ammonia are added; on the addition of a drop or two of a freshly prepared solution of sodium nitro-prusside a beautiful purple colour is slowly produced, which varies in depth with the amount of acetone present, and fades after a short time. Aceto-acetic acid also gives this test, which is called Rothera's test.

Tests for Diacetic Acid in Urine.—(1) On adding a solution of ferric chloride, in excess of that required to precipitate the phosphates, the appearance of a deep red colour indicates the presence of diacetic acid.

(2) *Hurtley's Test.*—2·5 c.c. of concentrated hydrochloric acid and 1 c.c. of a 1 per cent. solution of sodium nitrite are added to 10 c.c. of urine, which is then allowed to stand for two minutes. 15 c.c. of strong ammonia and 5 c.c. of a 10 per cent. solution of ferrous sulphate are added: the mixture is shaken, poured into a glass cylinder, and allowed to stand. A violet or purple colour is slowly produced if aceto-acetic acid is present. The test is extremely delicate.

There is no simple test for β-oxybutyric acid.

Since carbohydrate is readily converted into fat in the body, it might be expected that the converse change would also occur. Such a possibility is indicated by the fact that in hibernating animals the respiratory quotient is low, and may fall even to 0·3. A quotient of this size could occur if fat were being transformed into glucose, since, in such a process, much of the oxygen taken into the body would not reappear as carbonic acid.

SECTION III

THE METABOLISM OF CARBOHYDRATE

The carbohydrates are absorbed from the digestive tract and enter the blood-stream mainly as glucose, and to a small extent as fructose and galactose. The arterial blood contains 0·1 to 0·15 per cent. of glucose, and this amount is not increased after a carbohydrate meal, even though, in such circumstances, 100 grams or more of sugar may be rapidly absorbed from the digestive tract into the portal blood. The sugar in the portal blood, however, does vary in amount, being slightly less than that in the general circulation during starvation, and distinctly greater after a carbohydrate meal; and it is clear that the sugar absorbed

during digestion undergoes some change as the blood passes through the liver. This change consists in the conversion of sugar into *glycogen*, which is stored in the liver-cells.

Preparation of Glycogen.—A rabbit is killed a few hours after a meal rich in carbohydrates, and the liver is rapidly excised, chopped into small pieces, and thrown into boiling water. After two or three minutes the pieces of liver are taken out of the water, ground up with sand, and returned to the boiling water, which is made slightly acid with acetic acid. The mixture is boiled for a minute or two and is then filtered; the coagulated proteins remain behind, and the filtrate, which is free from protein, is an opalescent solution containing glycogen.

Glycogen, like dextrin, gives a mahogany-brown colour with iodine, and does not reduce Fehling's solution; when boiled with dilute mineral acids it is converted into glucose. It differs from dextrin, first, in forming an opalescent solution, whereas a solution of dextrin is clear, and, secondly, in being precipitated more readily by alcohol. Further, glycogen is precipitated by basic lead acetate, which does not precipitate dextrin.

If the liver is kept for some hours before being treated in the manner just described, the filtrate contains an abundance of glucose, but no glycogen. The amount of glycogen present in the fresh liver varies with the previous condition of the animal, and, if the latter has been well fed, may form 10 per cent. of the total weight of the liver. When an animal has been starved for a few days, and particularly if during this period it has been made to take exercise, the liver may be almost free from glycogen. Both in the well-fed and in the starved animal the percentage of sugar in the arterial blood remains unaltered. These observations can be confirmed by histological examination of the liver. When the liver of a well-fed animal is hardened in alcohol and examined microscopically, the cells are seen to be full of glycogen, which can be stained with iodine (fig. 175); and the protoplasm may be reduced to a meshwork in the spaces of which the glycogen lies. Histological examination of the liver of a starved animal shows that glycogen is present in very small amount.

From these and other observations Claude Bernard, who discovered glycogen, concluded, first, that the sugar absorbed from the digestive tract entered the portal blood, and that the liver removed the sugar from the blood and stored it as glycogen. Secondly, he believed that the percentage of sugar in the systemic blood normally remained constant, and that, as the sugar was removed from the blood by the tissues for their metabolism, some glycogen was converted into sugar by the liver; this passed

into the general blood-stream, thereby keeping the percentage of sugar in arterial blood at the normal level. He regarded the rapid conversion of glycogen into sugar after death as being due to a ferment, the activity of which was no longer controlled, as it had been during the life of the animal. This view has been generally accepted, and glycogen may be regarded as a store of carbohydrate which is increased at each meal, and which is continuously being drawn upon by the tissues. In all probability the conversion of glycogen into sugar, and of sugar into glycogen, is carried out by a ferment which has a reversible action. We may perhaps regard glycogen as a sort of current account, which fluctuates from day to day, whereas the store of fat in the body represents a more permanent reserve, or capital account, which can be called upon in times of stress.

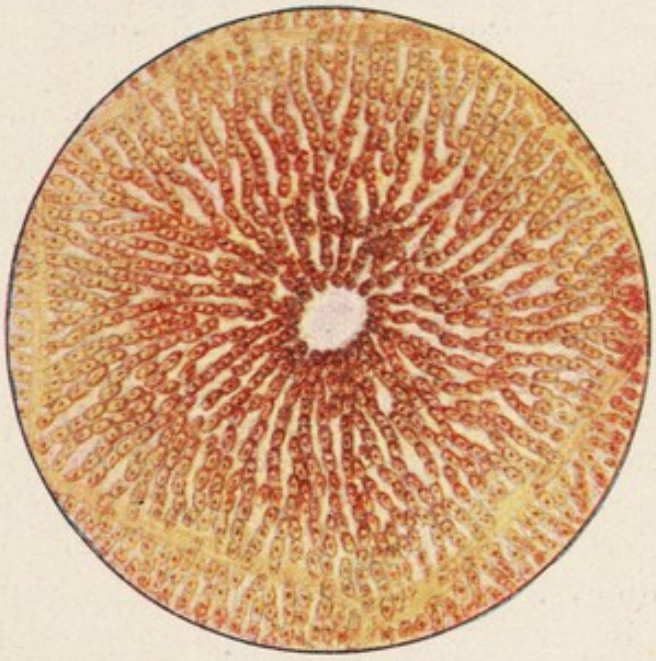


FIG. 175.—Section of a lobule of a rabbit's liver, stained with iodine. Glycogen stained reddish-brown. × 50.

Although the main source of glycogen is carbohydrate food, it can also be formed to some extent from protein, since, when an animal is starved until its liver is presumably free from glycogen and is then killed shortly after a large meal of protein, some glycogen is found in its liver. There is no evidence that glycogen can be formed from fat except perhaps in hibernating animals.

Glycogen is found most abundantly in the liver, but it occurs in muscles, being especially plentiful in fœtal muscles, and it is also present in the white blood-corpuscles.

FATE OF SUGAR

The carbohydrate taken into the body ultimately undergoes one of two changes. Some of it, more particularly in herbivora, is converted into fat; the remainder passes from the blood to the tissues, where it is oxidised and used as a source of energy. There is direct evidence that sugar is made use of by the tissues.

Using the heart-lung preparation (p. 223), Starling found that the normal heart used up sugar at the rate of about 4 milligrams per gram of heart per hour. Further indirect evidence to the same effect is furnished by the fact that the glycogen disappears most rapidly from the liver when the functional activity of the tissues is greatest. Thus severe muscular exercise or the convulsions induced by strychnine lead to the rapid diminution of the amount of glycogen in the liver. Neither the conditions which determine the taking up of sugar by the tissues from the blood, nor the intermediate stages in its oxidation, are fully known, but it is probable that lactic acid and pyruvic acid are intermediate products in the conversion of sugar into carbonic acid and water.

Some light is thrown on the conditions which influence the setting free of glucose from the liver and its further oxidation in the tissues by certain abnormal conditions in which glucose appears in the urine, and which are known as glycosuria.

Glycosuria.—The urine normally contains from 0·03 to 0·05 per cent. of glucose, and does not reduce Fehling's solution; the term glycosuria is only used when the urine contains glucose in sufficient amount definitely to reduce such a solution. This may occur in a variety of circumstances. (1) If glucose is injected into the circulation or under the skin, the percentage in the blood rises (hyperglycæmia), and the sugar is at once excreted by the kidneys. A similar condition, known as *Alimentary Glycosuria*, is observed when very large amounts of glucose are taken by the mouth. The ingestion of starch, even in large quantities, does not lead to glycosuria, since its digestion and absorption are sufficiently slow to allow the liver to convert the sugar into glycogen.

(2) *Adrenalin Glycosuria.*—The injection of a small quantity of adrenalin into the circulation is often followed by the appearance of glucose in the urine; at the same time glycogen disappears from the liver, and the percentage of sugar in the blood is increased. Evidently the adrenalin causes the liver to discharge its glycogen into the blood as glucose, which is excreted by the kidneys. Glycosuria may also occur under any conditions in which adrenalin is set free into the blood-stream in larger amount from the suprarenal glands. For example, it may follow stimulation of a splanchnic nerve or chloroform anæsthesia.

(3) *Diabetic Puncture.*—Claude Bernard was the first to show that puncture of the floor of the fourth ventricle in rabbits is followed by hyperglycæmia, glycosuria, and the disappearance of glycogen from the liver; if the animal has been previously

starved to rid its liver of glycogen, glycosuria does not follow the puncture. This experiment was regarded by Bernard as a further proof of his theory as to the function of glycogen in the body. The diabetic puncture fails to produce glycosuria after division of the splanchnic nerves or removal of the suprarenal glands, and, in all probability, the puncture stimulates the medulla oblongata in such a way that adrenalin is set free into the circulation and causes glycosuria.

(4) *Phloridzin Glycosuria.*—Phloridzin is a glucoside which, on hydrolysis, yields glucose and phloretin. A small amount of phloridzin or phloretin, when injected into an animal, produces glycosuria and the disappearance of glycogen from the liver; but phloridzin glycosuria differs from those just described in that the percentage of sugar in the blood is not increased, but tends rather to be diminished. Phloridzin acts upon the kidneys, as may be shown by collecting the urine separately from the two kidneys, and injecting a small dose of phloridzin into one, *e.g.* the right, renal artery; the urine flowing from the right kidney is then found to contain sugar five to eight minutes before it appears in the urine from the opposite kidney. The drug appears to act directly upon the cells of the renal tubules, and this view is supported by the observation that the repeated administration of phloridzin produces definite histological changes in the cells of the renal tubules.

When repeated doses of phloridzin are given to an animal, the glycosuria persists after the glycogen has disappeared from the liver, and even when the animal is not receiving carbohydrate food. The sugar in this case is not derived from carbohydrate, but is formed from protein. This is shown by the fact that, if the animal receives no food, the ratio of the amount of glucose in the urine to that of nitrogen, expressed as $\frac{G}{N}$, becomes constant, varying in different animals from 2·5 to 3·5. The constancy of the ratio shows that the glucose and nitrogen must have a common source and that, since the urinary nitrogen is formed by the breaking down of protein, the glucose must also originate from protein. Further, it has been found that the administration of amino-acids to such an animal increases the amount of glucose excreted in the urine. For example, in one experiment, the ingestion of 20 grams of alanine led to the appearance of as much sugar in the urine as did the ingestion of 16 grams of glucose.

Owing to the energy lost to the body by the passage of sugar into the urine, the tissues are compelled to use an excessively large amount of protein as a source of energy, and the rapid

disintegration of protein increases the output of nitrogen in the urine, the animal wastes, and its condition resembles that seen in severe diabetes.

(5) *Experimental Diabetes.*—The complete removal of the pancreas in dogs and other animals is followed in a few hours by glycosuria, which soon becomes very severe. The animals waste rapidly, the urine contains β-oxybutyric acid and acetone, as well as glucose, and death occurs in one to two weeks. During life the urine contains an excess of sugar, and after death the liver is found to be almost free from glycogen. These symptoms are not due to the absence of the pancreatic juice from the digestive tract, since ligature of the pancreatic duct does not lead to glycosuria. Nor do they occur if a small portion, one-tenth or more, of the pancreas is left in the body, although the subsequent removal of this fragment is followed by the train of symptoms just described.

Some light has been thrown on the nature of experimental diabetes by a study of the respiratory quotient in this condition. It has been pointed out (p. 388) that the respiratory quotient furnishes an index of the kind of food-stuff which is being oxidised in the tissues, and that in the normal animal it varies with the character of the diet ; it is low on a diet free from carbohydrate, and high when food contains abundant carbohydrate. After removal of the pancreas the respiratory quotient is low, even on a liberal carbohydrate diet, and although the blood reaching the tissues contains an excess of sugar (hyperglycæmia). The conclusion has been drawn, therefore, that in experimental diabetes the tissues are unable to take up and to utilise the sugar presented to them by the blood, and that, as a result, sugar accumulates in the blood and is excreted by the kidneys. There is evidence, however, that, even after complete removal of the pancreas, the power of the tissues to oxidise sugar is not completely lost. The heart of a diabetic dog still possesses some power of taking up sugar from the blood and of utilising it, though to a lesser degree than in the normal animal. Further, the respiratory quotient in dogs after extirpation of the pancreas can be slightly raised by a liberal carbohydrate diet, though it never reaches the normal level.

It is generally assumed that the pancreas furnishes an internal secretion, that is to say, some substance which passes directly into the blood-stream, and that this substance links the sugar to the tissue-cells ; in the absence of this link the tissues are unable to take up sugar, and therefore cannot oxidise it. The formation of the internal secretion is attributed by many observers to the islets of Langerhans, which are scattered throughout the

pancreas (fig. 164). The cells forming these islets differ in appearance from the secretory cells of the acini of the pancreas, and contain numerous fine granules which do not stain with eosin, as do the secretory granules, but can be stained by neutral gentian. Further, the islets do not communicate with the secretory ducts, and are clearly not concerned with the formation of pancreatic juice.

That the islets probably take some part in carbohydrate metabolism is shown by two observations. In the first place, ligature of the pancreatic duct leads, eventually, to atrophy of the secreting tissue, but the islets are unaffected and glycosuria does not occur. In the second place, it might be expected that, if the islets produce an internal secretion essential for normal carbohydrate metabolism, the removal of the greater part of the pancreas would lead to over-activity of the islets still remaining in the body, which might be demonstrated by histological or other methods; and this has been found to be the case. When the pancreas is almost completely removed, only a small fragment being left intact, the animal remains well for a time, but eventually develops diabetes of a mild character. Subsequent examination of the small pieces of pancreas left in the animal reveals the fact that the tissue of the islets has lost its granules, and has undergone other histological changes. It has yet to be proved, however, that these changes are the cause and not a result of the diabetes.

The failure of the tissues to utilise carbohydrate also affects the metabolism of both fat and protein. In the first place, the oxidation of fat is incomplete, and acetone, β-oxybutyric and aceto-acetic acids appear in the urine. In the second place, since carbohydrate is not available, the tissues are compelled to rely solely on fat and protein as sources of energy for the production of heat and the performance of work; as a result the excretion of the end-products of protein metabolism in the urine is increased. Indeed, it is probable that, although glycosuria is the most obvious symptom of experimental diabetes, this condition also involves serious disturbance of many other metabolic processes in the body.

(6) *Diabetes in man* is a progressive disease characterised by glycosuria, and due to a gradual failure of the tissues to assimilate and oxidise glucose; this is shown by the fact that, in severe cases, the respiratory quotient is low, even when the diet contains abundance of carbohydrate. The blood contains an excess of glucose, and at first this is derived only from carbohydrate. Eventually glucose is also formed from protein, and, even on a diet almost free from carbohydrate, large amounts of glucose may be excreted in the urine, and the G : N ratio may be high.

In the later stages of the disease, the urine also contains β-oxybutyric acid, aceto-acetic acid and acetone, often in large amount.

Many patients finally pass into a state of coma, associated with slow, deep breathing (air-hunger), and die in a few hours. These symptoms were formerly attributed to an *acid intoxication* caused by the accumulation of β-oxybutyric acid in the blood and a consequent increase in its H-ion concentration. Recent observations have shown, however, that in diabetic coma the reaction of the blood may be absolutely normal, and that the symptoms are not due to acid intoxication. There is some evidence that coma may be the result of a direct poisonous action of the salts of aceto-acetic acid on the nervous system. After death the liver is almost free from glycogen; in most cases the pancreas shows signs of disease, though in others it appears normal. Whether diabetes depends upon the deficiency or absence of an internal secretion from the pancreas is not known, though from analogy with experimental diabetes this seems very probable.

SECTION IV

THE METABOLISM OF PROTEIN

It has already been pointed out (p. 374) that the products of the digestion of protein are absorbed almost entirely as amino-acids, which pass into the blood-stream. They are then taken up from the blood, partly by the liver and partly by the muscles and other tissues, and rapidly undergo a change which is called *deamination*.

Deamination.—This consists in the removal of the amino-group, and its replacement either by oxygen or by a hydroxyl radicle. A simple illustration of this change is represented in the following equation :—

$$\underset{\text{Alanine.}}{CH_3 . CH . NH_2 . COOH} + H_2O = \underset{\text{Lactic acid.}}{CH_3 . CHOH . COOH} + NH_3.$$

The amino-acids are thus converted into either oxy- or keto-acids, which on reduction become ordinary fatty acids. This change is probably brought about by an enzyme, and takes place chiefly in the liver and to a smaller extent in other tissues. Its occurrence in the liver is proved by the observation that, when amino-acids are added to pounded liver-substance under aseptic conditions, the amount of ammonia rapidly increases. The removal of the amino-group does not appreciably diminish the calorie-value of amino-acids, or their usefulness as a source of

energy to the body. Thus 89 grams (1 gram-molecule) of alanine, when fully oxidised, give out 389 calories ; if its amino-group is replaced by hydroxyl, alanine is converted into 90 grams (1 gram-molecule) of lactic acid, which, if completely oxidised, would yield 329 calories.

In the course of the digestion of protein some ammonia is set free in the small intestine. This is absorbed by the villi, and carried in the portal circulation to the liver.

FORMATION OF UREA

The ammonia set free by the deamination of amino-acids in the muscles and other tissues is carried to the liver, and, together with that similarly formed in the liver itself, is converted into urea. If we regard the ammonia set free as entering into combination with carbonic acid to form ammonium carbonate or carbamate, the change taking place in the liver may be represented thus :—

(1) $$OC\begin{matrix}O-NH_4\\O-NH_4\end{matrix} - 2H_2O = OC\begin{matrix}NH_2\\NH_2\end{matrix}.$$
Urea

(2) $$OC\begin{matrix}ONH_4\\NH_2\end{matrix} - H_2O = OC\begin{matrix}NH_2\\NH_2\end{matrix}.$$

The formation of urea in the liver has been proved in several ways. In the first place, when the liver of a recently killed animal is removed from the body and perfused with oxygenated blood to which ammonium carbonate or carbamate is added, the ammonium salt gradually disappears from the blood, being replaced by urea ; this change does not occur when blood containing ammonium salts is perfused through other organs.

Secondly, it is possible to unite the portal vein with the inferior vena cava in such a way that the blood flowing from the digestive tract along the portal vein is diverted into the vena cava, and thus into the general circulation, without going through the liver ; the fistula between the two veins is known as Eck's fistula. The liver is still supplied, in this case, with blood through the hepatic artery. Dogs in which such a fistula has been made remain well when their diet consists chiefly of carbohydrate, but when they are fed on meat, or receive ammonium salts or amino-acids by the mouth, they become convulsed ; during the convulsions their arterial blood contains four or five times as much ammonia as is

present in a normal animal, and the percentage of ammonium salts in the urine rises. It may be concluded that the liver, when supplied only with blood by the hepatic artery, no longer converts into urea the large amounts of ammonia entering the blood after a protein meal.

Thirdly, in extensive disease of the liver in man, the amount of ammonia in the urine is increased, and the amount of urea is correspondingly diminished. It is thus evident that the formation of urea from ammonium salts takes place solely in the liver, probably by the action of a ferment.

Urea can also be formed in other parts of the body and from other substances than ammonium salts, the most important of these being arginine. Arginine occurs in the tissues, and can be broken down by a ferment known as arginase into urea and ornithin ; this ferment is most abundant in the liver and kidneys.

ENDOGENOUS AND EXOGENOUS METABOLISM

When the composition of the urine excreted in 24 hours by a man taking very little protein food is compared with that of the same person when taking an abundance of protein food, very great differences are observed, and are shown in the following table (Folin) :—

	Abundant Protein Diet.	Percentage of Total Nitrogen.	Low Protein Diet.	Percentage of Total Nitrogen.
Quantity of urine	1170 c.c.	...	385 c.c.	...
Total nitrogen . .	16·8 grams	...	3·6 grams	...
Urea . . .	14·7 ,,	87·5	2·2 ,,	61·7
Ammonia . .	0·49 ,,	3·0	0·42 ,,	11·3
Uric acid . .	0·18 ,,	1·1	0·09 ,,	2·5
Creatinine . .	0·58 ,,	3·6	0·60 ,,	17·2
Total SO_4 . .	3·64 ,,	...	0·76 ,,	...
Inorganic SO_4 .	3·27 ,,	...	0·46 ,,	...
Ethereal SO_4 .	0·19 ,,	...	0·10 ,,	...

The amount of urea and sulphates in the urine is greatly increased by a protein meal, whereas the creatinine is but little affected, this difference being due to the fact that the metabolism of protein in the body is of two kinds, *endogenous* and *exogenous*. The metabolic changes concerned in the production of creatinine and much of the uric acid are known as endogenous metabolism, since these substances are formed by the breaking down of protein and nucleic acid respectively in the tissues as part of their ordinary wear and tear, and are unaffected by the amount of protein food eaten, unless this contains creatinine or nucleic acid. On the

contrary, the amount of urea and inorganic sulphates in the urine depends chiefly upon the quantity of protein in the food, the urea being formed mainly from the ammonia set free by the deamination of the amino-acids absorbed into the blood-stream during digestion. The sulphur of the inorganic sulphates is derived from the sulphur present in protein, being split off and oxidised without being built up into the tissues. The formation of urea and sulphates thus represents a change taking place in the amino-acids before they undergo metabolism in the muscles and other tissues, and is independent of the metabolic changes in the tissues themselves. For this reason, the formation of urea and sulphates is described as exogenous metabolism. But some urea is also derived from the breaking down of the proteins of the tissues themselves, and is therefore endogenous in origin; and the whole of the urea appearing in the urine during starvation is formed from tissue-protein.

The correctness of this view is proved by the rapidity with which urea is excreted in the urine after a protein meal; the excretion of urea begins to increase within two hours after the meal, and, within five hours, half the total nitrogen taken in with the food may be excreted as urea. It would be almost impossible for the body to have built up the amino-acids into the living tissues, and to have broken them down into urea within so short a time. The amount of urea in urine, therefore, serves as an index, not of the total katabolism of protein in the tissues, but of the quantity of protein taken in the food; and the removal of ammonia from amino-acid, and its rapid excretion as urea, furnishes a means by which the body rids itself of nitrogen which is not needed, while retaining the resulting oxy-acids as a source of energy.

Endogenous Metabolism.—The amino-acids formed during the digestion of protein serve two purposes in the body.

(1) The greater part of the amino-acids, after being deaminated, is carried to the tissues and oxidised to carbonic acid and water, thereby serving as a source of energy. In this respect protein has no advantage over other food-stuffs as a source of energy, since the amino-acids are converted by the removal of their amino-group into fatty acids.

(2) A certain proportion of the amino-acids is built up in the tissues into living substance to replace that which is constantly being broken down. The proteins in the tissues of different animals and of different tissues in the same animal vary in composition; and the synthesis in each tissue of its characteristic proteins is made possible by the previous disintegration of the proteins in the food into their ultimate constituents, namely

amino-acids. These acids are often spoken of, therefore, as "building-stones" which can be put together in varying combinations in the building up of different proteins present in the tissues of the body. Convincing proof that the tissue-proteins are synthesised from amino-acids is furnished by the following experiment. If an animal receives as its sole nitrogenous food the mixture of amino-acids formed by the prolonged pancreatic digestion of casein, with the addition of fat, carbohydrate, salts and water, it remains in good health and may gain weight.

Hopkins has applied this method to the study of the part played by individual amino-acids in the building up of protein, and has shown that animals fed on the diet just described, except that tryptophane is absent from the mixture of amino-acids, rapidly lose weight and die. Hence tryptophane is essential for the synthesis of the tissue-proteins. On the contrary, if only glutamic and aspartic acid are absent from the diet, the animals remain well and gain weight.

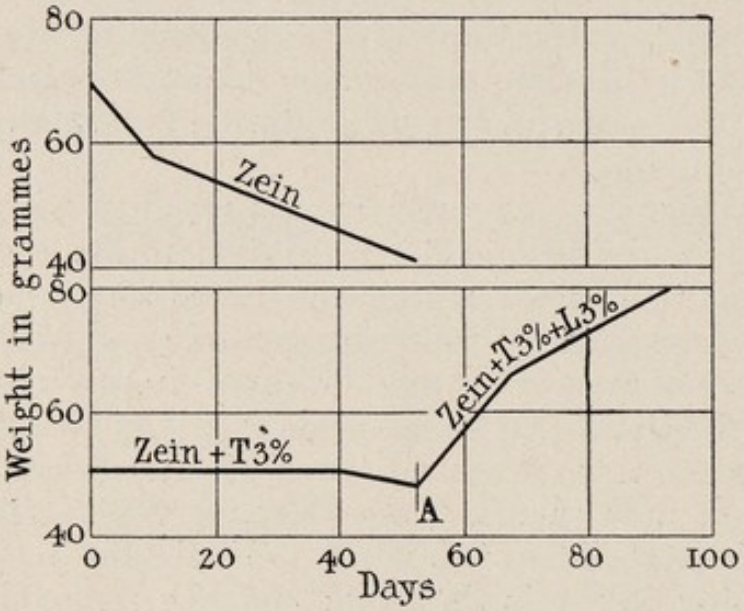


FIG. 176.—Chart showing the effect of different diets on the weight of young rats. (After Osborne and Mendel.)

T = tryptophane; L = lysine.

Experiments of this kind make it clear that the amino-acids fall into two groups. (1) One group, which includes tryptophane, tyrosine, phenyl-alanine, arginine and histidine, is essential for the building up of the tissues and therefore for life; these compounds cannot be produced in the body and must be supplied in the food. Substances which are deficient in one or more of these groupings cannot act as tissue-builders in the body, and therefore cannot maintain life. Thus, zein, which is a protein in maize, contains neither tryptophane nor lysine, and young animals fed on zein, with the addition of fat, carbohydrate, salts and water, rapidly lose weight, and die after a short time. Animals fed on the same diet, with the addition of tryptophane, remain well and maintain their weight; and if lysine, as well as tryptophane, is added to the diet, normal growth occurs (fig. 176).

It has also been observed that young animals fail to grow when their sole protein food is gliadin, which contains no lysine, although adult animals can maintain their weight on this diet. Lysine appears, therefore, to be essential for growth, but not for the maintenance of the body. Further, some of the amino-acids seem to be necessary for the production of certain definite substances in the body, one of which perhaps is adrenalin.

(2) The other group, including most of the other amino-acids, is not essential to life, and is used in the body chiefly as a source of energy. If these acids are not supplied in the food, some of them, for example, glycine, can be formed by the tissues, probably from ammonia and carbohydrate derivatives.

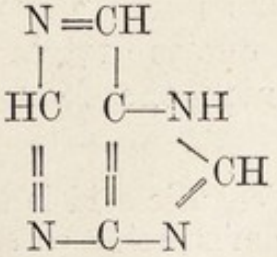
Further, in the course of their metabolism in the tissues, the amino-acids stimulate metabolism as a whole and largely increase the production of heat in the body ; this influence is called the *specific dynamic action* of protein.

Comparatively little is known as to the intermediate stages in the breaking down of protein in the tissues, though the composition of the urine during starvation shows that the end-products include urea, uric acid, and creatinine.

PURINE METABOLISM

The nucleo-proteins of the food are broken down in the digestive tract first into nuclein and protein, the nuclein subsequently undergoing further digestion with the setting free of nucleic acid, which is absorbed unchanged. Nucleic acid, when hydrolysed, is found to consist of the following bodies :—(1) phosphoric acid, (2) the amino-purines, guanine and adenine, (3) pyrimidine bases, and (4) a carbohydrate, which is usually a pentose in vegetable nucleic acids and a hexose in those of animal origin. The same products are yielded by the disintegration of the nucleins present as nucleo-protein in the tissues. The nucleic acids found in the different tissues vary in composition, and do not necessarily contain all the constituents just mentioned.

The purine bodies are all derivatives of a substance called purine, $C_5H_4N_4$, which has the constitutional formula :—



Purine itself is of purely theoretical interest, but five of its derivatives are found in the body, namely :—

Hypoxanthine (monoxy-purine) .	$C_5H_4N_4O$.
Xanthine (dioxy-purine) . .	$C_5H_4N_4O_2$.
Adenine (amino-purine) . .	$C_5H_3N_4.NH_2$.
Guanine (amino-oxy-purine) . .	$C_5H_3N_4O . NH_2$.
Uric acid (trioxy-purine) . .	$C_5H_4N_4O_3$.

After its absorption the nucleic acid taken as nucleo-protein in the food is broken down by a series of enzymes, called *nucleases*, which are found in many tissues, notably the liver and spleen, first into complex groupings called nucleotides, and then into adenine, guanine, and other bodies. Other ferments subsequently convert adenine and guanine by a process of deamination into hypoxanthine and xanthine. Finally, a third set of enzymes oxidise hypoxanthine to xanthine, and the latter to uric acid. Uric acid is thus the end-product of the action of these enzymes on nucleic acid.

The amount of uric acid appearing in the urine does not represent the whole of that formed from the nucleo-proteins of the food, but is derived partly from them, forming exogenous uric acid, and partly from the breaking down of the nucleins in the tissues, endogenous uric acid. It will be seen from the table on p. 402 that, as a rule, half the uric acid in the urine is of endogenous, and half is of exogenous, origin.

When the diet is free from nucleo-protein, the excretion of endogenous uric acid is extremely constant, but it is increased after severe muscular exercise, and also in fever, owing to a greater breaking down of the nuclei in the cells of the body.

The exogenous fraction varies in amount with the character of the diet, being absent when this contains no nucleo-protein, and increased by foods such as kidney, sweetbread, and liver, which are rich either in nucleo-protein or in the precursors of uric acid, such as hypoxanthine.

Normally the nucleins broken down in the wear and tear of the tissues are probably replaced by the synthesis of fresh nucleo-protein from the purine material taken in the food. If the diet is free from nucleo-protein, this must be manufactured in the body from amino-acids ; and it has been shown that the amino-acids required for this purpose are arginine and histidine. In the growing infant, nucleo-protein is rapidly being laid down in the body, although the food (milk) contains hardly any nucleo-protein.

In birds and reptiles, uric acid is the chief end-product of protein metabolism, and, if amino-acids or ammonium lactate are perfused

through the surviving liver of a bird, uric acid is formed. Further, the existence in birds of a vein (Jacobson's vein) connecting the mesenteric vein with the renal portal vein renders it possible to excise the liver in birds without stopping the circulation through the digestive tract. It is found that, after excision of the liver in a goose, the formation of uric acid is greatly diminished, its place being taken in the urine by ammonium lactate. It is believed, therefore, that most of the uric acid of bird's urine is formed by a process of synthesis from ammonia and lactic acid.

SECTION V

TOTAL METABOLISM

The separate consideration of the changes undergone by fat, protein, and carbohydrate, though convenient, represents very imperfectly the complex nature of the metabolic changes, as a whole, in the body. Not only does the presence or absence of each food-stuff modify the character of the metabolism of the other food-stuffs but, within certain limits, one kind of food-stuff can be transmuted into another. In other words, many of the chemical changes occurring in the tissues and constituting metabolism are reversible. For example, glucose can be formed from some amino-acids, and, conversely, amino-acids may be produced from ammonia and carbohydrate derivatives. The possible course taken in the body by many of these reactions is indicated in the following scheme :—

Scheme (modified from Bayliss). Double arrows represent a reversible reaction—

Glucose.
↓ ↑
Glyceric aldehyde ⇄ Glycerol.
↓ ↑
Pyruvic aldehyde ⇄ Alanine.
↓ ↑
Lactic acid.
↓
Acetaldehyde → Aceto-acetic acid.
↓
Acetic acid.
↓
Carbonic acid and water.

Nevertheless, the metabolism of the amino-acids differs from that of fat and carbohydrate in some important respects. In the first place, both fat and carbohydrate can be stored in the body as a reserve, whereas this holds to a very small extent for protein.

In the second place, fat and carbohydrate are used mainly as a source of energy, and for this purpose they can be almost entirely replaced by protein; but fat and carbohydrate can only replace protein to a limited extent, since some of the amino-acids required for the building up of protein cannot be formed in the body. It is clear, from these considerations, that the general character of metabolism must be greatly influenced both by the nature of the food and by the absence of one or more of the foodstuffs from the diet.

Starvation.—The metabolism during starvation has been studied in professional fasting men, and also in the lower animals. When food is withheld, the store of glycogen in the body is rapidly used up, and after two or three days the animal derives its energy solely from fat and protein. The metabolism as a whole is diminished, and the consumption of protein is reduced as far as possible, most of the energy needed by the body being obtained by the oxidation of the fat previously present in the fat depôts. After three or four days the output of nitrogen in the urine reaches a low level, which is maintained until the body-fat has been used up and the sole available source of energy is the tissue-protein. When this stage is reached, the output of nitrogen in the urine shows a sudden rise for a day or two, this being followed by a rapid fall in the excretion of nitrogen and by the death of the animal.

The body loses weight, this being due, partly to the gradual consumption of the fat previously stored up in the depôts, partly to wasting of other tissues. The loss falls most heavily on the less vital organs, such as the muscles, whereas the heart and central nervous system lose little or no weight. The breaking down of protein during starvation is probably brought about by a process of *autolysis* or self-digestion in the tissues; the amino-acids formed by the disintegration of the less important tissues are carried in the blood-stream and made use of by the vital organs to make good their daily wear and tear. A similar process of autolysis has been observed in the salmon; during its stay in fresh water the salmon takes little or no food, and the development of the sexual organs, which takes place during this period, is effected at the expense of the skeletal muscles, which undergo autolysis. In man, the character of the metabolism of fat and protein is modified during starvation, as is shown by the appearance of creatine and of β-oxybutyric acid and aceto-acetic acid in the urine.

In man, the daily excretion of nitrogen in the urine during starvation falls to 9 or 10 grams or even less, and it might be expected that, if this amount of nitrogen were taken in the form of protein food, it would be used in replacing the daily disinte-

gration of tissue in the body, and would not appear in the urine. Experiment shows, however, that, in these circumstances, the additional protein is almost entirely used to supply energy to the body, and that almost all the nitrogen taken in the protein meal appears in the urine in addition to that which was previously being excreted, so that the disintegration of protein in the tissues is only slightly diminished. When protein is the sole article of diet, it is necessary, in fact, to give by the mouth a quantity of protein containing 3 to 5 times as much nitrogen as that which was previously being excreted during starvation in order to obtain a balance between the intake and output of nitrogen. This balance is called *nitrogenous equilibrium*. A further increase in the amount of protein taken by the mouth does not lead to a retention of nitrogen in the body, but the amount of nitrogen excreted increases until nitrogenous equilibrium is again reached at a higher level than before.

Day.	Intake of Protein.	Output of Nitrogen in Urine in Terms of Protein.
1	80 grams	80 grams
2	238 ,,	194 ,,
4	238 ,,	220 ,,
6	238 ,,	228 ,,
8	238 ,,	238 ,,

In the experiment recorded in the foregoing table the animal on the first day was in nitrogenous equilibrium. When it received three times as much protein, it again reached nitrogenous equilibrium in the course of the next seven days.

If the food does not consist solely of protein, but also contains fat and carbohydrate, most of the energy of the body is derived from the latter, and nitrogenous equilibrium can be maintained on a comparatively small amount of protein; in this case the protein is used mainly to repair tissue-waste.

The Sources of Muscular Energy.—The muscles form about 40 per cent. of the weight of the body, and their metabolic activity furnishes the greater part of the energy set free as heat or work in the body. This energy can be derived from all the food-stuffs, and the relative amount of the different food-stuffs used by the muscles during muscular exercise may be ascertained by observing (1) the total excretion of nitrogen in the urine, and (2) the respiratory quotient.

If protein is the principal or sole food, the amino-acids serve as a source of muscular energy, and the output of nitrogen in

the urine (which serves as an index of protein katabolism) is increased by muscular exercise. This has been clearly shown in dogs which were made to do work when fed entirely on lean meat; their bodies contained hardly any fat or carbohydrate, so that amino-acids must have been the chief source of muscular energy. If, however, as is usually the case, the diet contains an adequate supply of fat and carbohydrate, the excretion of nitrogen in the urine is not appreciably increased by muscular work, and the energy must be supplied by the oxidation of fat and carbohydrate.

The respiratory quotient varies with the nature of the food-stuffs which are undergoing oxidation in the tissues; and the fact that the respiratory quotient rises slightly during muscular work, whether the diet is rich or poor in carbohydrate, indicates that the active muscle obtains a rather larger proportion of its energy from carbohydrate than does the resting muscle. But, although

Nature of Diet.	Respiratory Quotient in Man.	
	Rest.	Work.
(1) Rich in carbohydrate .	0·85	0·90
(2) Poor in carbohydrate .	0·79	0·82

the active muscles appear to display some preference for carbohydrate as a source of energy, there is every reason to believe that the energy expended during muscular work is normally derived from the oxidation not only of carbohydrate but also of fat.

SECTION VI

THE LIVER

The liver consists of an enormous number of lobules, each having a diameter of about 1 mm.; they are roughly pear-shaped, and show facets on the surface from mutual compression of adjacent lobules. The narrow end of the pear is the point of emergence of a vein, the *intralobular* vein, which occupies the centre of a transverse section of the lobule. The substance of the lobule is composed of columns of cells, arranged radially in relation to the intralobular vein. The portal vein and hepatic artery enter, and the bile duct emerges from, the liver at the hilum. The three structures have a sheath of connective tissue, known as "Glisson's capsule," the whole forming the "portal

tract." The portal tract branches in a tree-like manner, the smallest divisions being interlobular. From the interlobular branches of the portal vein blood passes to the intralobular vein in each lobule through sinusoids, which lie between the columns of liver-cells. The sinusoids are wider than capillaries, and their walls are incomplete. The hepatic artery also opens into the sinusoids, supplying oxygenated blood for the nutrition of the liver-cells. The intralobular vein opens into a *sublobular* vein, and the sublobular veins unite to form the tributaries of the hepatic vein.

A liver-cell is roughly cubical in shape and contains a large spherical nucleus. Its protoplasm is granular, and in the well-fed animal contains small masses of glycogen, which in the fresh or alcohol-hardened liver can be stained brown with iodine (fig. 175). The cell contains iron in organic combination ; this can be demonstrated by treating the liver with dilute hydrochloric acid and ferrocyanide of potassium, a blue colour being produced. Small droplets of fat may also be present in the cells. Each cell is penetrated by fine canaliculi continuous with the bile-capillaries, and cavities are also described which communicate with the sinusoids. On the side of each cell applied to the adjacent cell is a channel, which, with a corresponding channel on the neighbouring cell, forms a bile-capillary. The bile-capillaries form a network, the contents of which flow into the small bile-ducts at the periphery of the lobule. The ducts are lined by cubical epithelium.

Most of the *functions* of the liver have already been considered in connection with digestion or metabolism, and it is only necessary at this point to summarise these functions.

The liver plays an important part in the metabolism of all three classes of food-stuffs, especially in the preliminary changes which they undergo after absorption. (1) It serves as a store-house for glycogen, which it forms from the carbohydrate absorbed during digestion, and which it converts into glucose and returns to the blood-stream in order to keep constant the percentage of sugar in the blood. (2) It desaturates the fatty acids reaching it from the fat-depôts, and prepares them for the further metabolic changes which occur in the tissues. (3) It removes the amino-group from part of the amino-acids absorbed from the digestive tract, converting them into keto- or oxy-acids, and transforming the ammonia thus set free, and also that reaching it from the portal vein, into urea. (4) In birds and reptiles, the liver forms uric acid instead of urea from amino-acids or ammonium lactate (p. 406).

Interference with these functions, which sometimes occurs in extensive disease of the liver in man, leads to the appearance

of intermediate metabolic products such as leucine, tyrosine, and other substances in the urine, and to disturbance of the normal course of the metabolism of fat ; similar effects are seen in animals poisoned with phosphorus, which greatly reduces the metabolic activity of the liver.

Apart from its metabolic activities, the other functions of the liver are the secretion of bile and the conversion of the blood-pigment into bile-pigment.

THE SPLEEN

The spleen is often included among the ductless glands, but it seems advisable to describe it in connection with metabolism, because (1) of its anatomical relations with the pancreas, intestines, and liver ; (2) there is no reliable evidence that it produces a hormone which would justify its classification with the other ductless glands (p. 457) ; (3) it is known to have an influence on purine metabolism.

The spleen is a solid organ enclosed in a capsule, which is partly fibrous and partly consists of plain muscular tissue. The capsule sends trabeculæ, also containing unstriated muscle, into the interior of the organ ; these branch to form a framework, in the interstices of which lies the splenic pulp. This consists of a fine meshwork of connective tissue fibrils, covered at the nodes by endothelial cells, and containing in its spaces lymphocytes, red blood-corpuscles, and large cells (splenic cells) which are amœboid and often contain partly broken-down red corpuscles. Multinucleated giant-cells are also occasionally present.

The outer coat of the arteries in the spleen consists of lymphoid tissue, an enlargement of which is present on each arteriole and forms a Malpighian corpuscle. Some capillaries are found in the Malpighian bodies, but, with this exception, the arteries open directly into the splenic pulp, from which the blood is again gathered up to leave the spleen in the splenic vein. The blood thus comes into direct contact with the tissue-elements of the spleen, whereas in almost every other organ of the body it is separated from the tissues by a capillary wall.

The flow of blood through the spleen is assisted by the alternate contraction and relaxation of the muscular tissue in its capsule and trabeculæ ; this rhythmic contraction, which takes place about once a minute, can be recorded by enclosing the spleen in a plethysmograph connected with a tambour. The muscular fibres are supplied with nerves from the sympathetic system, and the direct or reflex stimulation of these nerves, or the injection

of adrenalin, produces contraction of the muscle and diminution of the volume of the spleen.

The *functions* of the spleen are not fully known, but it is not essential to life, and can be removed without serious after-effects. The presence of partially disintegrated red blood-corpuscles in the phagocytic cells of the pulp indicates that the spleen is concerned in the destruction of red cells, but the extent to which this takes place is not known. The spleen normally contains a relatively large amount of iron, and, when the destruction of red cells in the body is excessive, this amount is increased. Further, the Malpighian bodies undoubtedly form lymphocytes.

In all probability the spleen also takes part in the production of uric acid, since it contains enzymes which can oxidise xanthine and hypoxanthine, converting them into uric acid. These purine bases are found in relatively large amount in the normal spleen, and, if splenic pulp is kept at the temperature of the body and supplied with oxygen, they disappear, giving place to uric acid. Moreover, if more xanthine or hypoxanthine is added to the pulp, these added purines undergo the same change.

In many infective diseases the spleen is enlarged, and it seems to play a part in the protection of the body against disease by removing micro-organisms from the blood, possibly also by destroying the poisons formed by such organisms.

CHAPTER XI

ANIMAL HEAT

From the point of view of their temperature, animals fall into two groups, namely (1) *poikilothermic*, or cold-blooded animals, whose temperature varies with that of their surroundings, and (2) *homoiothermic*, or warm-blooded animals, whose temperature remains constant except for slight daily variations, and is independent of that of their surroundings.

To the former group belong fishes and amphibia, to the latter birds and mammals, including man. In man the normal temperature is 37° C. (98·4° F.); it shows a daily variation of approximately 1° F., being highest in the afternoon and lowest in the early morning. It is lowered by starvation or prolonged lack of sleep, and is raised by muscular exercise. The constancy of the temperature is due to the fact that production and loss of heat balance each other.

Production of Heat.—The chemical changes in the body which constitute metabolism involve the production of heat, and this takes place chiefly in the muscles, and to a smaller extent in the liver and other glandular organs; the blood leaving the liver, for instance, is warmer than that entering it. The production of heat in the glandular organs is greatest during the periods of their activity associated with the digestion of food, and is comparatively constant from day to day. The heat formed in the muscles, however, varies greatly, being enormously increased by muscular exercise; and in warm-blooded animals the amount of heat formed in the body depends largely upon the degree of activity of the skeletal muscles. As has been pointed out (p. 35), the greater part, three-fourths or more, of the total energy set free during muscular contraction appears as heat.

The heat formed in the body can be measured by means of a calorimeter, the most suitable form of which for man is the Atwater-Benedict calorimeter (p. 384).

Loss of Heat.—Heat is lost from the body principally through the skin, and to a smaller extent in warming the expired air and the excreta. On the average, 77 to 80 per cent. of the heat-loss

takes place through the skin, 17 to 20 per cent. is lost from the respiratory tract, and 3 per cent. in the excreta. The total daily loss varies greatly with the conditions under which the individual is living, being as a rule from 2500 to 3500 calories.

The skin consists of two layers, a superficial layer, the epidermis, consisting of stratified squamous epithelium, and a deeper layer, the dermis, formed of fibrous tissue. The dermis rests upon connective tissue of a looser texture, which is called the subcutaneous tissue and contains a variable amount of fat.

The *epidermis* consists of two principal layers, a deeper layer of cells called the *rete mucosum*, and a superficial layer known as the *stratum corneum* or horny layer. The cells of the rete mucosum are mostly irregular in shape and are connected by protoplasmic bridges, between which are tiny channels along which lymph flows for the nourishment of the cells.

In the horny layer a transformation has occurred whereby the protoplasm has been converted into *keratin*; at the same time the cells have become flattened and scaly and possess no visible nuclei. Between the rete mucosum and the horny layer can be seen two narrow layers, the *stratum granulosum* and the *stratum lucidum*, in which the cells are undergoing transformation. The surface cells of the epidermis are continually being shed, and are replaced by the multiplication and subsequent alteration of the cells of the rete mucosum.

The *dermis* consists of dense fibrous tissue which presents papillæ or projections on its surface. The epidermis is moulded on these papillæ, and, where they are arranged in rows, as on the palmar surface of the hand and fingers, the epidermis shows corresponding ridges. Blood-vessels run in the dermis and form capillary loops in the papillæ. Lying near the junction of the dermis and subcutaneous tissue over the whole surface of the body are the *sweat-glands*, consisting of coiled tubes, the ducts of which run in a spiral manner through the dermis and open into corkscrew-shaped channels in the epidermis leading to the surface.

The skin is protected and kept supple by sebum, which is a fatty material secreted by the *sebaceous* glands. These glands are found wherever hairs are present, and their ducts open into the upper part of the hair-follicles. Each gland is composed of a solid mass of cells, in the central part of which the cells are loaded with fat and the protoplasm has largely disappeared. The fatty material in sebum is not a true fat, but consists chiefly of fatty acids combined with cholesterol.

The secretion of sebum is always taking place, the semi-liquid central part of the gland being squeezed on to the surface of the skin, whenever the hairs are erected, by the contraction of the

arrector pili muscles. The latter are composed of unstriated muscular fibres, and are attached to the hair-follicle and to the epidermis. The sebaceous gland lies between the muscle and the hair-follicle.

The Sweat.—Sweat is a clear, colourless fluid containing 99 per cent. of water; sodium chloride is the most abundant solid constituent, and traces of protein, fatty acids, and urea may also be present.

The secretion of sweat is under the control of the central nervous system, the nerves to the sweat-glands belonging entirely to the sympathetic system. Leaving the spinal cord by the anterior roots, they pass to the ganglia of the lateral sympathetic chain, where they have their cell-stations; from these ganglia non-medullated fibres enter the grey rami, and run with the spinal nerves to their peripheral distribution. Sweating is generally brought about by a rise in the temperature of the body and it usually begins as soon as the temperature of the body rises from 0·5° to 1°C. above the normal. In this case the effective stimulus is the raised temperature of the blood passing through the brain; sweating may be produced by warming the blood passing through the carotid artery to the brain, even though the temperature of the rest of the body remains unchanged.

Sweating may also be produced reflexly by the local application of heat to the skin, so that one arm, if warmed, may sweat, and not the rest of the body. It is not necessarily associated with increased vascularity of the skin, and may occur, even in an amputated and therefore bloodless limb, when the sympathetic fibres are stimulated. On the contrary, in fever there may be dilatation of the cutaneous vessels without an accompanying secretion of sweat.

The skin not only protects the delicate underlying structures and serves as a sense-organ, but by means of the secretion of sweat plays an important part in effecting the loss of heat from the body. The loss of heat from the skin takes place by radiation, conduction, convection, and evaporation. In *radiation*, heat-waves pass into the air in all directions; in *conduction*, heat is transferred to substances, such as clothing, in contact with the skin; *convection* signifies the movement of warmed air by air-currents surrounding the body. The loss taking place as a result of these processes is greater when the blood-vessels of the skin are dilated and the skin is flushed than when the vessels are constricted.

More important than any of these is the loss of heat by the *evaporation* of sweat, which is continually being formed on the surface of the skin. When the amount of sweat is small, it evaporates so quickly as to be unnoticed, the process being called

insensible perspiration. When the amount formed is increased, or its immediate evaporation is prevented, it becomes visible on the surface of the skin as *sensible perspiration.*

In the process of evaporation over 580 small calories become latent for every gram of water converted into vapour, and are lost to the body ; and the rate at which this loss takes place may be increased either by greater formation of sweat or by hastening the rate of evaporation by exposing the body to a current of air. Conversely, the loss of heat in this way is checked when an individual is surrounded by air which is already nearly saturated with moisture.

Owing to the heat taken up by water as it evaporates, heat continues to be lost by the evaporation of sweat even when the temperature of the surrounding air is higher than that of the body, provided the air is dry ; and in tropical climates the loss of heat from the skin takes place chiefly by evaporation.

When sweating is profuse, the amount of heat lost by the skin relatively to that lost through the lungs is increased, whereas, when the skin is cold and perspiration is scanty, the reverse is the case. In dogs, in which, owing to their hairy coat and paucity of sweat-glands, loss of heat by evaporation is comparatively slight, an increase in the loss of heat is largely effected by increased respiratory movements.

The Regulation of Temperature.—In cold-blooded animals metabolic activity, including the production of heat, varies with the external temperature, resembling in this respect chemical reactions in the laboratory, which are accelerated by a rise of temperature. Hence the amount of oxygen consumed and of carbonic acid given off by a poikilothermic animal varies directly with the temperature of its surroundings. These animals possess no regulative nervous mechanism by which they can counteract the effects of heat or cold. When the surrounding temperature falls, their metabolic activities diminish until they sink into a state of torpor. When the temperature rises, their metabolic activities increase, and their only means of evading the ill effects of an unduly high temperature is to hide in a stream or to burrow into moist earth.

The maintenance of a constant temperature in warm-blooded animals is effected by an exact adjustment through the central nervous system of the production and loss of heat. That the production of heat takes place mainly in the muscles and is under the control of the central nervous system is shown by two observations. In the first place, when the motor nerve-endings are paralysed by curare so that the muscles are cut off from nervous influences, the animal behaves like a cold-blooded animal. In

the second place, when the spinal cord is injured in man or in the lower animals in such a way that the lower part of the body no longer receives impulses from the brain, this portion becomes poikilothermic, and when it is warmed, its metabolism becomes more active; the heat produced warms the blood passing through it, and may be sufficient to raise the temperature of the whole body several degrees. When the lower part of the body is cooled, its metabolism is diminished, and the temperature of the whole body may thereby be lowered, in spite of the fact that the rest of the body still possesses its regulative mechanism.

The loss of heat from the body depends upon the amount of blood passing through the vessels of the skin and upon the amount of sweat formed, both of these being under the control of the central nervous system. The maintenance of the body-temperature when the surrounding air becomes colder might be effected either by an increased production or by a diminished loss of heat. In many animals the adaptation is brought about by changes in the production of heat, more heat being evolved; in man the adjustment is made in a more economical manner, chiefly by variations in the loss, and to a much smaller extent by alterations in the production, of heat. On a cold day the vessels of the skin are constricted, so as to diminish the loss of heat by radiation and convection, and the formation of sweat is scanty. Conversely, on a hot day the skin is flushed and moist, and the loss of heat is more marked.

Within moderate limits of external temperature the production of heat during rest varies but little, though it is diminished when the surrounding temperature becomes high. During muscular exercise both heat-production and heat-loss are increased, the production exceeding the loss, so that for a time the temperature rises above the normal level.

The intimate relation between production and loss of heat is also shown in the relationship between production of heat and the size of the animal. The greater loss of heat relative to its weight which occurs in a small animal (p. 387) is met by a correspondingly larger production of heat, with the result that the animal's temperature remains constant. In many animals, including man, the regulative mechanism is not fully developed at birth; and the temperature of the new-born infant falls unless an excessive loss of heat is prevented by keeping the child in a warm atmosphere.

The part of the nervous system which regulates the production and loss of heat and keeps the temperature constant appears to be the corpus striatum. Experiments have been made in which, by an ingenious device, the corpus striatum could be

warmed or cooled at will. Cooling of the corpus striatum increased the production and diminished the loss of heat ; warming had the opposite effect. In the normal animal the temperature of the corpus striatum depends upon that of the blood flowing through it. If the temperature of the body, and therefore of the blood, rises, the corpus striatum reacts by sending out impulses which lessen the production of heat in the muscles and increase the loss of heat from the skin ; conversely, a fall of body-temperature increases heat-production (*e.g.* by shivering) and diminishes heat-loss. The mechanism is so perfect that in man the temperature remains constant, whether he lives in the tropics or in the arctic regions, though the adjustment fails when the heat or cold is extreme. When a man is exposed to excessive cold, the temperature gradually falls till consciousness is lost, and finally death supervenes. When the surrounding temperature is extremely high, and particularly if loss of heat by sweating is interfered with, the temperature of the body rises very considerably, producing the condition of *heat-stroke*. This occurs more readily if the production of heat is also increased, for example by muscular exercise, or if the evaporation of sweat is checked by a humid atmosphere ; in these circumstances the regulative mechanism may fail even though the surrounding temperature is not very high.

In fever the temperature of the body is raised, the regulative mechanism again bringing about a balance between production and loss of heat, but at a higher level than in the normal person. Owing to the raised temperature of the body, metabolism is more rapid, the breaking down of the tissues is increased, the output of nitrogen in the urine rises, and a loss of weight generally takes place.

CHAPTER XII

FOOD AND DIET

The substances used as food by man and animals contain protein, fat, carbohydrate, salts, and water; and, in order to construct a suitable diet for man, it is necessary to know, first, what amount of these substances in the food best meets the needs of the body, and, secondly, the composition of the different food-stuffs.

The mere composition of the food-stuffs, however, is an uncertain guide to their true nutritive value, since this depends upon the ease with which they can be digested and assimilated; it is important, therefore, that the food should be palatable, digestible, and readily absorbed.

The food is derived either directly or indirectly from vegetable substances which are synthesised by plants from inorganic materials, the energy of the sun's rays being used in the process. The kinetic energy of the sun's rays is thus transformed into the potential energy of the organic food-stuffs, and, when these are consumed, their potential energy is again converted in the body into kinetic energy as heat and muscular work.

DIET

From this point of view the body may be regarded as a machine, which converts potential energy into the kinetic energy of muscular work and heat, the daily loss of kinetic energy being replaced by the potential energy of food. The living tissues also undergo a constant wear and tear, the tissue which is broken down being replaced by the building up of fresh tissue from the absorbed food-stuffs. A suitable diet, therefore, fulfils two functions. On the one hand, it serves as a source of energy, and, on the other, it contains the constituents necessary to replace loss of tissue.

(1) **Diet as a Source of Energy.**—If the muscular work performed is calculated in terms of heat, it is found that the daily loss of energy in man in the form of heat and work is usually about 3000 large calories (fig. 177). The daily expenditure of energy

is less in those who lead a sedentary life, and is reduced to a minimum during complete rest in bed. Even then, however, energy is being used in maintaining the temperature of the body and in the carrying out of respiration, digestion, and other internal bodily functions. The energy expended in carrying out these processes, which are essential for the continuance of life, constitutes the "basal metabolism" of the body; it is approximately 1 calorie per 1 kgm. of body-weight per 1 hour, and amounts to 1700–2000 calories a day. On the contrary, hard physical work may increase the daily loss of energy to 4000 to 5000 calories or even more.

It is clear that the amount of potential energy which must

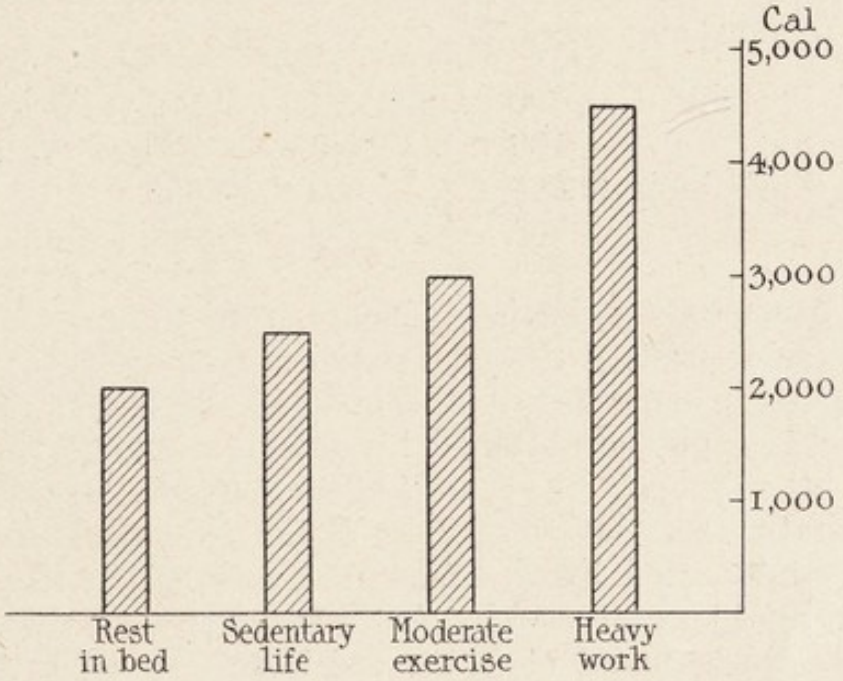


FIG. 177.—Chart showing the average daily expenditure of energy (in calories) under various conditions.

be supplied in the food, in addition to the indispensable minimum compatible with life, to replace the daily loss of energy depends mainly on the amount of physical work performed by the individual. If the supply of energy in the food is insufficient, a man can perform muscular work only at the expense of the fat and carbohydrate, or even the protein, stored in his body. Another factor which influences the daily loss of energy, and hence the food requirements of the individual, is the external temperature. Generally speaking, the loss of heat from the surface of the body is greater in winter than in summer, and, since external cold stimulates metabolism, there is a corresponding increase in the amount of food required.

Mental work has comparatively little influence on the daily expenditure of energy by the body.

As we have seen (p. 384), the average physiological calorie-value of the food-stuffs is as follows :—

1 gram fat	= 9·3	calories
1 ,, carbohydrate	= 4·1	,,
1 ,, protein	= 4·1	,,

From these data it is easy to draw up a diet containing the food-stuffs in such amount that, when oxidised in the body, they will furnish sufficient energy to replace the daily loss. Experience has shown that the following represents the proportions of the different food-stuffs most suitable for a man doing a moderate amount of muscular work :—

Protein	100 grams	× 4·1 =	410	calories
Fat	100 ,,	× 9·3 =	930	,,
Carbohydrate	500 ,,	× 4·1 =	2050	,,
			3390	calories

At least 5 per cent. must be deducted from the calorie-value of this diet, since part of the food eaten is not absorbed from the digestive tract, being lost to the body in the fæces. The same calorie-value could be obtained by combinations of these food-stuffs in other proportions ; and, particularly as regards fat and carbohydrate, the relative amount of the food-stuffs in the diet is greatly influenced by the readiness with which they can be obtained, by their cost, and by the tastes of the individual.

(2) **The Replacement of Wear and Tear.**—In order to replace the breaking down of the tissue-proteins, the diet must contain a certain minimum of protein, and much discussion has arisen as to the amount of protein in the food which is most suitable for the needs of the body. Chittenden has put forward the view that the amount of protein consumed by most people is excessive. He considers that it can be largely replaced by fat and carbohydrate as a source of energy, and that a comparatively small amount of protein is needed to repair tissue-waste and to maintain nitrogenous equilibrium. Any excess of protein beyond this minimum is regarded by him merely as throwing additional work on the liver and kidneys in excreting its nitrogen. Chittenden found by observation on himself and others that it was possible to maintain health and nitrogenous equilibrium for six to eighteen months, and to carry out muscular work, on a diet containing much less protein than that in the dietary mentioned above ;

in many cases the daily intake of protein did not exceed 40 to 60 grams.

His views have not met with general acceptance. In the first place, individuals living on such a low protein diet are apt to suffer in general health and in their ability to resist infection. Secondly, the diet of the infant contains much more protein than the minimum which would be necessary according to Chittenden's

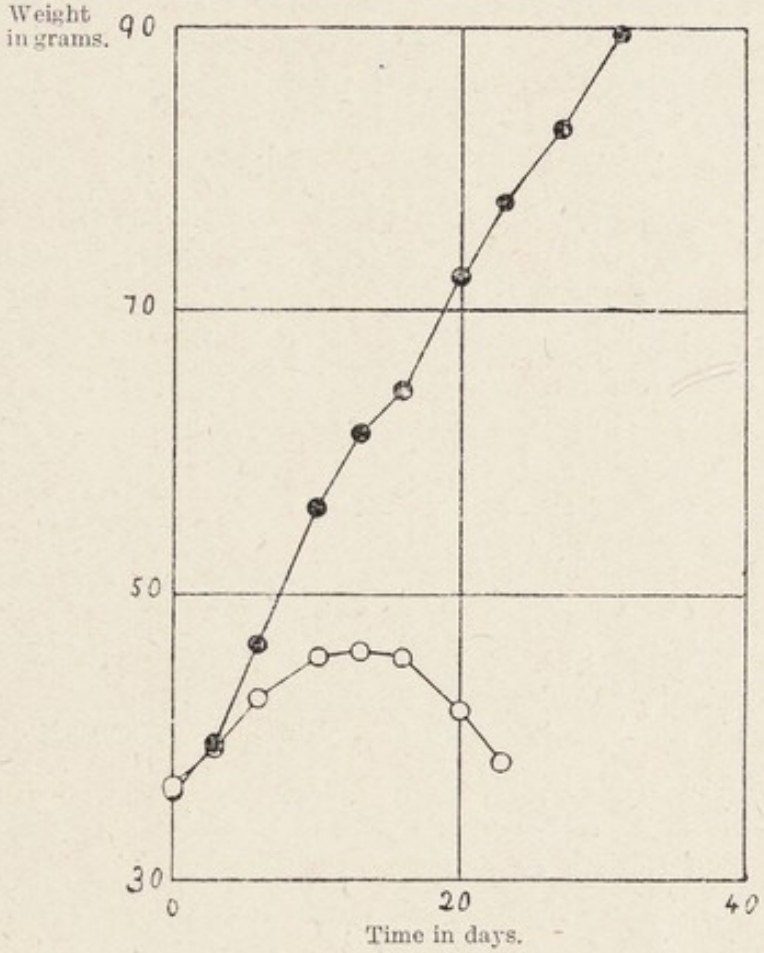


FIG. 178.—Curves showing the effect of nature of diet on growth. (Hopkins.)

Lower curve (white circles)—rats fed on artificial milk alone.
Upper curve (black circles)—rats fed on artificial milk + 2 c.c. of cow's milk daily.

views, and, since nature provides more than the minimum of protein, the minimum is probably not the optimum. Thirdly, in view of what has been already said (p. 404) as to the amino-acids which are essential for growth and maintenance, it is obvious that different proteins will vary in their nutritive value, sometimes called their "biological" value, according to the nature and proportions of the various amino-acids contained in them. Some, as for example gelatin, will be of use solely for the supply of energy, whereas others, containing tyrosine, tryptophane and cystine. will be of value for the building up of the tissues. Hence,

while a diet containing 60 grams of one protein, say caseinogen, might provide the amount of the essential amino-acids required by the body, a diet containing the same weight of certain other proteins might be totally inadequate. Broadly speaking, we may regard 100 to 110 grams of mixed proteins as representing the optimum daily intake for most men. The protein requirements of women are rather less, being from 80 to 90 grams. Violent exercise increases the wear and tear of the muscles, and, under conditions of severe physical stress, for example in soldiers during war, considerably larger amounts of protein may be necessary to maintain health.

Although the diet in man usually conforms in a general way to the principles just laid down, it must be remembered that wide individual variations occur and are compatible with health.

Accessory Factors in Diet.—In addition to serving as a source of energy and supplying a sufficiency of protein, the diet normally contains minute quantities of certain substances, known as accessory substances or *vitamines*. Hopkins has shown that the presence of these substances in food is essential for normal metabolism and for the process of growth in a young animal. He found that when young rats are fed upon an artificial milk containing perfectly pure caseinogen, fat, and milk-sugar in the same proportions as in milk, together with salts and water, the animals fail to grow (fig. 178), although their diet is adequate both as a source of energy and as regards the amount of protein present. On the addition to the diet of very small quantities of fresh milk, growth takes place in a normal manner. Evidently the natural food contains something essential to growth, which is removed in the purification of the constituents of the artificial milk. Further investigation has revealed the fact that two accessory substances are concerned in growth, and that, in order to ensure normal growth, both these substances must be supplied in the food (fig. 179). One of these, known as *fat-soluble A*, occurs in certain cereal embryos, in green vegetables, in eggs, milk, and butter, and also in animal fats with the exception of lard ; it is absent from fats of vegetable origin. The other, called *water-soluble B*, is present in the embryo and pericarp of most cereal seeds, for example, wheat and rice, in peas and beans, and in eggs, milk, yeast, and meat. Nothing is known as to their nature or mode of action.

Apart from their influence on growth, the accessory factors play an important part in the maintenance of health, and the absence or deficiency of one or other of these factors from the diet may give rise to impairment of health, and even to actual

disease. This was first shown in connection with the disease known as beri-beri, which is characterised by nervous symptoms

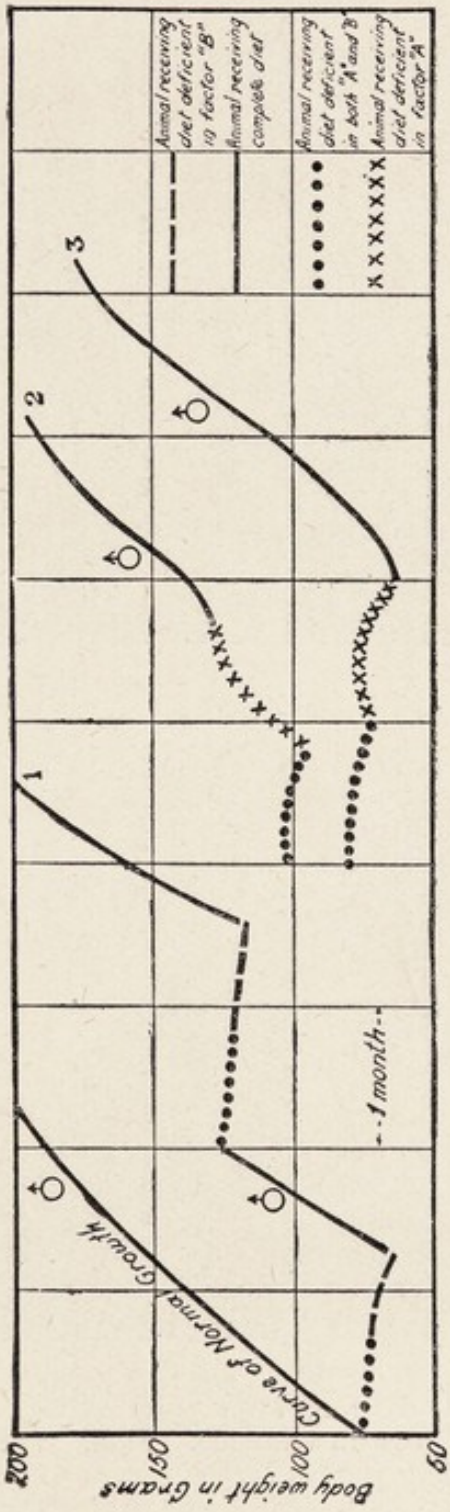


FIG. 179.—Chart showing the influence of the accessory factors A and B on the growth of young rats. (*By permission of the Controller of H.M. Stationery Office from Special Report No. 38 of the Medical Research Committee.*)

and by wasting; the symptoms are caused by inflammation and subsequent degeneration of the peripheral nerves (polyneuritis). Beri-beri occurs in individuals whose diet consists solely or almost solely of " polished " rice, that is, rice from which the

husk has been removed. Polyneuritis is also produced in birds placed on this diet (fig. 180), and they are unable to stand or to hold up their heads. The birds can be cured by adding to

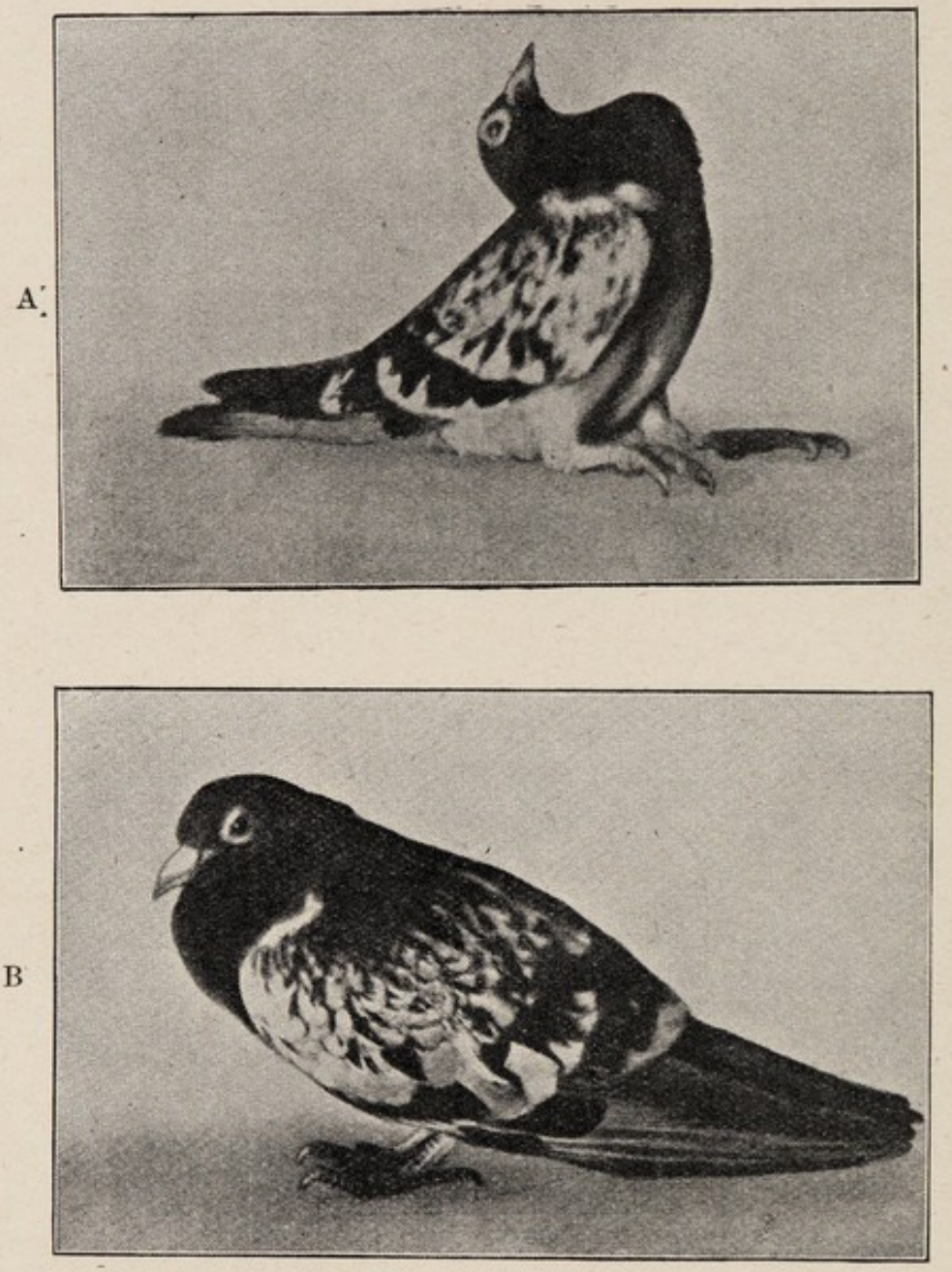


FIG. 180.—A. Pigeon suffering from polyneuritis. B. The same bird after treatment with vitamine. Funk. (From the *British Medical Journal.*)

the diet an extract made from the "polishings" of rice. In man beri-beri is cured or prevented by a diet of unpolished rice, or by the addition of meat, yeast, or other substances to the diet. The process of polishing the rice involves the removal of the pericarp and embryo of the rice grain, and it is clear that the accessory factor which is essential for the prevention of

beri-beri is contained in these parts of the rice grain. It appears to be identical with that known as water-soluble B.

Scurvy is another disease which is brought about by the absence of an accessory factor from the dietary. The accessory factor responsible for the prevention of scurvy is known as *water-soluble C*, and is found in fresh milk, meat juice, fresh vegetables, and lemon juice, and the disease can be prevented or cured by the administration of these substances.

Beri-beri and scurvy are described as "deficiency diseases," because each is brought about by the absence from the diet of an essential constituent. Recent evidence suggests that rickets also may be a deficiency disease, and that one factor in its causation is the absence of fat-soluble A from the diet.

The animal body is unable to manufacture the accessory factors, and animals (including man) can obtain these factors only from their food. It is of the utmost importance, therefore, that the diet should be sufficiently varied in character to provide an adequate supply of all the necessary factors; and a varied and carefully chosen diet appears to be particularly necessary in childhood, since there is some reason to believe that, as compared with the adult, the growing child requires a relatively large amount of the accessory factors.

We see, therefore, that in order to maintain health the diet must fulfil the following conditions. In the first place, it must provide sufficient potential energy to replace that lost as work and heat. In the second place, it must contain enough of the amino-acids necessary to replace the breaking down of the tissues and to provide the complex chemical groupings which the body cannot make for itself. In the third place, it must contain the accessory factors requisite for maintenance and growth.

Salts and water must also be present in the diet, although they do not supply energy. Further, in young growing animals the diet, especially protein food, must be relatively more abundant than in adults. Not only is metabolism more active in young animals, but an additional amount of protein is required to provide material for the laying down of new tissue during growth.

THE COMPOSITION OF FOOD-STUFFS

MILK

Milk contains all the alimentary principles of a dietary, combined in the proportions necessary for the early stages of life. The proportion of the constituents of milk varies

somewhat with the species, as will be seen from the following table :—

	Woman.	Ass.	Cow.
Proteins . .	1·5	1·9	3·5
Fats . .	3·5	1·4	4·0
Lactose . .	6·5	6·3	4·5
Salts . .	0·2	0·4	0·7
Water . .	88·3	90·0	87·3

By a comparison of these figures, it will be seen that cow's milk contains too large a proportion of protein, and too small a proportion of lactose, for the human infant. It is therefore advisable, if an infant is fed on cow's milk, to dilute the latter with water and to add lactose and a little cream in order to obtain the correct proportions.

Fresh cow's milk has a specific gravity of 1028 to 1034, and is neutral to litmus. Microscopically, it consists of small globules of fat floating in an almost colourless fluid, that is, it is a permanent fine emulsion. The globules appear to be prevented from running together by the proteins of the milk forming a fine pellicle on the surface of each globule.

The proteins of milk are caseinogen and lactalbumin. Caseinogen is a phospho-protein, and is insoluble in water, but soluble in dilute alkalies. It exists in milk as a compound with calcium, and is precipitated by the addition of acetic acid, the precipitate being soluble in excess of the acid. The precipitate of caseinogen obtained from milk by the addition of acetic acid carries down the fats entangled with it, and may be purified from these by washing with ether. When purified, it is a white powder. Lactalbumin remains in the filtrate when the caseinogen and fats have been filtered off. If the excess of acid in the filtrate be almost neutralised so that only a trace of acidity remains, the lactalbumin may be coagulated by heating the fluid.

The fats of milk consist mainly of tripalmitin, tristearin, and triolein ; the complex fat, lecithin, is also present. There are, in addition, small quantities of fatty acids lower in the scale—myristic, caproic, caprylic, capric, and lauric acids.

Lactose is the carbohydrate present in milk. It is a disaccharide, $C_{12}H_{22}O_{11}$, and reduces an alkaline solution of copper sulphate on boiling. It is not fermented by ordinary yeast, and in this way it can be distinguished from glucose. If milk is treated with acetic acid so as to precipitate caseinogen, and is then filtered, the filtrate contains lactose; if the filtrate is

allowed to evaporate slowly at a comparatively low temperature, the lactose crystallises out.

The salts of milk consist chiefly of phosphates and chlorides of potassium, sodium, calcium, magnesium, and iron, calcium phosphate being the most abundant. Analyses have shown that these salts are present in the milk of any one species in exactly the same proportions in which they occur in the young animal which is nourished on that milk. A large proportion of calcium phosphate is of especial importance in view of the formation of bone in the growing animal.

When milk is allowed to stand it becomes sour. The acidity is due to the formation of lactic acid from the lactose by the agency of certain organisms, such as *bacterium lactis*, which readily make their way into milk. The lactic acid has the same effect on the caseinogen as the addition of acetic acid ; that is, it precipitates the caseinogen, and the latter entangles the fats, forming a curd. The precipitation of caseinogen in this way must not be confused with the clotting of milk which is brought about by ferment action in the stomach (p. 342). In the latter process the caseinogen undergoes a chemical change, being converted into casein.

The suitability of the maternal milk for the needs of the growing animal does not depend only on the fact that the various constituents are in the correct proportions. As has already been pointed out, every protein consists of a characteristic grouping of amino-acids, some of these acids being present to a special extent in one protein, and others in another. Caseinogen is remarkable in that nearly all the amino-acids which enter into the composition of the various proteins are represented in its structure to a greater or less extent, so that it may form a source from which any of the body proteins may be built up. The only amino-acid absent from caseinogen is glycine, and glycine can be synthesised in the body. Caseinogen contains very little cystine, but this defect is remedied in milk by the presence of lactalbumin, which contains a considerable amount of cystine.

When acted on by "rennet" ferment the caseinogen of human milk is thrown down in the form of a flocculent precipitate, whereas cow's milk forms a firm, massive clot. For this reason cow's milk, even when diluted, does not form a satisfactory substitute for maternal milk in the case of the human infant. Other drawbacks to the "bottle-feeding" of infants are (1) the difficulty of obtaining sterile cow's milk ; (2) the fact that sterilisation can only be effected at the cost of losing a proportion of the accessory factors ; and (3) the loss to the child of anti-bodies,

which are present in the maternal milk, and help to protect it from certain infective diseases.

Food-stuffs Derived from Milk.—The *cream* of milk contains 14 to 44 per cent. of fats, and is a useful means of administering fat when an extra amount is required in the dietary.

Butter is obtained by separating the fats from cream, and is almost pure fat with a trace of protein and a small percentage of water.

Cheese is made by the compression of clotted milk so as to express as much as possible of the water. Cheese is thus rich in protein and fat, the protein being chiefly casein. It contains hardly any sugar.

BREAD

Flour contains 68 per cent. of starch, 12 per cent. of proteins, and small quantities of cellulose, fats, and salts. When it is kneaded with water, a change takes place in its proteins. These are two in number, namely, *gliadin*, which is soluble in alcohol, and *glutenin*, which is insoluble in alcohol. When flour is mixed with water these two substances are converted into the sticky material, *gluten*. Dough is thus formed mainly of gluten and starch. It is made spongy by the liberation of gases in its interior, usually by the action of yeast. In the process of baking, the starch in that portion of the loaf which is most exposed to the high temperature, namely, the crust, is partially converted into dextrin and caramel.

BEEF AND OTHER FLESH FOODS

The composition of lean beef is given in the table on p. 432. Fat beef contains nearly as much protein, more fat, and less water. Mutton, poultry, and white fish contain about the same proportions of the various constituents, but poultry contains rather more protein and a smaller proportion of salts than beef, whereas white fish contains less protein and more water.

EGGS

The white of egg contains three proteins, egg-albumin, egg-globulin, and ovomucoid. The yolk contains a small amount of vitellin (a phospho-protein), and a large proportion of fats, with smaller quantities of cholesterol, lecithin, sugar, and salts.

GREEN VEGETABLES

Green vegetables are of little value as a source of proteins, carbohydrates, and fats. They have, however, three important functions in a dietary: (1) as a source of iron, (2) as a source of the three accessory factors (p. 424), and (3) as mechanical stimulants to the peristaltic movements of the digestive tract, in virtue of the indigestible cellulose which they contain.

GELATIN

Gelatin is a sclero-protein, and is formed by boiling collagen, the principal solid constituent of connective tissue. Gelatin cannot entirely replace other proteins in a dietary, because it is deficient in three essential amino-acid groups, phenylalanine, tyrosine, and tryptophane; moreover, cystine, the sulphur-containing amino-acid, is absent from the gelatin molecule. In one experiment on a dog, it was found that nitrogenous equilibrium could be maintained when five-sixths of the protein of the diet was replaced by gelatin. In other experiments on animals, it has been found possible to maintain nitrogenous equilibrium for a time on a diet of gelatin to which tyrosine and tryptophane were added.

BEVERAGES

Tea and *coffee* owe their fragrance to aromatic substances, and their stimulating properties to the presence of caffeine (trimethylxanthine). *Cocoa* contains about 30 per cent. of fat and 20 per cent. of protein, and is therefore a food. It has also stimulating properties owing to the presence of theobromine (dimethylxanthine).

Alcohol undergoes oxidation in the body to a limited extent, and to that extent it acts as a food. Its value as a food is, however, more than counterbalanced by its action as a poison. If taken in any quantity, it interferes first with the inhibitory powers of the higher centres of the brain, later it disturbs the mechanism for muscular co-ordination, and finally it paralyses the whole nervous system. The continued use of alcohol, moreover, leads to degenerative changes in the tissues and organs of the body, and in that way it shortens life.

THE CONSTRUCTION OF A DIETARY

The amount of protein, carbohydrate, fat, salts, and water required daily being known, a dietary can be constructed with

the aid of a table showing the composition of food-stuffs, such as that given below. Fig. 181 gives a graphic representation of the composition of certain staple food-stuffs.

Approximate Composition of some Common Food-stuffs.

	Protein.	Carbo-hydrate.	Fat.	Salts.	Water.	Unavailable.
Lean beef . .	20·3	...	7·5	1·1	70·0	1·1
Eggs . . .	13·0	...	10·0	0·8	73·7	2·5
Milk (cow) . .	3·5	4·5	4·0	0·7	86·8	0·5
Cheese . . .	25·1	2·4	32·0	2·9	34·2	3·4
Peas (dried) . .	17·3	62·5	0·9	2·2	9·5	7·6
Oatmeal . .	13·4	65·2	6·6	1·4	7·8	5·6
Rice . . .	6·5	76·9	0·3	0·3	12·3	3·7
Bread . . .	7·1	52·3	1·2	0·8	35·3	3·3
Potatoes . .	1·7	17·7	0·1	0·8	78·3	1·4
Carrots . . .	0·7	8·9	0·4	0·8	88·2	1·0
Butter . . .	1·0	...	80·8	2·3	11·0	4·9

It will be observed that the animal foods are especially rich in protein and fat, and in ordinary life most of the necessary protein is taken in the form of beef, mutton, and eggs. Vegetable foods,

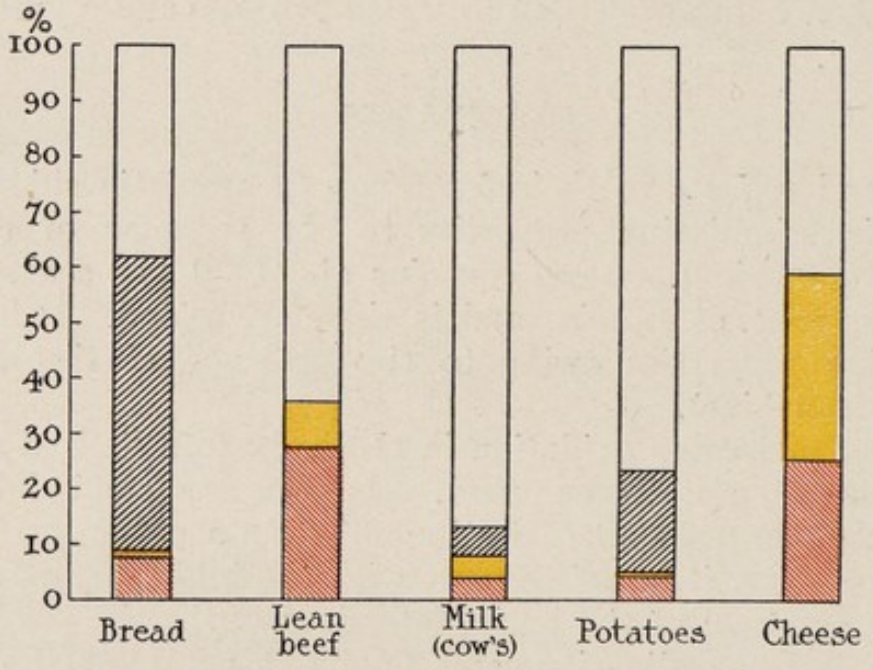


FIG. 181.—Composition of staple foods shown diagrammatically.

Red = protein; yellow = fat; shading = carbohydrate; unshaded part = water and salts.

on the other hand, are the chief source of carbohydrates, and the latter substances in a dietary are usually derived from bread, rice, and potatoes. Some vegetable foods contain a considerable amount of protein, but the vegetable proteins are not so easily and completely digested and assimilated as those contained in

animal food, and therefore, from a physiological point of view, it is more wasteful to obtain the necessary protein from vegetable than from animal sources. Moreover, in order to get the requisite amount of protein, a vegetable diet must be considerably more bulky than a diet which is partly composed of animal substances.

If the amounts of the alimentary principles required daily be taken as :—

Protein	100 grams
Carbohydrate . . .	450 „
Fat	100 „
Salts	30 „

a dietary may be constructed from the table of food-stuffs as follows :—

	Protein.	Fat.	Carbohydrate.	Salts.
450 grams bread . . .	32	5·4	233·3	4·5
180 „ meat . . .	37·2	13·5	...	1·8
600 „ milk . . .	21·0	24·0	27·0	4·2
20 „ butter . . .	0·2	20·0	0·2	0·3
300 „ potatoes . .	5·1	0·3	53·1	2·4
60 „ jam . . .	...	...	36·0	...
50 „ rice . . .	3·2	0·1	38·0	0·1
60 „ sugar . . .	...	...	60·0	...
60 „ bacon . . .	5·7	35·4	...	2·0
	104·4	98·7	447·6	15·3
Calorie-value . . .	3181			

It will be observed that the salt content of the diet is deficient, and would have to be supplemented by means of common salt.

CHAPTER XIII

THE URINARY SYSTEM

SECTION I

THE STRUCTURE OF THE KIDNEY

The kidney is a compound tubular gland having a duct, the ureter, which connects it with the bladder and is expanded at its upper end to form the pelvis of the kidney. On dividing the kidney lengthwise from its outer to its inner border, it is seen to consist of two layers, an outer reddish-brown *cortex*, and an inner pale layer, the *medulla*. The latter is composed of a number of pyramids, the apices of which project as papillæ into the pelvis of the kidney. The larger sub-divisions of the renal artery and vein lie between the cortex and medulla, this region being known as the *boundary zone*. Prolongations of the medullary tissue extend radially into the cortex, forming the medullary rays.

The kidney consists of a mass of tubules, held together by connective tissue. Each tubule begins in the cortex by a blind expanded end (Bowman's capsule), which may be compared with a small ball indented so that its opposing walls almost touch; the capsule consists of a single layer of squamous epithelium. A bunch of capillaries, known as a *glomerulus*, projects into the indentation. At the pole opposite the entrance of the blood-vessels Bowman's capsule opens into the tubule proper, which at first takes a tortuous course and is known as the first convoluted tubule; it then becomes spiral or nearly straight (spiral tubule), passes into the medulla, where it forms a loop (loop of Henle) and returns into the cortex. Here it becomes irregular and angular (zigzag tubule), and then convoluted (second convoluted tubule), and ultimately joins a straight collecting tubule (fig 182). The collecting tubules run into the medulla, and open at the apices of the pyramids into the pelvis of the kidney.

The convoluted, spiral, and zigzag tubules are lined by columnar or cubical cells, the lateral surfaces of which dovetail into each other; the cells are very granular, the granules tending to

be arranged in rows at right angles to the lumen, so that the cells have a rodded appearance. The descending part of the loop of Henle is lined by clear, flattened epithelium; the cells of the ascending limb resemble those of the convoluted tubules. The collecting tubules are lined by clear, cubical cells. Throughout

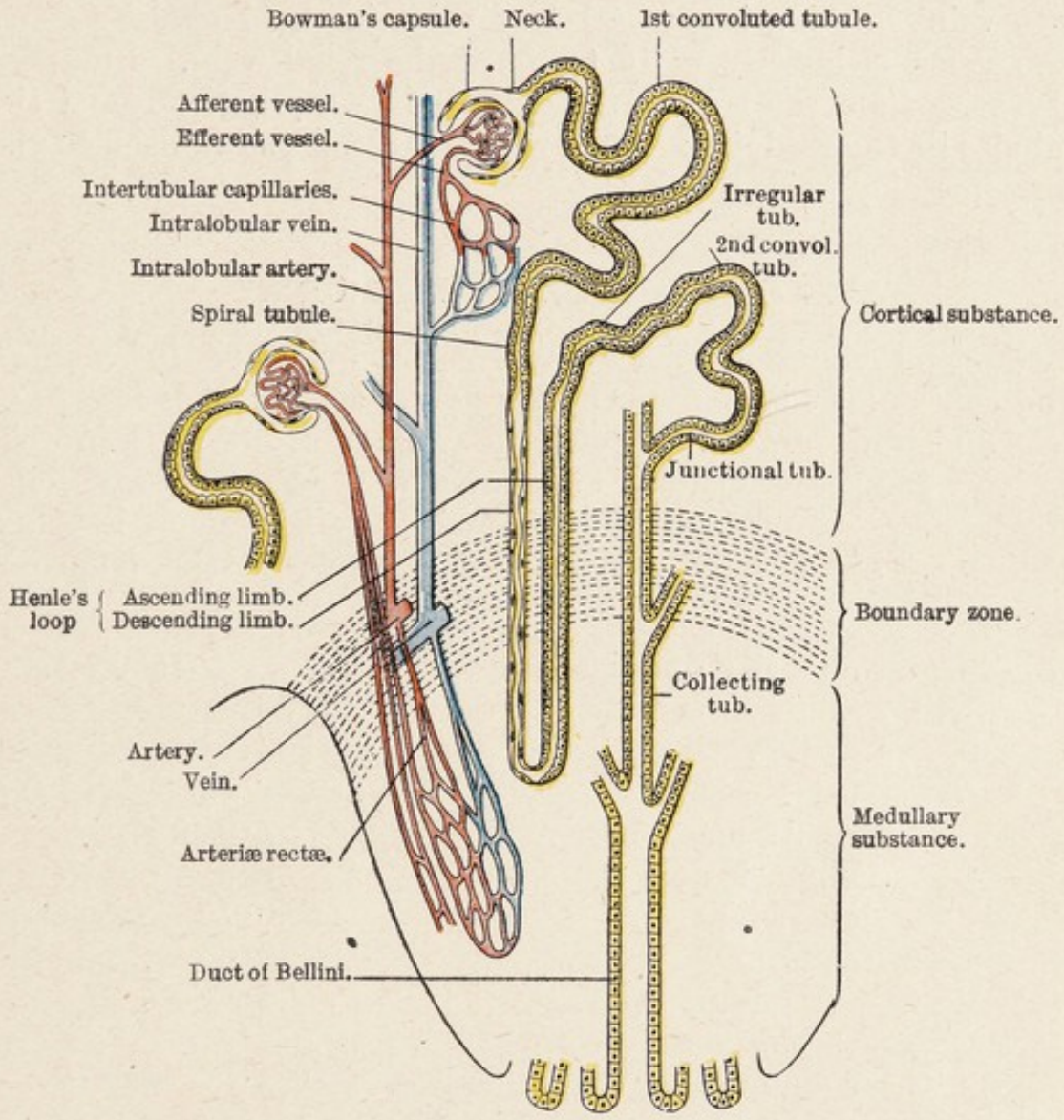


FIG. 182.—Scheme of a renal tubule and its vascular supply. (From Gray's *Anatomy*.)

the whole length of the tubules the cells rest upon a well-marked basement-membrane.

The Blood-Supply.—The distribution of the blood-vessels in the kidney is best seen if the vessels are injected with a medium containing a barium salt, and an X-ray photograph of the kidney is taken. The renal artery enters the kidney close to the origin of the ureter and divides into "interlobar" branches, which lie in the boundary zone between the cortex and the medulla. From these vessels smaller branches pass outwards, and give off straight

" intralobular " arteries directed towards the surface of the kidney. The intralobular arteries give off short " afferent " vessels, one to each adjacent glomerulus. The blood leaves the capillaries of the glomerulus by an " efferent " vessel, which is smaller than the afferent and, after a short course, breaks up into capillaries round the convoluted tubules; from these capillaries the blood passes into veins opening into the larger veins in the boundary zone. The veins ultimately unite to form the renal vein. Branches also arise from the large arteries to end in capillaries round the tubules in the medulla; from these the blood passes back to the corresponding veins.

THE COMPOSITION OF THE URINE

Normal human urine is a clear, yellow fluid, acid in reaction, and containing about 4 per cent. of total solids; it is free from cells and from protein, except for a small trace of nucleo-protein derived from the bladder and urinary passages. Its specific gravity varies from 1015 to 1025, and its daily amount is about 1500 c.c. Its average composition is shown in the following table:—

Total quantity of urine		1500 c.c.
,, solids	60	grams
,, urea	33	,,
,, uric acid	0·75	,,
,, creatinine	1·0	,,
,, hippuric acid	0·5	,,
,, ammonia	0·75	,,
,, chlorine	10·0	,,
,, phosphoric acid	2·5	,,
,, sulphuric acid	2·5	,,
,, sodium	5·0	,,
,, potassium, ,, calcium, ,, magnesium	4·0	,,

Since the nitrogenous end-products of the metabolism of protein are excreted almost entirely in the urine, its composition largely depends upon the quantity of protein food consumed, and on the katabolic changes in the tissue-proteins. The characters of urine vary, therefore, not only in different individuals, but even in the same individual from day to day, and almost from hour to hour.

Amount and Specific Gravity.—The fluid taken by the mouth leaves the body partly in the urine, and partly through the skin

and lungs. In hot weather or during exercise, when evaporation of sweat from the skin is considerable, the urine is decreased in amount and is proportionately concentrated. When the secretion of sweat is scanty, for example on a cold day, a larger proportion of water is excreted by the kidneys, and the urine is abundant and of low specific gravity; copious draughts of water produce the same effect. In diabetes the presence of sugar may raise the specific gravity to 1040 or more, while in some forms of renal disease the specific gravity is always low (1005 to 1015).

Reaction.—The acid reaction of normal urine is due to acid sodium phosphate (NaH_2PO_4); no free mineral acid is present. The bases and acid radicles mentioned in the foregoing table are combined to form salts, and are derived from the food. Sulphuric and phosphoric acids are formed by the oxidation of the sulphur and phosphorus contained in protein, and, when the food contains much protein, the amount of these acids is increased in the urine, which becomes strongly acid in reaction. Vegetable foods contain organic salts, such as citrates and tartrates of potassium and sodium, in abundance, and in the body these organic acids are completely oxidised, whereas the bases are excreted in the urine. Hence in herbivorous animals, and in man on a vegetarian diet, the urine is neutral or alkaline, though a starving herbivorous animal which is living on its tissue-proteins, and is for the time being carnivorous, excretes an acid urine.

Colour.—The colour of urine is almost entirely due to a pigment, *urochrome*, of uncertain origin, the spectrum of which shows no absorption bands. In addition, urine may contain three other pigments, namely, (1) urobilin, (2) uroerythrin, and (3) hæmatoporphyrin.

Urobilin is formed in the digestive tract from bilirubin by bacterial action, and, after absorption into the blood, is excreted into the urine chiefly as a colourless chromogen, which can be converted into urobilin by the addition of a mineral acid. Urobilin itself occurs in urine in considerable quantity when the amount of bile-pigment formed in the liver is increased by an unusually rapid destruction of red cells in the body, for instance in pernicious anæmia. It shows an absorption band at the junction of the green and blue part of the spectrum, and gives a green fluorescence with zinc chloride and ammonia.

Uroerythrin occurs in combination with deposits of urates, giving them a pink colour, which is changed to green on the addition of an alkali; its composition is unknown.

Hæmatoporphyrin (p. 181) normally occurs in minute traces, but may be present in large amount in poisoning by sulphonal.

UREA

The presence of urea in urine may be shown by evaporating the urine to dryness on a water-bath, and extracting the residue with acetone, which dissolves urea. On evaporation of the acetone extract, the urea crystallises out.

Urea (CON_2H_4) is a solid, crystallising in colourless rhombic prisms which are easily soluble in water, alcohol, and acetone. When heated, the crystals decompose, giving off ammonia and yielding a body called *biuret*. When treated with a drop of a solution of copper sulphate and a few drops of strong caustic potash, biuret gives a rose-red colour. Urea combines with nitric or oxalic acid, forming characteristic crystals. It is decomposed by nitrous acid, in the presence of nitric or hydrochloric acid, with the evolution of carbonic acid and nitrogen, or by alkaline sodium hypobromite, according to the following equation :—

$$CON_2H_4 + 3NaBrO = CO_2 + N_2 + 2H_2O + 3NaBr.$$

The carbonic acid is absorbed by the alkali, and the nitrogen is given off ; and, by collecting and measuring in a graduated burette the amount of nitrogen evolved from 5 c.c. of urine, the percentage of urea can be ascertained. Theoretically, 1 gram of urea yields 371 c.c. of nitrogen at 0° C. and 760 mm. Hg, but actually only 354 c.c. are evolved from 1 gram of urea in urine.

Another and more accurate method of estimating the amount of urea is to treat a known volume of urine with an extract of Soya bean, which converts urea into ammonia ; the ammonia formed is passed into a known volume of $\frac{N}{10}$ acid, and the amount of uncombined acid is subsequently estimated by titration with $\frac{N}{10}$ caustic soda. The action of the Soya bean is due to a ferment known as urease.

When urine is exposed to the air the urea soon becomes decomposed by micro-organisms, being converted into ammonium carbonate, and the urine becomes strongly alkaline.

The nitrogen present as urea usually forms about 85 per cent. of the total nitrogen existing in one combination or other in the urine. The total nitrogen in urine is estimated by *Kjeldahl's method* as follows :—

A known volume of urine is boiled with pure sulphuric acid until all its carbon is fully oxidised, the nitrogen being converted into ammonia, which combines with the acid. The solution is

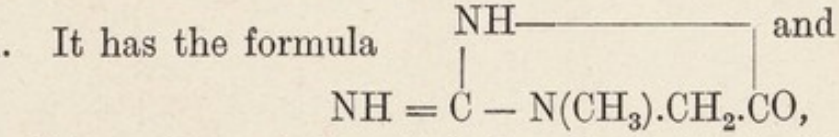
then made alkaline with caustic potash and boiled, the ammonia, which distils off, being collected in a known volume of $\frac{N}{10}$ sulphuric acid. The amount of acid neutralised by the ammonia is determined by subsequent titration of the uncombined acid with $\frac{N}{10}$ caustic potash.

Urea is the most abundant nitrogenous constituent of urine, its amount varying, as seen in the table on p. 402, with the quantity of protein food consumed; in starvation, urea is derived entirely from the breaking down of the tissue-proteins.

AMMONIA

The ammonia normally found in the urine represents the small amount which escapes conversion into urea by the liver, and is but little affected by the amount of protein in the diet. In some forms of acidosis the abnormal acids formed in the body combine to a large extent with ammonia in the blood, being excreted as ammonium salts in the urine, and the amount of urea is correspondingly diminished. The amount of nitrogen excreted as ammonia in these circumstances is sometimes 20 per cent. or more of the total urinary nitrogen.

CREATININE AND CREATINE

Creatinine is an anhydride of creatine, which occurs in muscle, and it may be formed from the latter by boiling it with strong hydrochloric acid. It has the formula  and

$$NH = C - N(CH_3).CH_2.CO,$$

gives a red colour with caustic potash and picric acid (Jaffé's test). It is derived solely from the endogenous metabolism of protein; and the amount excreted in the urine by the same person from day to day is remarkably constant, and serves as an accurate index of the extent of endogenous protein metabolism.

The origin of creatinine and its relation to the creatine present in muscle are not fully understood, though creatinine appears in the urine in increased amount in fever, and in other conditions in which rapid wasting of muscular tissue is taking place. Creatine also, though not usually present in the urine of adults, is found during starvation, in diabetes, in acute fevers, and in women during involution of the uterus. It is possible that normally the creatinine in the urine is formed from creatine, and that in the conditions just mentioned an increased amount of creatine is set

free by decomposition of protein, some of it being converted into creatinine, while a portion is excreted in an unaltered form. If a small quantity of creatine is ingested, however, it is entirely oxidised in the body. If a larger quantity is eaten, some appears in the urine unchanged.

URIC ACID

Uric acid exists in urine in the form of biurates. On adding strong hydrochloric acid to urine and allowing it to stand for twenty-four hours, uric acid separates out as small pigmented crystals having a characteristic whetstone shape (fig. 183). Uric acid itself is colourless, but it usually carries down uroerythrin when it is deposited in urine. It is almost completely insoluble in water, but dissolves in weak alkalies. It slightly reduces Fehling's solution (p. 442), and will also reduce an alkaline solution of silver nitrate (Schiff's test). A solution of uric acid, when evaporated to dryness with nitric acid at a moderate temperature, yields a purple colour on the subsequent addition of ammonia (murexide test).

FIG. 183.—Deposit of uric acid (after Funke). (From Plimmer's *Practical Organic and Bio-Chemistry.*)

The uric acid in urine is derived partly from the nuclein in food and partly from the breaking down of the nucleins of the tissues.

In addition to uric acid, small amounts of the purine bases are found in urine.

HIPPURIC ACID

is synthesised in the kidney, and possibly in the liver, from benzoic acid and glycine, the synthesis being brought about by an enzyme. It is the only urinary constituent which is formed in the kidney itself. The synthesis can be brought about *in vitro* by mixing minced kidney, or liver, with a benzoate and glycine, and keeping the mixture at body-temperature for a time. It will not occur if the kidney-cells are destroyed, for instance by grinding them with sand.

SULPHATES

The sulphates are of two kinds, namely, (1) inorganic, and (2) ethereal. The latter are compounds of sulphuric acid with phenol, indoxyl, or skatoxyl, and potassium. Indol and skatol are formed from tryptophane by bacterial action in the digestive tract; and, after absorption into the blood, they are first converted by oxidation into indoxyl and skatoxyl, and then combined with sulphuric acid, and excreted by the kidneys. Phenol, also, is a product of decomposition of protein.

As a rule the ethereal sulphates form about one-tenth of the total sulphates, but when the products of bacterial changes accumulate in the digestive tract (*e.g.* in constipation), the proportion of ethereal sulphates is increased.

Some sulphur is also excreted in organic combination, and is known as " neutral " sulphur.

The sulphuric acid of the urinary sulphates is formed almost entirely by the oxidation of the sulphur contained in protein, and the total amount of sulphates varies, therefore, with the quantity of protein food ingested.

Urine also contains **sodium chloride** and **phosphates,** the latter being of two kinds, namely, (1) acid phosphates of sodium and potassium, and (2) earthy phosphates of calcium and magnesium.

URINARY DEPOSITS

On standing, normal urine deposits a cloud of mucus (nucleoprotein) derived from the urinary passages. When the urine is concentrated, *biurates of sodium and potassium* are often deposited as an amorphous sediment, coloured pink by uroerythrin, and dissolving when warmed *Earthy phosphates* are deposited from neutral or alkaline urine: they dissolve on the addition of acetic acid.

Crystalline deposits may also occur in urine, and are usually indicative of abnormal processes taking place either in the body or in the urine itself. The nature of the deposits varies with the reaction of the urine. In acid urine those most frequently seen are, first, *uric acid* crystals, which assume the form of whetstones or cylinders, and are usually, though not invariably, pigmented; and, secondly, *calcium oxalate,* occurring as small, colourless octohedra, often called " envelope " crystals from their appearance under the microscope.

Uric acid and oxalate crystals are frequently found together. Other crystalline deposits, occasionally met with in acid urine,

are *cystine* (flat hexagonal colourless plates) and the *acid urates of sodium or ammonium*, which form spheroidal masses with projecting spikes.

In alkaline urine, the crystals most commonly met with are (1) *calcium phosphate*, occurring as prisms arranged in rosettes, and (2) *ammonio-magnesium phosphate*, NH_4MgPO_4. The latter, often called "triple phosphate," is formed when urine becomes alkaline as a result of the bacterial decomposition of urea; the crystals are large and very characteristic, resembling knife-rests or coffin-lids (fig. 184).

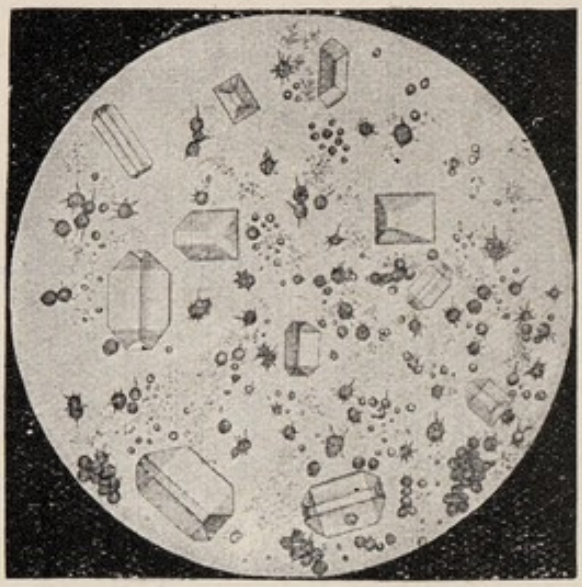


FIG. 184.—Deposit of triple phosphate and ammonium urate. (From Plimmer's *Practical Organic and Bio-Chemistry*.)

OTHER ABNORMAL CONSTITUENTS IN URINE

(1) **Coagulable Protein.**—Except for a trace of nucleo-protein, normal urine contains no protein. In disease of the kidney, serum-globulin and serum-albumin escape from the blood into the urine, and are coagulated on boiling the urine (after the addition of a drop or two of dilute acetic acid). Further, when urine containing protein is poured on to the surface of strong nitric acid, a precipitate forms at the junction of the two fluids (Heller's test).

(2) **Sugar.**—The conditions under which sugar occurs in urine have already been dealt with (p. 396). In man the usual cause of glycosuria is diabetes, and the sugar is glucose. In rare cases the urine contains lævulose or pentose. Lactose is sometimes found during lactation, even in healthy women. The amount of glucose present in the urine in diabetes may vary from mere traces up to 350 to 500 grams daily.

Glucose reduces alkaline solutions of copper sulphate, yielding cuprous oxide. The solutions generally used in testing for glucose are (1) Fehling's solution, containing copper sulphate, caustic potash, and Rochelle salt; the latter keeps in solution the cupric hydrate formed by the interaction of the copper sulphate and caustic potash: (2) Benedict's solution, which contains copper sulphate, sodium carbonate, and sodium citrate. Benedict's solution is the more satisfactory, since, unlike Fehling's

solution, it is not reduced at all by uric acid or creatinine, nor does it become self-reducing when kept for some time. Other tests for glucose are (1) the preparation of the osazone with phenylhydrazine, and (2) the fermentation test with yeast, which converts glucose into carbonic acid and alcohol.

The estimation of sugar may be effected by Benedict's method. The solution used contains copper sulphate, sodium carbonate and citrate, potassium thiocyanate, and potassium ferrocyanide. 25 c.c. of the solution and 3 or 4 grams of anhydrous sodium carbonate are placed in a small flask and boiled. The sugar solution is added from a burette until the blue colour of the reagent disappears ; this is the end-point. The thiocyanate forms a *white* precipitate with the cuprous hydroxide formed by the reduction of the copper sulphate, and the end-point is quite sharp. 25 c.c. of the solution are reduced by 0·05 gram of glucose.

Glycuronic acid ($COOH(CHOH)_4, CHO$) sometimes occurs in urine, either after the administration of certain drugs, such as chloral, or in combination with indoxyl. It reduces Fehling's and Benedict's solutions and forms an osazone, but may be distinguished from glucose by means of yeast, which does not ferment it.

(3) **Bile** is present in the urine in jaundice, giving it a greenish or brownish colour ; its presence may be recognised by Gmelin's test for bile-pigments or Hay's test for bile-salts (p. 362).

(4) **Blood** occurs in urine as the result of hæmorrhage in the kidneys or urinary passages, and may be identified by observing the red corpuscles under the microscope, or by spectroscopic examination.

(5) **Products of Abnormal Metabolism.**—These include β-oxybutyric acid, diacetic acid and acetone (p. 392) ; leucine and tyrosine, which are present in acute atrophy of the liver ; cystine, and homogentisic acid.

Cystine is set free in the course of the digestion of protein and, after being absorbed, it is normally either oxidised or built up into tissue-protein. In rare cases the cystine escapes oxidation and is excreted as such, and may form crystalline deposits or calculi.

Homogentisic acid,

$CH_2.COOH$, is a derivative of tyrosine.

In certain persons the oxidation of tyrosine is incomplete, and stops with the production of homogentisic acid, which appears in the urine. The condition is known as *alcaptonuria*, and the

urine darkens on standing and reduces Fehling's solution. In persons suffering from alcaptonuria the amount of homogentisic acid in the urine varies from 3 to 6 grams daily ; it is proportional to the quantity of phenylalanine and tyrosine present in the proteins of the food, and is increased when these substances are given as such by the mouth. Thus the whole of the tyrosine and phenylalanine taken into the body is excreted as homogentisic acid. An allied substance, parahydroxyphenylacetic acid, may appear in the urine of normal persons when the passage of the intestinal contents is slow.

Cystinuria and alcaptonuria, when they occur, are present at birth and persist through life ; they are due to "inborn errors" of metabolism, probably to the lack of certain ferments, and do not lead to any disturbance of health.

SECTION II

THE FORMATION OF URINE

Broadly speaking, the function of the kidney is to keep the composition of the blood constant by excreting into the urine any excess of substances normally present in the blood, such as water, sodium chloride and glucose, or other substances which are not normal constituents of the blood. The abolition of this function by the complete removal of the kidneys leads to the retention of the urinary constituents in the blood, and the animal dies in two or three days ; the kidneys are, therefore, essential to life. A very important part of their function is to regulate the reaction, that is, the H-ion concentration, of the blood and tissues, and, for this purpose, a close correlation exists between the activity of the kidneys and that of the respiratory mechanism. For example, there is reason to believe that during sleep the respiratory centre is less active than usual, with the result that carbonic acid accumulates in the blood and the reaction of the blood tends to become acid. This tendency is at once corrected by the kidneys, which excrete a more acid urine and thus maintain the reaction of the blood at its normal value. It is clear, therefore, that the kidneys are extraordinarily sensitive to the slightest change in the reaction of the blood, and respond by excreting in the urine any excess of acid or base which is present in the blood. Recent observations on man show that in some diseases of the kidneys the normal balance of acid and base in the blood is no longer maintained, and the H-ion concentration of the blood rises slightly. This stimulates the respiratory centre, as already described (p. 298), leading to hyperpnœa.

So far as is known, there are no secretory nerves to the kidney ; its functional activity is excited solely by any alteration in the chemical composition and amount of the blood flowing through it, and is thus largely determined by metabolic changes occurring in other parts of the body.

The structure of the renal tubule is extremely complex, much more so than that of most of the other glands of the body. Many views have been held as to the functions of its different parts, and even now the problem is not completely solved. The structure of the convoluted tubule and of the capsule of Bowman is so different that it seems certain that their functions must also be different ; and Bowman, on purely histological grounds, suggested that the glomeruli filtered off water and salts, the remaining urinary constituents being secreted by the tubules.

Heidenhain regarded both the tubules and glomeruli as possessing a secretory function, the latter secreting water and salts by a selective and vital process. This view is still accepted by some authorities, whereas others believe that the glomeruli form by filtration a fluid identical in composition with the blood-plasma minus its proteins, and that the tubules secrete into this fluid, as it passes along them, water and other urinary constituents. The latter theory is really a slight modification of Bowman's theory.

Ludwig believed that the whole of the urine was formed by the filtration through the glomeruli of a fluid identical in composition with the blood-plasma minus its proteins, and that, in the passage of this fluid down the lumen of the tubules, much of the water and some of the salts were reabsorbed by diffusion, so that the composition of urine, as it left the kidney, differed greatly from that of blood-plasma. Since blood-plasma contains about 0·02 to 0·05 per cent. of urea, whereas urine contains 2 per cent. of urea, this theory demands that at least 60 litres of fluid should be filtered off daily by the glomeruli, of which all but 1·5 litres are reabsorbed.

The question as to whether the formation of urine takes place by a process of filtration or of secretion can be answered by ascertaining whether the conditions under which it is formed conform to those known to hold for filtration or secretion elsewhere. In filtration, the amount of filtrate varies directly with the difference of pressure on the two sides of the filtering membrane, and it usually contains the same percentage of crystalloids as the fluid undergoing filtration. When a true secretion, such as that of saliva, takes place, the pressure of the saliva in the ducts may rise higher than that of the blood, and the amount of secretion is, within wide limits, independent of the blood-pressure ; moreover, the composition of the secretion differs greatly from

that of the blood. Further, during secretion, the secreting cells perform work and take up more oxygen from the blood.

In the discussion of this question it is convenient to consider separately the functions of the glomeruli and of the tubules.

THE FUNCTION OF THE GLOMERULI

In the mammalian kidney it is impossible to obtain separately the urine formed by the tubules and glomeruli respectively, though there is evidence that, when the flow of urine is profuse, it is derived mainly from the glomeruli. If urine is simply filtered through the walls of the glomeruli, its amount should be increased by raising the capillary pressure in the glomeruli and decreased by lowering that pressure, since the pressure in the ureter is nil. Further, its composition should be that of the blood-plasma minus proteins.

Experiment shows that such is the case. The capillary pressure in the kidney is increased by dilatation of its arterioles, so long as the general blood-pressure remains constant, or by a rise in the general blood-pressure, if this is not accompanied by active constriction of the renal arterioles. In either case the amount of blood flowing through the kidney is increased, and more blood is present in it at any moment. Conversely, the capillary pressure is diminished either by a fall in the general arterial pressure, or by constriction of the arterioles, the general arterial pressure remaining unchanged.

The changes in capillary pressure cannot be observed directly, but may be measured indirectly by recording either the alterations in volume of the kidney, or the rate of blood-flow through it, by one or other of the methods already described (p. 253); an increase in the volume of the kidney indicates a rise of pressure in the capillaries of the glomeruli.

The capillary pressure in the glomeruli is high, partly because the renal arteries arise directly from the aorta, and partly because the efferent vessels of the glomeruli are smaller than the afferent vessels; it is probably only about 20 to 30 mm. Hg below that in the renal artery.

The kidneys are amply supplied with vaso-constrictor nerves from the sympathetic system, and the calibre of the arterioles can be altered by section or stimulation of these nerves. On section of the renal vaso-constrictor nerves the kidney dilates, the rate of blood-flow through it is increased, and more urine is formed; stimulation of the nerves causes shrinking of the kidney, and the flow of urine diminishes or ceases altogether. Division of the spinal cord in the cervical region leads to dilatation of all

the arterioles, including those in the kidneys; but the general arterial pressure falls so low that, although the renal arterioles are dilated, the rate of blood-flow through the kidney is much diminished and the flow of urine ceases altogether. Stimulation of the spinal cord in the neck leads to constriction of arterioles and a large rise of blood-pressure; and the renal arterioles become so constricted that, in spite of the rise in blood-pressure, the volume of the kidney is lessened, and the flow of urine is small or absent. The injection of adrenalin has the same effect as stimulation of the spinal cord. These and other experiments make it clear that, as seen in the following table, the amount of urine formed by the kidney varies directly with the volume of the kidney, that is to say, with the capillary pressure in the glomeruli; and, if the arterial blood-pressure falls below 40 to 50 mm. Hg, the flow of urine ceases.

Procedure.	General Arterial Pressure.	Renal Vessels.	Kidney-Volume.	Urinary Flow.
Division of spinal cord in neck	Falls to 40 mm. Hg.	Relaxed.	Shrinks.	Ceases.
Stimulation of cord	Rises.	Constricted.	Shrinks.	Diminished.
Stimulation of cord after section of renal nerves	Rises.	Passively dilated.	Swells.	Increased.
Stimulation of renal nerves	Unaffected.	Constricted.	Shrinks.	Diminished.
Stimulation of splanchnic nerves	Rises.	Constricted.	Shrinks.	Diminished.
Hydræmic plethora	Rises.	Dilated.	Swells.	Increased.
Hæmorrhage	Falls.	Constricted.	Shrinks.	Diminished.

If the blood-plasma is filtered through peritoneal membrane soaked in gelatin, it is found that, when the difference of pressure on the two sides of the membrane is 40 mm. Hg or more, the filtrate contains the dissolved constituents of plasma with the exception of protein; with a lower difference of pressure no filtration occurs. This is due to the fact that the proteins in plasma exert an osmotic pressure equal to about 25 mm. Hg, and water tends to pass back by osmosis from the filtrate into the plasma. It is for this reason that the passage of fluid through the glomerular wall ceases when the arterial blood-pressure falls below 40 mm. Hg. If the osmotic pressure of the blood is diminished by decreasing the amount of protein in the plasma, for instance by diluting the plasma, urine may be formed when the blood-pressure is considerably less than 40 mm. Hg. In hydræmic plethora (p. 270), not only is the plasma more dilute, but the renal vessels are dilated and the pressure in the glomeruli is raised;

and the formation of urine may be extremely rapid and profuse. The difference of pressure on the two sides of the walls of the glomeruli may be diminished, not only by lowering the capillary pressure, but also by raising the pressure in the ureter. When the escape of urine from the ureter is prevented, the formation of urine continues until the pressure in the ureter is 40 to 50 mm. Hg below the general arterial pressure, after which no more urine is formed.

We may conclude, therefore, that the amount of urine passing through the glomeruli varies directly with the difference of pressure on the two sides of the glomerular membrane, and that it is formed by a purely physical process of filtration. An apparent exception is seen when the renal vein is ligatured : the capillary pressure rises, but the flow of urine ceases entirely. The reason is that the flow of blood through the glomeruli ceases, and their contents soon consist of little more than a mass of blood-corpuscles, rendering filtration impossible.

The more rapidly urine is formed by the kidney, the more nearly does its composition approximate to that of blood-plasma ; and, when the blood is greatly diluted, for example by repeated injections of Ringer's solution, the percentage of sodium chloride and urea in the plasma and the urine may be identical.

Analysis of Plasma and Urine in Hydræmia. (Barcroft.)

	Chlorides as NaCl.	Urea.
Plasma . . .	0·88 per cent.	0·04 per cent.
Urine . . .	0·88 „	0·05 „

Similar results have been obtained in animals in which the renal tubules were poisoned with corrosive sublimate, or other drugs, so as to eliminate their functions. The fluid passing through the glomeruli appears, therefore, to be isotonic with the blood-plasma, a fact which is intelligible if it is formed by filtration, but which does not fall into line with our knowledge of secretion.

THE FUNCTIONS OF THE TUBULES

As the glomerular filtrate flows along the rest of the tubule, its composition is greatly altered, and the urine which leaves the kidney contains a much higher percentage of urea, uric acid, ammonia, phosphates and sulphates than does the blood-plasma, whereas the concentration of chlorides and inorganic bases in plasma and in urine is almost the same. The following table

(Cushny) brings out the more important differences between blood-plasma and urine :

	Blood-Plasma per cent.	Urine per cent.	Change in Concentration in Kidney.
Water	90–93	95	...
Proteins, fats, and other colloids	7–9	...	...
Glucose	0·1	...	...
Urea	0·03	2·0	60
Uric acid	0·002	0·05	25
Na	0·32	0·35	1
K	0·02	0·15	7
NH_4	0·001	0·04	40
Ca	0·008	0·015	2
Mg	0·0025	0·006	2
Cl	0·37	0·6	2
PO_4	0·009	0·27	30
SO_4	0·003	0·18	60

This change in composition must be effected by means of the active intervention of the cells lining the tubules, and could be brought about in one of two ways. On the one hand, the cells might secrete urea and other substances into the glomerular filtrate as this flows along the tubule. On the other hand, they might absorb water, chlorides, and glucose from this fluid. A combination of these two processes is also possible, secretion taking place in one part, and absorption in some other part, of the tubule. The activity of the cells of the tubules, whether this be secretory or absorptive, is a vital process, involving the expenditure of energy, the consumption of oxygen, and the carrying out of work.

The actual work performed by the tubules can be approximately measured if the osmotic pressure of the blood-plasma and that of the urine are known. The osmotic pressure of any solution is proportional to the depression of its freezing-point below 0° C. (p. 17). Since the freezing-point of blood-plasma is – 0·56° C., and that of urine may be as low as – 4·5° C., the osmotic pressure of urine is very much greater than that of blood, and the amount of work done by the kidneys in producing urine of high osmotic pressure from blood, of which the osmotic pressure is low, is extremely large.

Secretion.—That the tubules can secrete urine has been clearly proved in the case of the frog, in which, owing to the arrangement of the blood-supply to the kidneys, the functions of the glomeruli and tubules can be studied separately. The glomeruli are supplied with blood solely through the renal artery, whereas the tubules have a double supply. On the one hand, the efferent vessels

from the glomeruli enter the network of vessels round the tubules; on the other hand, the tubules receive blood from the renal portal vein, which arises from the femoral vein (fig. 185).

When the renal arteries are ligatured in the frog, the circulation of blood through the glomeruli is completely cut off, but the tubules are still supplied with venous blood through the renal portal vein. The cutting off of the supply of arterial blood to the kidneys is followed by destruction of the epithelium of the tubules, and the frogs secrete no urine. If, however, the frogs are kept in an atmosphere of oxygen after ligature of the renal artery, sufficient oxygen is absorbed and carried to the tubules to replace that normally supplied to them by the arterial blood leaving the glomeruli, and the nutrition of the tubules is maintained. In these circumstances the frogs form small quantities of urine, and, since the glomeruli are excluded, this must come entirely from the renal tubules; it is acid in reaction, and contains urea and salts.

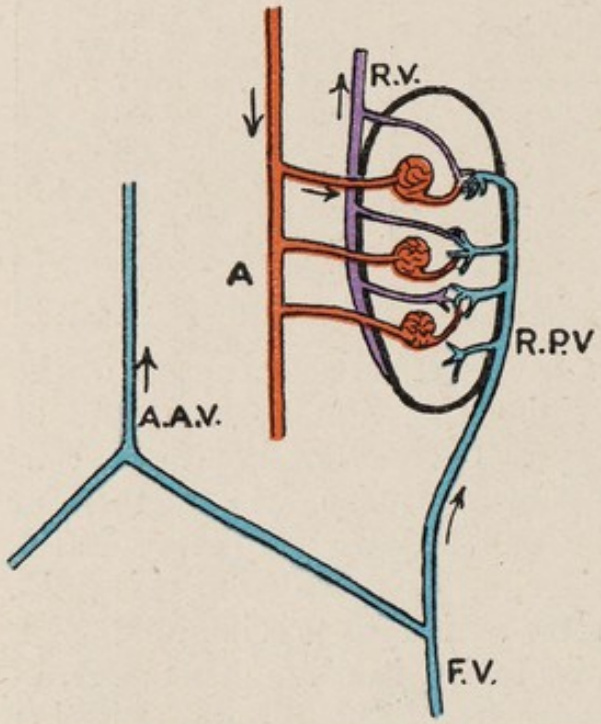


FIG. 185.—The blood-supply to the kidney of the frog.

A., aorta; R.V. renal vein; R.P.V., renal portal vein; F.V., femoral vein; A.A.V., anterior abdominal vein.

Since the tubules of the frog's kidney can secrete urine, it must be believed that the mammalian renal tubules also possess secretory power, unless the functions of the renal tubule of the frog differ fundamentally from those of the mammalian tubule; and there is no reason to suppose that this is the case.

Absorption.—When a mixture of sodium chloride and sodium sulphate is injected into the circulation of an animal, the percentage of chlorides in the urine gradually falls as the experiment continues, and may become less than that in the blood-plasma, while the percentage of sodium sulphate in the urine remains high. This is seen in the following table:—

	Chlorides.	Sulphates.
Blood-serum . .	0·49 per cent.	0·19 per cent.
Urine . . .	0·09 „	2·0 „

Accepting the view that the glomeruli filter off from the blood a fluid containing the same percentage of sodium chloride as that in the blood, this result can only be explained by supposing that as the glomerular filtrate passes down the tubules sodium chloride and water are absorbed.

Similar results have been obtained in frogs. When the kidneys of the frog are perfused through the renal arteries with oxygenated Ringer's solution, the urine is more dilute than the perfusing fluid; this is due to the fact that, as the glomerular filtrate passes down the tubules, the latter absorb sodium chloride. When the tubules are poisoned with corrosive sublimate, absorption no longer takes place, and the urine is isotonic with the perfusing fluid.

In all probability water, other salts and glucose are also absorbed, and the process of absorption serves to prevent the loss of substances which are needed in the body, especially when they are not being replaced in the food. That this is the case is suggested by the observation that, when animals are fed for some days on a diet free from chlorides, their urine is almost free from chlorides, although the percentage of sodium chloride in the blood-plasma may be normal.

While these experiments indicate that the tubules, both in the frog and in the mammal, can exercise both secretory and absorptive functions, much difference of opinion prevails as to the relative importance of the part played by these two processes in the conversion of the glomerular filtrate into normal urine. This arises largely from the fact that the amount and character of the urine formed by the kidney, under natural or experimental conditions, can often be equally well accounted for either on the view that certain urinary constituents have been added to the glomerular filtrate by secretion on the part of the tubules, or on the view that the tubules have absorbed water and salts from the glomerular filtrate. This is the case, for example, as regards the reaction of the urine and the action of diuretics.

Reaction of Urine.—The fluid filtered off from the glomeruli has the same reaction as the blood-plasma, and the acid reaction of normal urine is due to the activity of the cells of the tubules. This can be shown by repeatedly injecting into the dorsal lymph-sac of a frog acid fuchsin, which is almost colourless in neutral or alkaline solutions and red in acid solutions. When the kidneys are subsequently examined microscopically, the glomeruli are seen to be colourless, whereas the cells of the convoluted tubules are red.

Further, the more rapidly urine is formed in the mammal, the more nearly does its reaction approximate to that of the blood.

It has been thought that the acid reaction of urine is due to the fact that, as the glomerular filtrate passes down the tubule, an absorption of bases, especially sodium, takes place, so that the urine becomes acid. But the secretion of acid radicles by the tubules would bring about the same result. Since the urine formed by the frog's kidney after ligature of the renal arteries

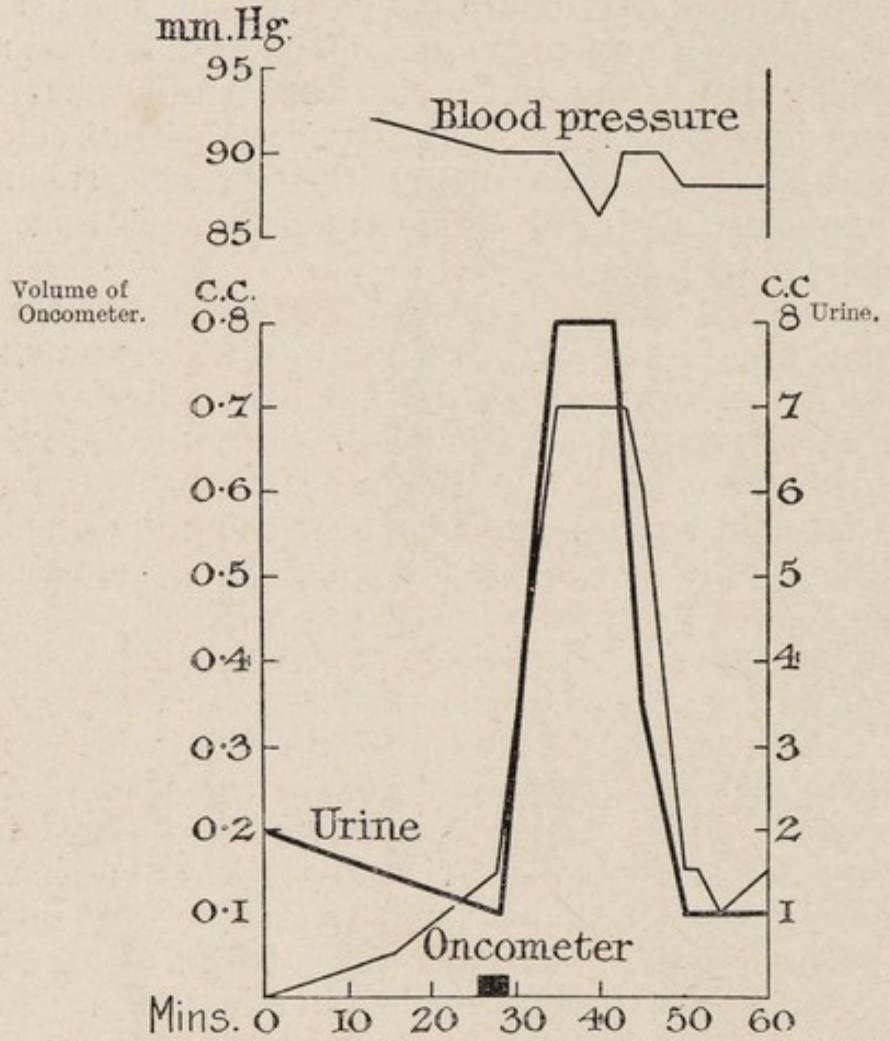


FIG. 186.—Volume of kidney, secretion of urine, and arterial pressure in a rabbit after intravenous injection of 10 c.c. 10 per cent. sodium chloride solution. (From Cushny's *The Secretion of Urine*.)

is acid, it seems probable that the acid reaction of urine is due to secretion of acid radicles rather than to the absorption of bases.

Diuretics.—Substances which, when they enter the blood-stream, increase the amount of urine formed by the kidneys are called *diuretics*. They fall into two groups. One group includes sodium chloride and potassium nitrate; when hypertonic solutions of these salts are injected into the circulation, they raise the osmotic pressure of the blood and bring about the condition of hydræmic plethora (p. 270). The volume of the kidney (fig. 186) and the pressure in the glomerular capillaries are in-

creased, and, as a result of the rise of pressure, more fluid is filtered through the walls of the glomeruli. It may be readily shown that diuretics such as sodium chloride have no specific action, but that they increase the flow of urine solely by raising the capillary pressure. If the usual action of these diuretics in raising the capillary pressure is prevented, the injection of the diuretic does not increase the amount of urine; this can be effected by keeping the volume of the kidney constant by means of a screw-clamp placed on the renal artery.

Under the influence of these diuretics, the amount of glomerular filtrate may be so large and its flow along the tubules so rapid that very little time is available for secretion or absorption on the part of the tubules, and the urine, which is very abundant, may differ but little in composition from blood-plasma minus its protein. That the tubules take no active share in this form of diuresis is shown by the fact that the consumption of oxygen by the kidney is unaffected.

To the other group of diuretics belong sodium sulphate and urea, and in mammals the injection of these substances into the blood-stream leads to an increased flow of urine containing a higher percentage of sodium sulphate or urea than is present in the blood-plasma. At the same time the kidney consumes more oxygen.

	Oxygen used by Kidney per Gram per Minute.	Percentage of Sodium Sulphate in Urine.
(1) Normal kidney . . .	0·04 c.c.	0·26 per cent.
(2) After the injection of sodium sulphate	0·09 c.c.	1·25 ,,

These results clearly point to the active intervention of the tubules as well as to increased glomerular filtration, and have been regarded by some authorities as evidence of secretory activity on the part of the tubules. Others, however, consider that the tubules absorb a large amount of water from the glomerular filtrate, but cannot absorb urea or sodium sulphate. Hence the concentration of these substances in the urine is greater than that of the blood, and the work done by the tubules in absorbing water in opposition to osmotic pressure involves a larger consumption of oxygen. On the whole, absorption of water, rather than secretion of urea or sodium sulphate, accounts most satisfactorily for the action of these diuretics.

Cushny has recently put forward the view that the *sole* function of the tubules is to absorb from the glomerular filtrate a fluid

practically identical in composition with Locke's fluid (p. 244) : in certain circumstances some other salts may be absorbed, but no absorption of urea, uric acid or sodium sulphate is possible. The essential features of this hypothesis are, first, the filtration through the glomeruli of a very large amount (60 litres or more in twenty-four hours) of fluid identical in composition with blood-plasma minus its protein ; and second, the absorption by the vital activity of the tubules of most of the water, and of sodium chloride and glucose, the composition of the fluid absorbed being practically constant, while the amount absorbed is variable. Hence the amount of the urine leaving the kidney is the resultant of the rate of filtration through the glomeruli and that of absorption by the tubules, and its composition is determined partly by these factors and partly by the composition of the blood-plasma. The fundamental difference between Cushny's and Ludwig's views is that Ludwig believed absorption to be a purely physical process, whereas Cushny regards it as being brought about by the vital activity of the tubules.

Summary.—From the foregoing evidence it may be concluded, first, that the glomeruli, in all probability, simply filter off from the blood a fluid identical in composition with blood-plasma minus its protein. Secondly, the tubules of the frog's kidney, and presumably also those of the mammalian kidney, can secrete into the glomerular filtrate water, urea, and other urinary constituents. Thirdly, the tubules absorb water, sodium chloride, and at times other dissolved substances from the glomerular filtrate, this process possibly occurring to a much greater extent than has hitherto been supposed.

In the normal kidney, it is probable that all these processes are taking place simultaneously in different parts of the tubule, one or other predominating according to circumstances.

SECTION III

MICTURITION

The urine formed in the kidneys passes along the ureters to the bladder, where it accumulates, the bladder being emptied from time to time by the process of micturition. The flow of urine along the ureters is assisted by rhythmic waves of contraction, passing down from the pelvis of the kidney to the bladder at intervals of a few seconds ; they can still be observed in the ureter when it is isolated from the central nervous system.

The wall of the bladder consists of unstriated muscular fibres

arranged in three layers, an outer and an inner longitudinal layer, and a middle layer of fibres running circularly ; it is lined by transitional epithelium. When the muscular walls contract they lessen the size of the cavity. The escape of urine from the relaxed bladder is prevented by two sphincters, namely, first, circular unstriped muscular fibres, forming a loop round the orifice of the bladder and called the *trigonal sphincter*, and, secondly, the *sphincter urogenitalis*, or compressor urethræ, which encloses the second part of the urethra, and is composed of striated muscular fibres. The bladder receives its nerve-supply from (1) the pelvic nerves, or nervi erigentes, stimulation of which causes it to contract, and (2) sympathetic fibres from the hypogastric plexus, stimulation of which is followed in some animals by inhibition, and in others by slight contraction, of the wall of the bladder. Afferent fibres also pass from the bladder in the pelvic nerves to the spinal cord.

Micturition is normally carried out as a reflex action which, in the adult, is controlled, and can be inhibited, by impulses from the higher parts of the brain. Distension of the bladder will give rise to impulses which, travelling to the spinal cord, reflexly bring about emptying of the bladder by the contraction of its muscular coat, the nerve-cells concerned in the reflex lying in the lumbo-sacral region of the cord ; the ready escape of urine is made possible by the simultaneous relaxation of the sphincter muscles. The intensity of the afferent impulses varies with the rate of filling of the bladder. When the bladder fills slowly, its muscular wall relaxes, and it may contain a considerable amount of urine before any appreciable tension is placed upon its muscular fibres. On the contrary, when urine is being formed rapidly, the tension within the bladder may be quickly and greatly increased by the presence of a comparatively small quantity of urine. In man, micturition usually occurs when the pressure within the bladder is about 150 mm. of water ; and, if the pressure is suddenly raised to this level by injecting fluid through the urethra into the bladder, the desire for micturition is experienced.

Transection of the spinal cord in the upper lumbar region does not destroy the reflex mechanism, though it severs the path by which sensory impulses reach the brain and voluntary impulses pass to the lumbo-sacral centre. By means of voluntary impulses the emptying of the bladder can be inhibited in the adult, but in the infant such impulses are lacking and the act of micturition is purely reflex. The emptying of the bladder is usually assisted by voluntary contraction of the abdominal muscles, and in man such a contraction, by raising the intra-abdominal pressure and

thereby increasing the tension within the bladder, frequently initiates the reflex action.

When the centre in the lumbo-sacral region is destroyed, for instance as the result of injury, the bladder still reacts like plain muscle elsewhere, and increased tension causes it to contract rhythmically and to expel part of its contents. As soon as the pressure within the bladder falls below a certain level, however, it fails to overcome the resistance offered by the sphincter muscles, and the bladder is not completely emptied.

CHAPTER XIV

THE DUCTLESS GLANDS

The ductless glands comprise the suprarenal glands, the pituitary body, the thyroid and parathyroid glands, the thymus gland, the pineal gland, the spleen, and some smaller glands such as the carotid body. They are characterised by the absence of a duct, the products of their activity passing into the blood-stream, either directly or by way of the lymphatic system, and therefore being described as *internal secretions*. The spleen differs from the other ductless glands in that it is concerned with metabolic changes in the constituents of the blood rather than with the production of a true internal secretion. Its function has already been discussed (p. 413).

The formation of an internal secretion is not confined to the ductless glands. It is an important function of the pancreas, the mucous membrane of the pyloric portion of the stomach, the mucous membrane of the small intestine, the testes, the ovaries, and probably many other organs, but in the case of the ductless glands it is the only function.

The internal secretions of the ductless glands, with the exception of the spleen, belong to the class of bodies known as hormones, whose general characteristics have already been dealt with (p. 345). The presence of these hormones in the body is in many cases essential to health and even to life; and the activity of the internally secreting glands is correlated with and regulates the functions of distant organs, the only link being the blood by which the hormone is carried from its place of origin to its place of action.

Sharpey Schafer uses the term "endocrine organs" to include the ductless glands exclusive of the spleen. He considers that the word hormone (exciting substance) is inapplicable to some internal secretions, which have an inhibitory function. He terms the latter "chalones," and groups hormones and chalones together as "autacoid substances," because of their drug-like action.

Much of our knowledge of the functions of the ductless glands is derived from the study of the symptoms observed in human beings in whom one or other of them is diseased. Hence it is usual in studying their functions to consider (1) the effects of disease in these glands in man, noting, on the one hand, the conditions associated with hypertrophy and, presumably, increased secretion, and, on the other, those associated with atrophy, when the secretion is diminished or absent, (2) the effect of their extirpation in animals, and (3) the effects of extracts of the glands, either upon normal animals or as therapeutic agents in man.

THE SUPRARENAL GLANDS

One suprarenal gland lies at the upper end of each kidney. Each consists of an outer, yellowish cortex partially or completely enclosing a darker, central portion, the medulla.

Structure.—The cortex is composed of cells arranged in radial columns and forming three zones : an outer or *zona glomerulosa*, middle or *zona fasciculata*, and inner or *zona reticularis*. The cells are polyhedral, the cell-substance being clear and often containing lipoid globules. A number of arteries penetrate the capsule of the gland and open into sinusoids, which run between the columns of cortical cells towards the medulla.

The cortical sinusoids open in the medulla into venous spaces, between which the medullary cells are closely packed. These cells are granular and often pigmented ; they contain a substance which stains brown with chromates, and which has therefore been described as *chromaffine* material. This is also found, apart from the suprarenal glands, in small masses of cells (paraganglia) lying along the large abdominal blood-vessels, and in or close to the sympathetic ganglia. The amount of the accessory chromaffine substance varies greatly in different groups of animals.

The venous spaces of the medulla open into the suprarenal vein, which leaves the gland at the hilum. The glands are supplied with nerve-fibres from the semilunar ganglia (cœliac plexus), and a few scattered nerve-cells are present.

The cortical and medullary parts of the glands have different origins, the cortex being developed from mesodermic tissue (the Wolffian body), whereas the medulla is ectodermic, forming part of the primitive sympathetic system, from which it finally becomes separated and differentiated. In some fishes the cortical and medullary tissue persist as anatomically separate organs, and it is not known whether their coalescence into a single organ in mammals implies any physiological relationship between them.

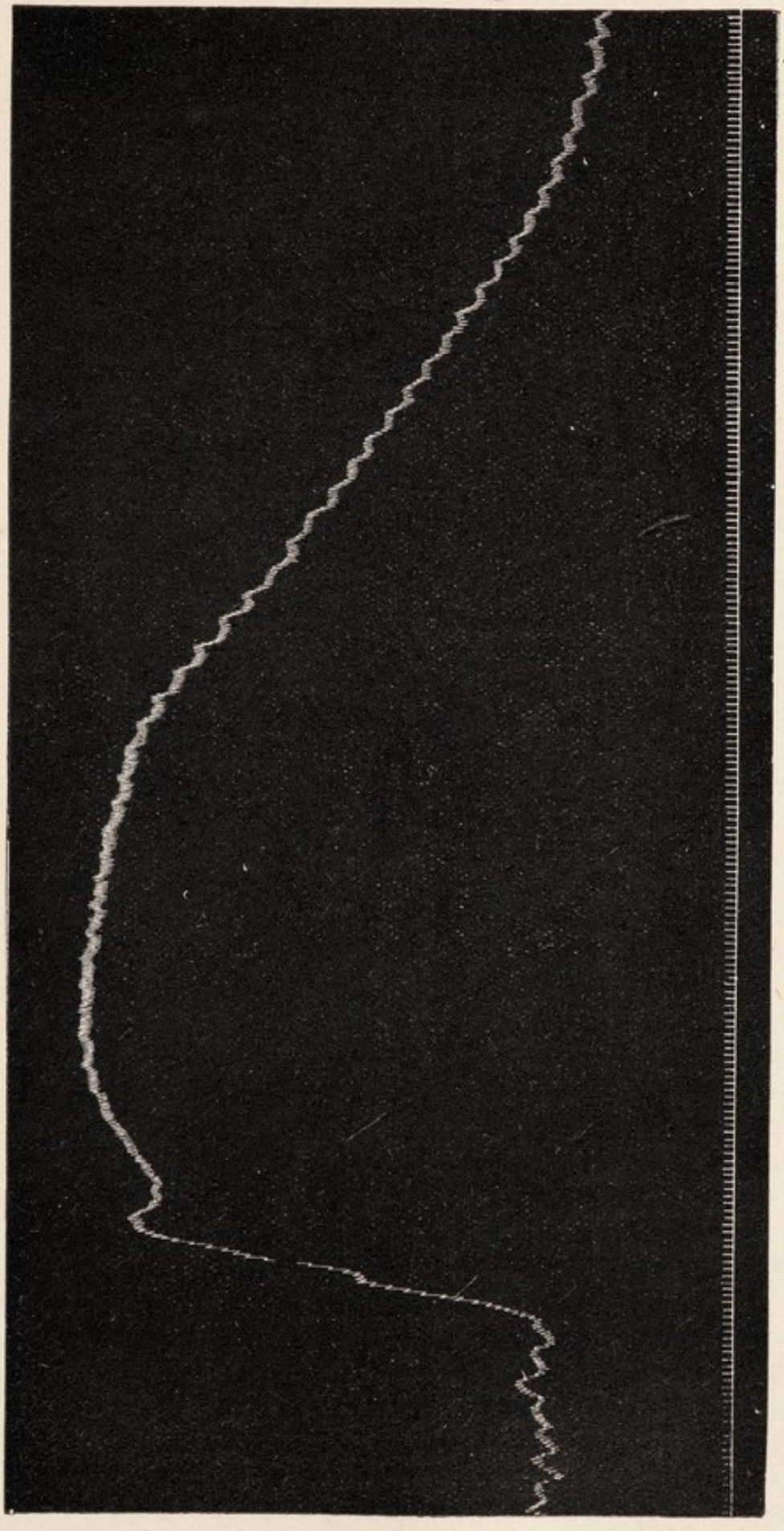
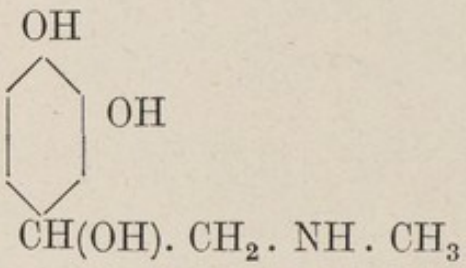


FIG. 187.—Arterial blood-pressure. Effect of injection of suprarenal extract. The vagus nerves have been divided. Time in seconds. (From *Practical Physiology*, by Pembrey and others.)

Function.—In 1855 Addison pointed out that, in man, a disease, of which the chief symptoms are prostration, muscular wasting, vomiting, and pigmentation of the skin, and which ends fatally, is associated with disease or atrophy of the suprarenal glands. This observation was soon followed by the study of the effects of the removal of the glands in animals; and it was found that, in mammals, this was followed by death in two or three days. The blood-pressure falls to a low level before the fatal termination. Removal of one suprarenal is followed by hypertrophy, mainly cortical, of the other.

Subsequent investigation has thrown but little light on the functions of the cortical part of the gland, beyond the fact that tumours of the cortex are sometimes associated with abnormally precocious sexual development. In fishes the removal of the interrenal body, which corresponds in structure and origin with the cortex of the mammalian suprarenal gland, is said by some observers to cause death, though others deny this.

The medulla contains a substance, *adrenalin*, which can be extracted from it in the pure condition, and which has the constitutional formula—



Adrenalin has also been prepared synthetically.

The brown staining of the medulla, when the gland is hardened in a chromate solution, is due to the combination of the chromate with adrenalin, and the depth of the colour is roughly proportional to the amount of adrenalin present. The accessory chromaffine material, which also stains with chromate, contains adrenalin. Adrenalin is completely absent from the cortex of the suprarenal glands.

When a small amount of adrenalin is injected into a blood-vessel, it produces constriction of almost all the arterioles of the body, and, if the vagus nerves have been divided, an enormous rise of blood-pressure is produced (fig. 187). When the vagus nerves are intact the rise of blood-pressure is less (fig. 188), because, in accordance with Marey's law (p. 249), slowing of the heart takes place.

The action of adrenalin is not confined, however, to the blood-vessels, but extends to every structure in the body which is normally supplied with nerve-fibres from the sympathetic system.

It stimulates the nerve-endings of these fibres in the structures which they supply, and the results of the injection of adrenalin are identical with those of stimulation of the entire sympathetic system. Thus it increases the force and (if the vagi are divided) the rate of the heart, and at the same time dilates the coronary vessels, so that, in spite of the rise in arterial pressure, the efficiency of the heart is maintained and its output may even become larger. It inhibits the movements of the digestive tract and (in many animals) of the bladder, but causes constriction of the ileo-colic sphincter; it may also produce sweating, erection of hairs, dilatation of the pupil, and contraction of the pregnant uterus.

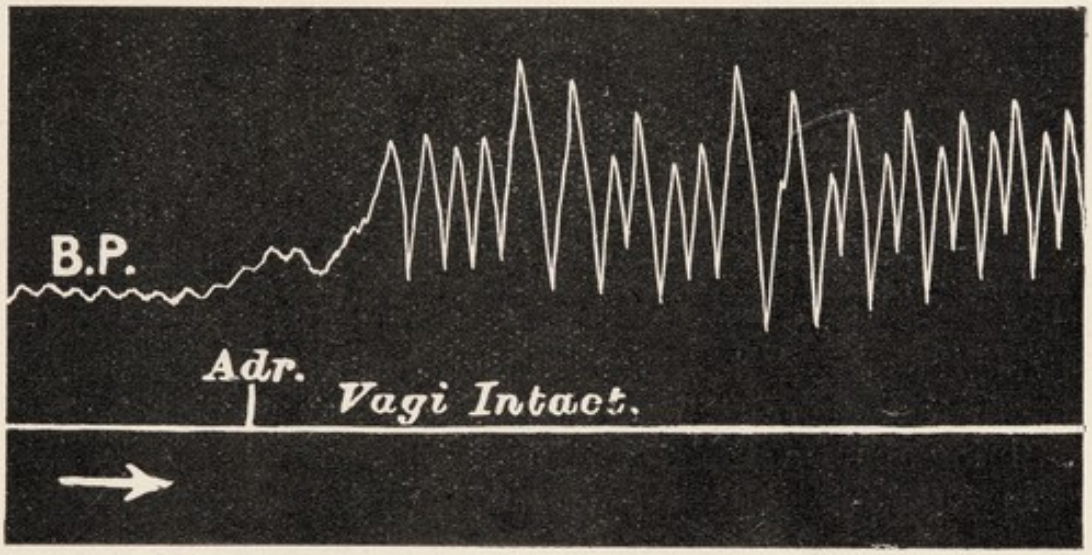


FIG. 188.—Tracing of arterial pressure. Effect of injecting 0·05 mgr. adrenalin into a vein.

Note the marked slowing of the heart.

Adrenalin is an extremely active substance, and even 0·0025 milligram per kilo of body-weight, when injected into the circulation, produces a definite rise of blood-pressure.

The exact point of action of adrenalin is not on the sympathetic endings proper, but probably on some receptive substance (neuro-muscular junction), which lies between the actual nerve-ending and the muscular fibre, and does not degenerate when the post-ganglionic fibres are divided. This can be shown by the following experiment. When the cervical sympathetic nerve, which supplies the iris, is stimulated, or when adrenalin is injected into a vein, the pupil dilates. If the superior cervical ganglion on one side is removed, the post-ganglionic fibres and their nerve-endings degenerate, and, when time has been allowed for their degeneration, electrical stimulation of these fibres produces no effect on the pupil, whereas on the injection of adrenalin the pupil dilates even more fully than in the normal animal.

Secretion of Adrenalin.—Adrenalin is constantly being formed by the suprarenal glands, from which it passes into the blood-stream, and it is thus a true internal secretion. This secretion can be increased in amount by stimulation of the splanchnic nerves, which contain secretory fibres for the suprarenal glands. The nerves may be stimulated either directly, *e.g.* by stimulation of the peripheral end of a divided splanchnic nerve, or reflexly, the centre for this reflex being very near the vaso-motor centre. The occurrence of reflex secretion of adrenalin by the suprarenal glands can be demonstrated in the following manner: one splanchnic nerve, *e.g.* the left, is divided in the cat, so as to cut off the efferent path to that gland; and it is found that, as the result either (1) of stimulation of sensory nerves, or (2) of violent emotion, such as pain or fear, the adrenalin is discharged more or less completely from the right suprarenal gland, while the left gland remains unaffected. Evidently division of a splanchnic nerve, by breaking the efferent side of the reflex arc, prevents any reflex secretion of adrenalin from the corresponding gland into the blood-stream. The effects of stimulation of the splanchnic nerve, and the consequent setting free of adrenalin, on the arterial blood-pressure and on the constriction of arterioles outside the splanchnic area, have already been described (p. 264). Anæsthetics, such as chloroform, also excite the adrenalin centre and bring about a discharge of adrenalin.

In all probability, the varying activity of the suprarenal glands, brought about by impulses reaching them along the splanchnic nerves, plays an important part in the adjustment of the vascular system to the changes constantly taking place in the body. A striking instance of this adjustment is seen in states of violent emotion, such as rage, pain, or fear. The additional adrenalin sent into the blood-stream, in these circumstances, increases the amount of glucose passing from the liver into the blood, thereby providing a further supply of sugar to the skeletal muscles; and, in so far as it raises the blood-pressure, it also improves the nutrition and efficiency of the heart and the blood-supply to the brain. In this way the reaction of the animal to these emotional states, by movements of attack or defence, is rendered more effective.

Owing to its action on the blood-vessels, adrenalin has proved of great value in checking hæmorrhage when applied locally. In Addison's disease the repeated injection of adrenalin is stated to have produced improvement in some cases, though the disease cannot be cured.

THE PITUITARY BODY (HYPOPHYSIS CEREBRI)

The pituitary body lies in the sella turcica, and is connected with the floor of the third ventricle by a hollow stalk. It consists of two lobes, differing from each other both in origin and

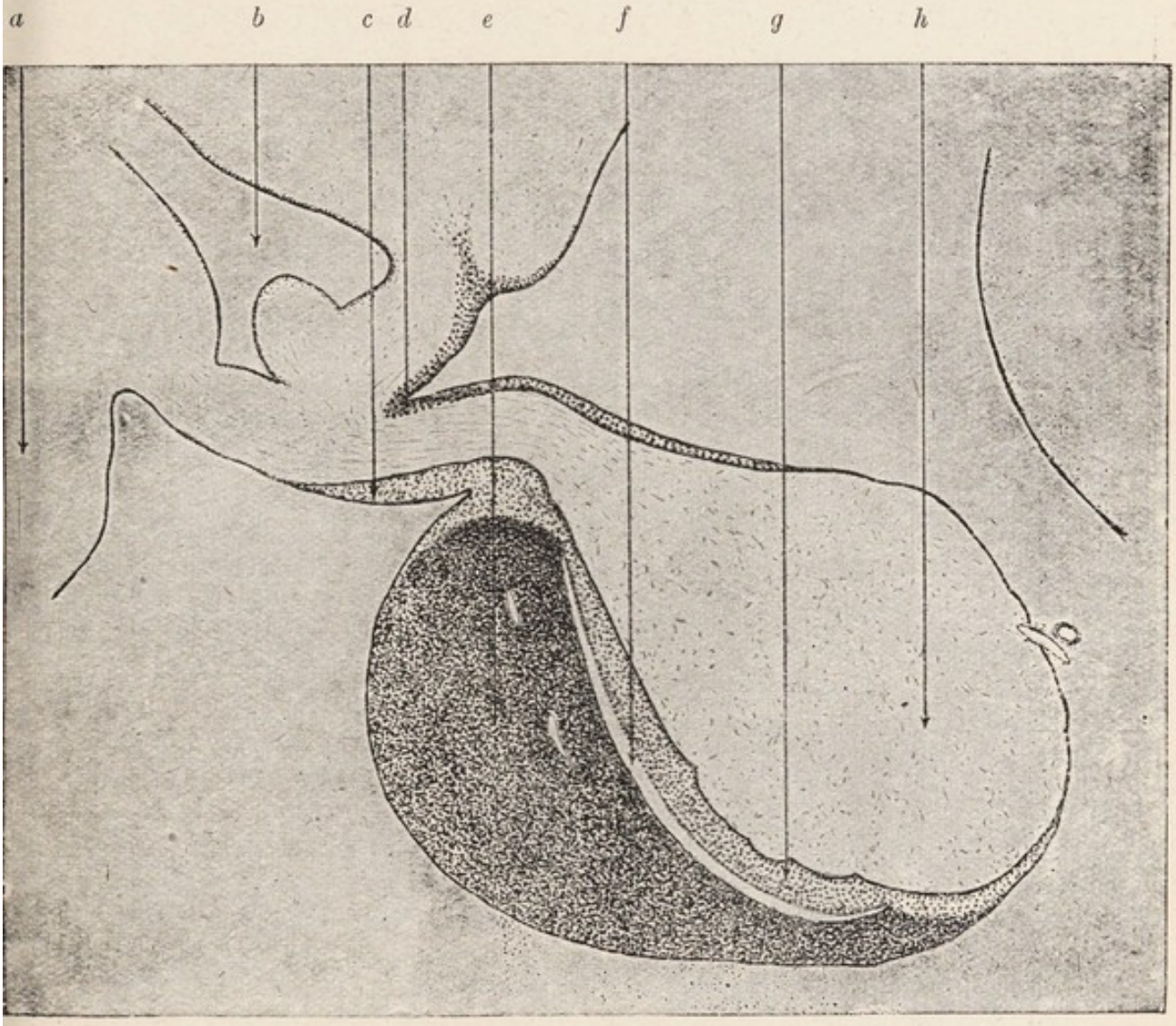


FIG. 189.—Mesial sagittal section through the pituitary body of an adult monkey (semi-diagrammatic). (Herring.)

a, optic chiasma; *b*, infundibulum; *c*, *d*, extension of pars intermedia round neck of pituitary; *e*, pars anterior; *f*, intraglandular cleft; *g*, pars intermedia; *h*, pars nervosa.

appearance (fig. 189). The anterior portion is formed from a hollow upgrowth of buccal ectoderm, the posterior part from a hollow downgrowth from the floor of the third ventricle. The cavity of the ectodermic portion persists as a cleft, separating the anterior and posterior lobes of the fully developed hypophysis. The cavity of the nervous portion becomes obliterated in man, except in the stalk. The anterior lobe, or *pars anterior*, is glandular in structure. The posterior lobe consists of two parts, (1) the *pars nervosa*, composed of neuroglia, and (2) the *pars*

intermedia, a thin layer, ectodermic in origin, applied to and partially surrounding the anterior portion of the pars nervosa.

Structure.—The pars anterior consists of columns and groups of cells, and has a rich blood-supply. The cells are of two kinds, clear and granular; most of the granular cells contain eosinophile granules, but some contain basiphile granules. The pars intermedia also consists of columns of cells, but these contain finer granules than the granular cells of the pars anterior, and some show a hyaline or colloid change. Colloid material is also present between the cells, and the same substance is found in spaces in the pars nervosa,

FIG. 190.—On the left a dog twelve months old: its pituitary body was partially removed at the age of eight weeks. On the right a normal dog of the same litter. (Aschner.)

(From *The Endocrine Organs*, Sharpey Schafer.)

and may sometimes be traced into the cavity of the infundibulum. The colloid of the hypophysis differs from that of the thyroid gland in containing no iodine.

Function.—Functionally the pars intermedia is associated with the pars nervosa, and the posterior lobe has apparently an entirely different rôle from that of the anterior lobe. This is shown by the observation that removal of the entire gland, or of the anterior lobe, is followed by death in a few days, although the animal survives after removal of the posterior lobe, provided that a portion of the anterior lobe is left intact. The anterior lobe is therefore essential to life, whereas the posterior lobe is not.

Removal of the greater part of the pituitary body in young animals leads to retardation of growth, to failure of sexual development, and to obesity (fig. 190). Similar results follow

accidental injury in children, but, in contrast with the effects of thyroid deficiency, mental development is not seriously impaired; when it occurs in the human subject, the condition is known as *infantilism*. The retardation of growth and the failure of sexual development are due to the partial removal of the anterior lobe, whereas the obesity is believed to result from removal of the posterior lobe.

Hypertrophy of the anterior lobe of the gland in man produces the disease known as *acromegaly*; the chief features of this disease are enlargement of the bones, especially those of the hands, feet, and face (fig. 191), thickening of the skin, diminu-

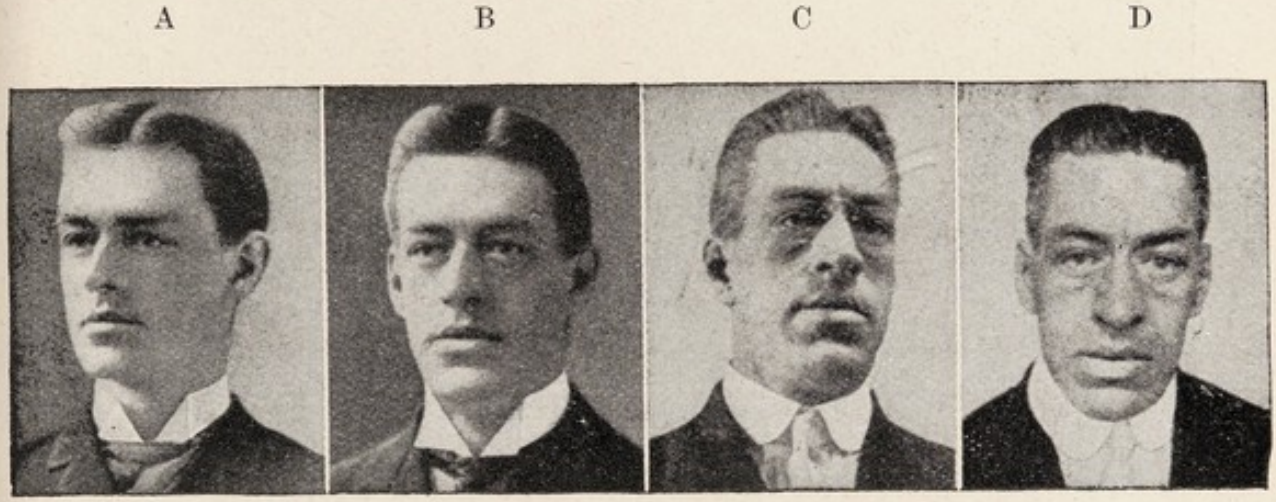


FIG. 191.—Four photographs of the same person showing the gradual development of acromegaly. A, at twenty-four years of age (normal); B, at twenty-nine (onset of disease); C, at thirty-seven; D, at forty-two. (Cushing.)

(From *The Endocrine Organs*, Sharpey Schafer.)

tion of sexual activity, and frequently glycosuria. If the enlargement of the pituitary body occurs in early life, before the epiphyses have united with the long bones, these bones increase greatly in length and the subject becomes abnormally tall, the condition being known as *gigantism*.

Both the experimental and clinical evidence make it clear that the anterior lobe produces, and sends into the blood-stream, one or more substances, presumably hormones, which influence growth and sexual development. It might be expected, therefore, that the administration of the anterior lobe, or of extracts of it, to young growing animals would stimulate their growth, and would cause them to attain a larger size than normal animals. Most observers state, however, that growth is either unaffected, or may even be retarded, by the addition of pituitary body or pituitary extract to the diet of young animals.

The posterior lobe has no influence on growth, but it plays a part in the metabolism of carbohydrate. This is shown by the

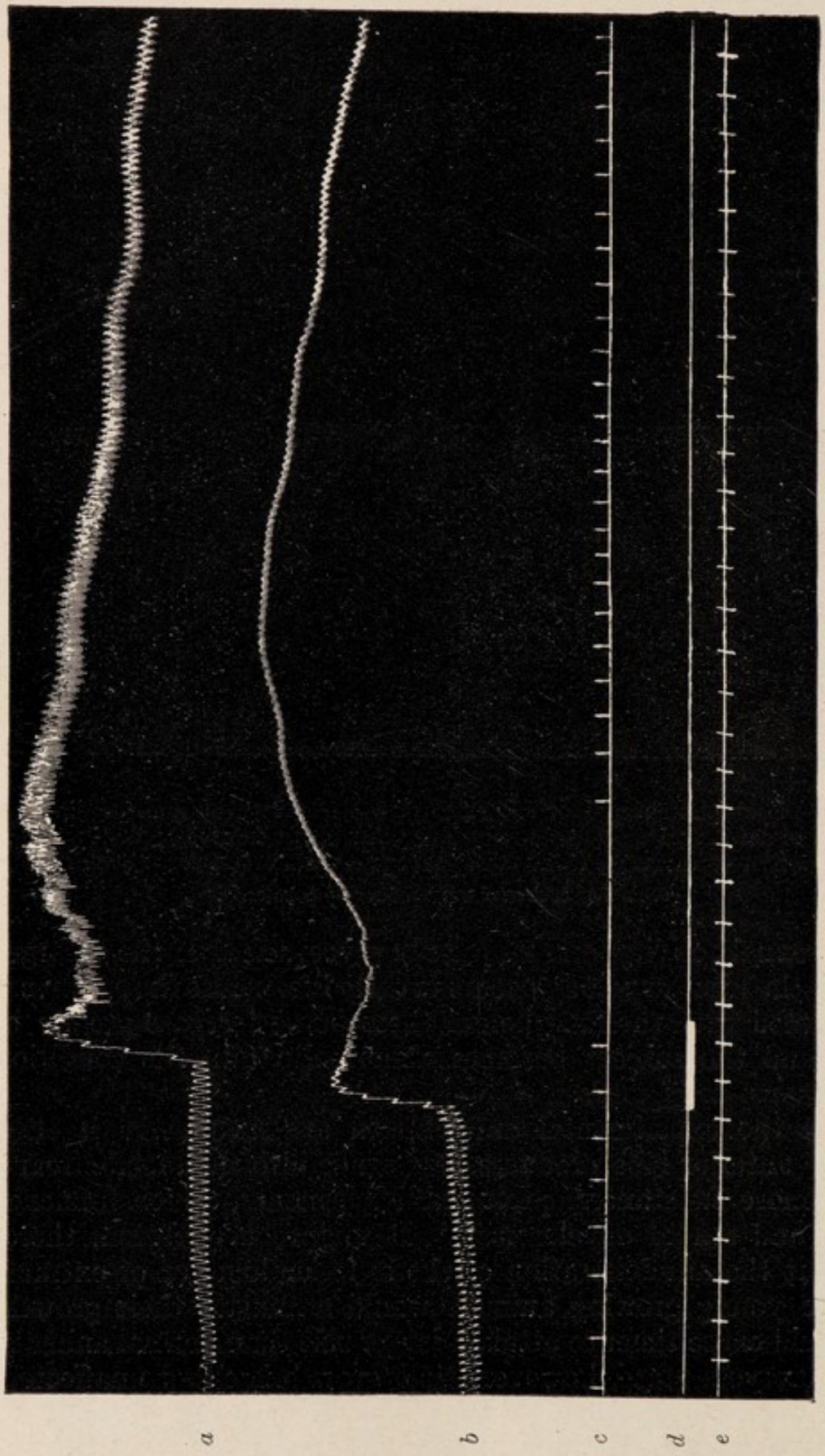


FIG. 192.—Tracing showing the effect of injecting an extract of the posterior lobe of the pituitary body (Sharpey Schafer and Herring.)

a, arterial pressure; *b*, tracing of kidney-volume; *c*, drops of urine; *d*, signal; *e*, time in seconds.

(From *The Endocrine Organs*, Sharpey Schafer.)

fact that over-activity of the posterior lobe leads to an excessive formation of urine (polyuria), and often to glycosuria, whereas atrophy of the lobe is followed by increased tolerance for sugar, and very large amounts of sugar can be rapidly ingested without setting up alimentary glycosuria. Further, a watery or saline extract of this lobe, when injected into the blood-stream, has a rapid and striking physiological action, causing contraction of unstriped muscle throughout the body, with the exception of the muscle of the renal blood-vessels. Owing to the constriction of the arterioles, there is a considerable rise of arterial blood-pressure, and, since the renal vessels are not constricted, the blood-flow through the kidney becomes more rapid and abundant, and its volume increases. Injection of pituitary extract has, as one of its results, an increased flow of urine (fig. 192), but this is probably due to the increased flow of blood through the kidney, rather than to any specific effect of the extract on the renal cells.

Other effects produced by the injection of extracts of the posterior lobe are contraction of the uterus, especially during and just after parturition, contraction of the bladder, increased peristaltic movements of the intestines, and constriction of the bronchioles.

When the mammary gland of a lactating animal is incised, and the milk which flows from it is collected, it is found that the injection of pituitary extract produces almost immediately an increase in the amount of milk escaping from the gland. Observations on normally lactating animals have shown, however, that the total yield of milk in the course of twenty-four hours is not increased beyond the normal by the administration of pituitary extract. It may be concluded, therefore, that the extract does not increase the formation of milk, but that it merely causes contraction of the unstriped muscle in the ducts and alveoli, so that the gland is more completely emptied than would otherwise be the case.

The action of pituitary extract on plain muscle differs in several respects from that of adrenalin. First, the former acts directly on the muscle, whereas adrenalin stimulates the sympathetic nerve-endings; secondly, pituitary extract leads to contraction of all unstriped muscle, in contrast with adrenalin, which inhibits some muscle, for example, that of the digestive tract; and, thirdly, the action of pituitary extract is more prolonged than that of adrenalin.

There is some evidence that the hormone (there may be more than one) which produces these effects is formed in the pars intermedia, and passes through the pars nervosa into the cerebro-spinal fluid. Herring has shown that extracts of the pars nervosa may be even more active than extracts of the pars intermedia;

and the presence of the pituitary hormone in cerebro-spinal fluid under certain conditions has been demonstrated. The hormone must eventually make its way into the blood-stream, but at present nothing is definitely known as to the circumstances in which it is set free from the gland, or as to the part which it plays in the normal life of the animal.

THE THYROID GLAND

The *thyroid* gland consists of two lobes, one on each side of the trachea, united by an isthmus ; and it is composed of closed

A B

FIG. 193.—Case of myxœdema (A) before and (B) after treatment. (By permission of the Editor of *The Practitioner.*)

spherical vesicles of varying size, held together by connective tissue. Each vesicle contains a viscid, colloid material surrounded by a single layer of cubical cells, with no basement-membrane. The thyroid gland contains iodine in organic combination, and it has recently been shown that the iodine is combined with tryptophane to form tri-iodo-tryptophane. This compound has been named *thyroxin.*

The gland is richly supplied with blood-vessels and nerves. Numerous lymphatic vessels are also found in it, and these may sometimes be seen to contain colloid material.

Function.—Attention was first called to the importance of the thyroid gland by the observation that it is atrophied in the disease known as *myxœdema* (fig. 193). The symptoms of

myxœdema are obesity, dryness and thickening of the skin, falling out of the hair, slowness of mental processes and of speech; indeed, all the metabolic processes in the body become more sluggish, and the respiratory exchange is diminished.

Deficiency or absence of the gland at birth gives rise to the condition known as *cretinism*, in which growth, both physical and mental, is extremely retarded; a cretin aged fifteen to eighteen years may resemble a child of two or three years of age in its size and mental development. The symptoms, both of cretinism and of myxœdema, are due to the absence of some substance normally formed by the thyroid gland, from which it passes into the lymphatics and thence into the blood-stream. This is shown by the fact that extracts of the gland, or the gland itself, when given by the mouth, lead to complete recovery in myxœdema and to very marked improvement in cretinism.

Fig. 194.—Case of exophthalmic goitre. (From *The Endocrine Organs*, Sharpey Schafer.)

The effect of operative removal of the thyroid in man, or experimental removal in animals, may be complicated by the results of simultaneous removal of the parathyroid glands, which, especially in carnivora, are often imbedded in the substance of the thyroid. When the latter is removed without interference with the parathyroids, typical myxœdema develops. This is especially well marked in monkeys. The myxœdema produced in this way can also be cured by feeding with thyroid gland substance or an extract of it.

In the disease known as *exophthalmic goitre* the thyroid is enlarged, and the symptoms are in marked contrast with those of myxœdema. The patient loses flesh, there is great nervous excitability, an increased pulse-rate, and protrusion of the eyeballs (fig. 194). Associated with the loss of flesh there is increased metabolism, with a corresponding increase of the output of nitrogen and carbonic acid. The vesicles of the thyroid gland show evidence of activity in the fact that the epithelial cells assume a more columnar shape, and the contents are more fluid than is normally the case.

Administration of thyroid gland or thyroid extract gives rise, either in a healthy man or in animals, to increased nitrogenous metabolism. Large doses may lead to increased pulse-rate, nervous excitability, sweating, glycosuria, and loss of weight.

The action of the gland seems to depend partly or wholly upon the presence of iodine in organic combination, since the activity of the extracts is greater when they contain much iodine. It is evident that the thyroid gland exerts an important influence on the metabolism of the body, including the nervous system. This is further shown by the observation that in myxœdema much larger quantities of sugar can be taken by the mouth without producing alimentary glycosuria than is the case in normal persons.

THE PARATHYROID GLANDS

The parathyroid glands are four in number, two on each side, and lie close to, or imbedded in, the thyroid gland. They are quite small, and each is composed of a mass of cells, sometimes arranged in columns. Many of the cells have clear cytoplasm, and some of these may contain glycogen. Others are characterised by containing eosinophile granules.

Function.—Our knowledge of the function of the parathyroids is derived almost entirely from observations on the effects of their removal in animals or in man. Extirpation of all four glands is followed in a day or two by acute symptoms, which are, for the most part, of nervous origin. The excitability of the central nervous system is increased, and reflexes are not only evoked more readily, but are unusually vigorous; tremors of the skeletal muscles, and from time to time prolonged muscular spasm and even convulsions, also occur. Since the muscular twitchings and the convulsions cease after section of the motor nerves, they must be central in origin; and it is probable that they result from abnormal excitability of the spinal motor neurons. The condition is known as *tetany*, and, although recovery frequently occurs, it is sometimes fatal in a few days, more especially in carnivora and in young animals. There is some evidence that vaso-motor reflexes are evoked more readily after parathyroidectomy, and that the irritability of the sympathetic system is also exaggerated.

Noel Paton has shown that the injection of guanidin is followed by symptoms which closely resemble those of parathyroid tetany, and he has brought forward evidence which suggests that the function of the parathyroid glands is to control the metabolism

of guanidin, and that this substance accumulates in the blood when the glands are removed.

THE THYMUS

The thymus is composed of lobules united by connective tissue; each lobule consists of an outer denser cortex and an inner medullary part, the cortex being subdivided by strands of connective tissue into a number of compartments. Both the cortex and medulla are composed of a meshwork of fibrils covered with flattened cells, the meshes being occupied by lymphocytes. In the medulla are found a number of small masses of flattened epithelial cells arranged concentrically; they are called Hassall's corpuscles, and represent the remains of part of the epithelium of the third visceral pouch. The gland is abundantly supplied with blood-vessels. In man it reaches its maximum size during the first two or three years of life, and then becomes smaller, usually disappearing with the occurrence of puberty, and being almost completely absent in the adult. After its removal in animals, the testes develop more rapidly, and, conversely, castration delays the atrophy of the thymus. When young animals receive fresh thymus with their food, sexual maturity is delayed, and, in the male, degeneration of the testis takes place.

The thymus thus appears to exercise a restraining influence on the development of the reproductive organs, and to undergo atrophy when its function has been accomplished. In rabbits the atrophy occurs at an earlier date if the animals are utilised for breeding purposes.

CHAPTER XV

REPRODUCTION

In all except the lowest forms of life, the continuance of the species is effected by means of certain tissues set apart for this purpose. These form cells which develop into a new animal of the same species, the process constituting reproduction. In most animals these cells are of two kinds, namely, spermatozoa and ova, formed by the reproductive organs of the male and female respectively; a spermatozoon and ovum fuse to form a new cell which develops into an animal resembling its parents in its general character. This, again, is capable of reproducing itself.

THE MALE REPRODUCTIVE ORGANS

These consist of the testes, which form spermatozoa, and of accessory organs, namely the vesiculæ seminales, the prostate gland, the glands of Cowper, and the penis.

Each **testis** is covered by a strong fibrous capsule, the *tunica albuginea*, from which trabeculæ pass into the gland, dividing it into lobules, which contain the seminal tubules. Each tubule is convoluted, and consists of a lining epithelium several layers thick, resting upon a laminated basement-membrane. The cells nearest the basement-membrane are called *spermatogonia*; these divide, giving rise to the *spermatocytes*, which lie more internally. Within the layer of spermatocytes, and formed from them by division, are the *spermatids*, which develop into *spermatozoa*. Lying in the connective tissue between the tubules are groups of polyhedral cells, called *interstitial cells*. The seminal tubules lead into straight tubules (*rete testis*) which open into the *epididymis*; this is a convoluted tube lined by ciliated cells, and is continued as the *vas deferens*, a tube with a thick muscular wall, which opens into the prostatic part of the urethra. The vesiculæ seminales are branched sacculated outgrowths from the vas deferens. The *prostate gland* surrounds the first part of the

urethra, and is made up of numerous branched, glandular tubes supported by connective tissue and unstriated muscular tissue.

The *penis* consists of erectile tissue, which forms the corpus spongiosum and the two corpora cavernosa, and it contains the urethra ; the erectile tissue is made up of a meshwork of elastic and muscular tissue ; arterioles open directly into the spaces in the meshwork, the blood escaping into veins. When the muscular fibres of the arterioles are relaxed, and the veins are compressed by the bulbo-cavernosus muscle, the spaces become distended with blood, causing erection of the organ.

The formation of spermatozoa begins at puberty, and each spermatozoon consists of a head, body, and tail, and is actively motile. The fully formed spermatozoa pass from the testis into the epididymis and vas deferens, and so to the seminal vesicles.

THE FEMALE REPRODUCTIVE ORGANS

The female generative organs are the ovaries, Fallopian (uterine) tubes, uterus, and vagina.

The **Ovary** is a solid organ composed of fibrous tissue (stroma), with many spindle-shaped cells, and is covered by a layer of cubical cells called the germinal epithelium. Groups of *interstitial cells* are found in the stroma, similar to those which occur in the testis. The ovary contains many vesicles of varying size (Graafian follicles), and a large number of primordial follicles ; the latter are formed during fœtal life from down-growths of the germinal epithelium into the stroma, and each consists of an ovum surrounded by a layer of flattened cells.

The *ovum* is a large spherical cell enclosed in a striated envelope called the zona pellucida (striata) ; its protoplasm, which is abundant, is filled with fatty and albuminous granules, and contains a spherical nucleus (germinal vesicle) with a nucleolus.

At puberty some of the primordial follicles develop into Graafian follicles (vesicular ovarian follicles). The epithelial cells covering the ovum multiply to form a mass in which fluid appears, separating the epithelium into two parts, an outer layer, the *membrana granulosa*, forming the wall of the follicle, and an inner layer, the *discus proligerus*, surrounding the ovum. At this stage the whole follicle is enclosed in a fibrous capsule derived from the stroma. As the amount of fluid increases, the follicle approaches the surface of the ovary, and eventually bursts, the ovum being set free and passing into the Fallopian tube. The process just described is called *ovulation*. The space left by the escape of the ovum and fluid is filled up by the ingrowth of vascular processes from the surrounding tissue, forming the

corpus luteum, so called because its cells are yellowish in colour owing to the presence of a fatty pigment, *lutein*. The corpus luteum gradually undergoes fibrous changes and disappears within two months. If pregnancy occurs, it becomes much larger and does not disappear until after parturition. The primordial ova are extremely numerous in the ovary, but only a small proportion of them develop into Graafian follicles, and only a few of the latter reach maturity, the others, after developing to a certain extent, undergoing atrophy. During sexual life ovulation usually occurs once a month, a single ovum being discharged on each occasion. The process is intimately bound up with menstruation.

The Uterus—The uterus consists of two parts, the body and the cervix. Its cavity is lined by a thick mucous membrane, composed of soft connective tissue covered by ciliated epithelium which dips down into the membrane to form long tubular glands.

The mucous membrane rests on a thick muscular coat, composed of unstriped muscle, and arranged in three layers. The outer (subserous) layer is comparatively thin, and the fibres are arranged in sheets arching over the fundus. The middle (vascular) layer is thick ; the fibres are arranged partly in sheets arching over the fundus, and partly in concentric rings round the larger blood-vessels. In the inner (submucous) layer, the muscular fibres form concentric rings round the body of the uterus.

The uterus receives its nerve-supply solely from the sympathetic system. The nerve-fibres leave the spinal cord in the anterior roots of the second to the fifth lumbar nerves, and reach the uterus by way of the inferior mesenteric ganglia and the hypogastric nerves. In the case of the human uterus, impulses passing along these nerves to the uterus always bring about contraction of the uterine muscle, whether the uterus is pregnant or non-pregnant.

The *Fallopian* (*uterine*) *tube* consists of a mucous membrane thrown into numerous longitudinal folds and lined by ciliated epithelium. The mucous membrane rests upon a muscular coat, consisting of smooth muscle, the outer fibres being longitudinal and the inner circular.

Both the uterus and Fallopian tubes are covered by a serous membrane derived from the peritoneum.

Menstruation.—This marks the onset of puberty, and the first menstrual period usually occurs between the ages of 13 and 16 ; as a rule, it recurs once a month until about the age of 45, its cessation at this age being called the *menopause*.

During each menstrual cycle the mucous membrane of the uterus undergoes a series of changes which are usually described

as taking place in four stages. (1) A few days before the onset of menstruation, the mucous membrane of the uterus becomes congested and thickened. (2) During the menstrual period, some of the blood-vessels of the mucous membrane rupture; the escaping blood, together with the superficial epithelium of the uterus and the secretion of the uterine glands, forms the menstrual flow, which lasts four or five days, the loss of blood varying from 100 to 200 c.c. (3) At the conclusion of the menstrual period, the uterine mucous membrane is gradually regenerated. This stage is succeeded by (4) a resting period lasting for some days and passing into the stage of congestion which initiates the next menstrual cycle.

Menstruation is associated with feelings of malaise and often with a slight rise of body-temperature. It is absent during pregnancy, and usually during lactation, and is normally associated with though not dependent upon ovulation. Menstruation ceases after the removal of the ovaries, and also at the menopause, when ovulation no longer takes place. Its object appears to be to render the condition of the uterus, at the end of the menstrual period, suitable for the reception and development of the ovum if fertilisation takes place. In many of the lower animals a somewhat similar change in the uterus, known as the *œstrus*, occurs at certain seasons of the year, and is accompanied by ovulation and sexual activity.

The close association between ovulation and menstruation has led to the view that the corpus luteum formed each month as a sequel to ovulation produces a hormone which brings about the uterine changes culminating in menstruation. Some observers, however, have found that ovulation is not necessarily followed by menstruation; and it is possible that the stroma or interstitial cells of the ovary produce the hormone responsible for the occurrence of menstruation.

Maturation of the Ovum.—After being discharged from the ovary, the ovum undergoes certain changes known as maturation. When a cell divides in the somatic tissues, the process is initiated by changes in the centrosome and nucleus, which constitute the process of *karyokinesis* or *karyomitosis* (fig. 195). The centrosome usually lies near the nucleus, and consists of a clear, spherical area containing a minute body, the *centriole*. The nucleus consists of a meshwork or *karyomitome*, described as *chromatin* because of its staining affinities, and containing in its meshes a fluid called *karyoplasm*. When a cell is about to divide, the centriole divides into two, which pass towards opposite poles of the nucleus, but remain connected by a spindle of fine threads, the *achromatic spindle*. Meanwhile the chromatin of

the nucleus becomes arranged in the form of a continuous thread, making a skein, which is then broken into short lengths, the *chromosomes*. The number of chromosomes is constant for any

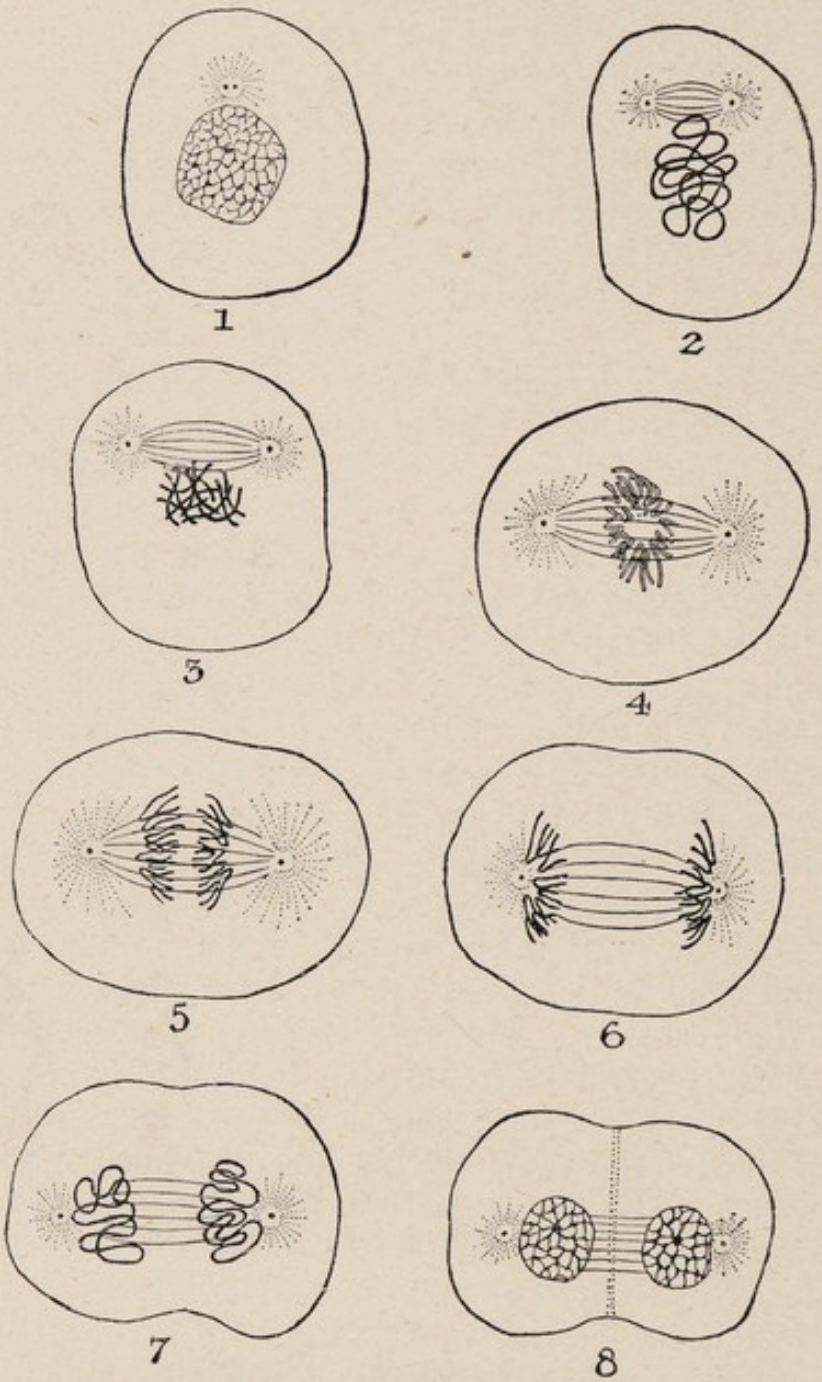


FIG. 195.—Karyokinesis. (From *Gray's Anatomy*.)
1 to 4, Anaphase; 5, 6, Metaphase; 7, 8, Kataphase.

one animal species, and in the case of man there are twenty-four. The chromosomes are arranged around the equator of the achromatic spindle, each being V-shaped, with the apex of the V pointing towards the centre. This forms the monaster, and completes the "anaphase" of the mitotic process. The "metaphase" commences by the splitting of each chromosome longitudinally to form two, one of which passes to each pole of the

achromatic spindle. The result of this is the formation of the diaster. The further changes consist in the formation of a daughter-nucleus by a reversal of the processes which occurred in the anaphase, that is, the chromosomes unite to form a skein, which then becomes transformed into the karyomitome. This constitutes the " kataphase " of the process. At the same time constriction of the protoplasm of the cell is taking place in the neighbourhood of the equator of the achromatic spindle, the spindle itself disappears, and finally each daughter-cell assumes a separate existence.

In the germ-cells the mitotic process is somewhat different. Each cell divides twice, the first division being by *heterotypical mitosis,* in which two of the original chromosomes become united by their free ends to form a ring. This breaks across, so that each daughter-nucleus possesses half the number of chromosomes found in the parent-cell. In the second division each chromosome splits longitudinally in the ordinary way (*homotypical mitosis*). In the case of the spermatocytes this process results in the formation of four spermatids, equal in size, each of which becomes a spermatozoon and contains half the number of chromosomes peculiar to the species of animal. In the case of the ovum the first division is into a large and a small cell (the first polar body). The large cell again divides into two cells of unequal size, the larger of the two being the mature ovum, and the smaller the second polar body. The first polar body may or may not divide into two small cells. If it does so, the two stages of subdivision result in the formation of four cells, each containing half the number of chromosomes peculiar to the species of animal, but only one of these is a mature ovum, and the other three undergo atrophy.

Fertilisation takes place as a result of the introduction of spermatozoa into the vagina during the act of coitus. The motile spermatozoa travel into the uterus and Fallopian tubes, where they may live for some days. If a spermatozoon penetrates into an ovum, the spermatozoon loses its tail, changes take place in its head and neck, and it is converted into a male pronucleus, which fuses with the nucleus of the ovum (female pronucleus) to form a new cell containing the normal number of chromosomes ; this process constitutes fertilisation.

The cell thus formed at once divides, and, when the ovum, which has been fertilised in the Fallopian tube, reaches the uterus, it has already divided and subdivided to form a small mass of cells called a *morula.*

The further development of the morula takes place in the uterus and constitutes *pregnancy.* The morula becomes imbedded in the uterine mucous membrane, which then consists of three

parts : namely, (1) the *decidua basalis*, lying between the embryo and the muscular wall of the uterus ; (2) the *decidua capsularis* (*reflexa*), between the embryo and the cavity of the uterus ; and (3) the *decidua vera*, lining the remainder of the uterus. As the embryo grows, it becomes enclosed in a sac filled with fluid and called the amnion ; surrounding the amnion is a vascular membrane, the chorion, from which blood-vessels pass in the umbilical cord to and from the fœtus. After the third month of pregnancy the fœtus receives its nutrition from the *placenta*, which is formed partly from maternal and partly from fœtal (chorionic) tissue. It consists essentially of large blood-spaces in the *decidua basalis*, into which open the uterine arteries, and from which the blood of the mother is carried into the uterine veins. Projections from the chorion (chorionic villi), containing fœtal blood-vessels, lie in these spaces and are bathed by the maternal blood ; the blood reaches the villi along the umbilical arteries, and is returned to the fœtus in the umbilical vein. The maternal and fœtal blood are thus separated by a double layer of epithelium, and the nutrition of the fœtus is effected by the diffusion of oxygen and nutritive material through this epithelium.

Parturition.—The average duration of pregnancy is 280 days, during which the muscular wall of the uterus not only increases in size, but becomes greatly thickened. Parturition is brought about by rhythmic contraction of the uterine muscle, and the fœtal membranes and their contained fluid are forced through the os uteri, which becomes fully distended. This, the first, stage of labour ends when the os uteri is fully dilated ; and the membranes rupture about this time.

The fœtal head then enters the pelvis, and the uterine contractions become more prolonged and frequent, being accompanied by voluntary contractions of the abdominal muscles. The fœtus is gradually forced through the pelvic canal and vulva, the head normally being born first. The second stage of labour ends when the child is born. The whole process of parturition varies greatly in duration, and may last twenty-four hours. Shortly after the birth of the child the uterus contracts further and expels the placenta. This is a large disc-shaped structure, one surface of which is smooth owing to the presence of a covering of amniotic membrane. The umbilical vessels enter the placenta at the middle of the smooth surface.

After parturition the uterus rapidly decreases in size, this being known as *involution*.

The Mammary Gland.—The mammary gland consists of a number of lobules imbedded in fat and areolar tissue. Each lobule is composed of alveoli, lined by cubical or columnar

epithelium resting on a basement-membrane. The ducts open on to the nipple, and are lined by cubical epithelium; their walls contain unstriated muscular fibres.

The Secretion of Milk.—When pregnancy occurs, it is associated with an increase in size of the mammary gland, due to growth of glandular tissue and increase in size of the alveolar cells. The glandular development is brought about by a hormone formed in the corpus luteum. This is indicated by the observation that, if a Graafian follicle is artificially ruptured in a non-pregnant animal, a corpus luteum is formed and the mammary glands develop for a short time. Further, it has been shown that the repeated injection of an extract of corpus luteum into a virgin rabbit leads to growth of the mammary glands. That their development is due to chemical, and not to nervous, influences is also indicated by the fact that, even after the severance of all nerves to a mammary gland, the gland undergoes normal development during pregnancy.

The *secretion* of milk (lactation) begins two or three days after the birth of the infant, and normally continues for six to nine months or even longer. The exciting cause of the onset of secretion appears to be somewhat complex. It is not nervous, for secretion can occur after division of all the nerves to the mammary gland. It must therefore be chemical, and more than one hormone appears to be concerned in lactation. In the first place, with the atrophy of the corpus luteum which takes place at this time, the anabolic stimulus is withdrawn, and katabolism tends to occur. Secondly, a hormone is formed by the uterus, as it undergoes involution, and excites secretion. Mackenzie has shown that the injection of an extract of an involuting uterus increases the flow of milk in a lactating animal. Thirdly, there is evidence that the fœtus itself furnishes a hormone which inhibits the production of milk, and after parturition this inhibitory influence is necessarily removed.

The continuance of lactation is dependent upon the suckling of the infant. In the absence of suckling, secretion ceases, and the glands diminish in size. This fact suggests that lactation may be reflex in origin, and there is no doubt that it is influenced by emotional states. The experimental evidence that the secretion may occur when all nerves to the gland have been divided, however, shows that it cannot be purely nervous in origin; and it is possible that the act of suckling may influence the secretory mechanism directly, probably mechanically.

Histological changes take place in the alveolar epithelium during lactation, and these do not occur uniformly throughout the gland. In a section, one group of alveoli may show active production of milk, while another group exhibits a resting stage.

The active cells are columnar in shape, and contain globules of fat ; these are larger towards the lumen of an alveolus, into which the ends of the cells project, and sooner or later become broken off. In the resting stage of the alveoli the lining epithelium is flattened, so that the cavity of the alveolus is large. The lumen is usually filled with milk in these circumstances.

SUBSIDIARY FUNCTIONS OF THE REPRODUCTIVE ORGANS

The reproductive glands not only form the essential reproductive elements, namely, spermatozoa and ova, but influence very markedly the growth and development of the rest of the organism.

In the male the onset of puberty, *i.e.* the formation of spermatozoa in the testes, is associated with the development of secondary sexual characteristics, such as changes in the larynx, deepening of the voice, and the growth of hair on the face and pubes. If the testes are removed before puberty, these characteristics do not develop, and the body remains infantile. After puberty, castration leads to atrophy of the accessory genital organs. In the lower animals castration also prevents the appearance of secondary sexual characteristics, such as the antlers of the stag, or the comb of the cock.

In the female, extirpation of the ovaries prevents the occurrence of menstruation and the development of the mammary glands which normally takes place at puberty ; their removal after puberty brings about the cessation of menstruation.

These facts point to the production by the testes and ovaries respectively of hormones, which influence the normal changes accompanying sexual development. Further evidence is found in cases of tumours of the testes and ovaries in children, accompanied by abnormal growth and premature sexual development. In such cases, removal of the tumour has been followed by disappearance of the signs of puberty. There is good reason for believing that the hormones which influence the development of the secondary sexual characteristics are derived from the interstitial cells of the testes in the male, and from those of the ovary in the female.

INDEX

Aberration, chromatic, 141.
  spherical, 141.
Absorption, from tissues, 272.
  in small intestine, 372.
Accelerator nerves, 248.
Accessory auditory nucleus, 102.
Accommodation of eye, 137.
Aceto-acetic acid (*see* Diacetic acid).
Acetone, 392.
Achromatic spindle, 475.
Achromic point, 329.
Achroo-dextrin, 8, 329.
Acid metaprotein, 10, 341.
Acidosis, 392.
Acoustic tubercle, 102.
  meatus, 156.
Acromegaly, 465.
Adaptation, 119, 147.
Addison's disease, 460.
Adenine, 13, 406.
Adequate stimulus, 118.
Adrenalin, 256, 263, 460.
  action on coronary arteries, 245.
  effect on heart, 252.
  secretion of, 462.
Adsorption, 18.
Aërotonometer, 286, 293.
Æsthesiometer, 123.
Afferent nerves, 52.
  projection-fibres, 94.
After-images, 149, 152.
After-loaded muscle, 26.
Air, alveolar, 281.
  atmospheric, 280.
  complemental, 279.
  expired, 280.
  quantity breathed, 279.
  residual, 279.
  supplemental, 279.
  tidal, 279.
  transmission of sound-waves through, 162.
Air-sacs, 275.
Alanine, 14, 400.
Albumin, 11.
  egg-, 15.
  serum-, 15, 186.
Alcaptonuria, 443.
Alcohol as a beverage, 431.
Aldehyde, 7.
Aldoses, 7.
Alimentary glycosuria, 396.
Alkali-metaprotein, 10, 355.
Alkali-reserve, 190.
All or none law, 24.
  in heart, 238.
  in muscle, 24.
Alveolar air, 281.
Amacrine cells, 131.
Ametropia, 140.
Amino-acids, 10, 13, 355, 366, 400.
  in blood, 374.
Ammonia in urine, 402, 439.
Amnion, 478.
Amœba, 1.
Amœboid movement, 184.
Ampulla, 169.
Amylolytic enzymes, 329, 356.
Anabolism, 382.
Anacrotic pulse, 231.
Anaphylaxis, 188.
Anarthria, 105.
Anelectrotonus, 47.
Animal cell, 2.
  heat, 414.
Anisotropic substance, 20.
Anode, 28.
Antagonistic colours, 151.
  muscles, reciprocal action of, 70.
Anterior cerebro-spinal fasciculus, 61.
Antero-lateral ascending tract, 63.
Antibodies, 187.
Anticoagulin, 193.
Antidromic impulses, 257.
Antigens, 187.
Antiperistalsis, 379.
Antithrombin, 193.
Antitoxin, 188.
Antrum, pyloric, 348.
Apex-beat, 216.
Aphasia, 105.
Apnœa, 280, 299, 310.
  in ducks, 310.
Appetite secretion, 333, 344.
Aqueduct, cerebral, 80.
Aqueous humor, 133.

Area, association, 104.
auditory, 101.
gustatory, 103.
kinæsthetic, 99.
motor, 97.
olfactory, 103.
visual, 100.
Arginase, 402.
Arginine, 14, 402.
Aristotle's experiment, 124.
Arteria centralis retinæ, 133.
Arterial blood-pressure, 202.
in asphyxia, 304.
Arteries, 200.
bronchial, 276.
coronary, 245.
elasticity of, 206.
in kidney, 435.
nerves of, 252.
pressure of blood in, 202.
rate of blood-flow in, 209.
umbilical, 478.
Arterioles, 201.
local changes in, 266.
Arytenoid cartilages, 166.
muscle, 166.
Aspartic acid, 15.
Asphyxia, 302.
Association-areas, 104.
fibres, 94.
tracts, 95.
Astasia, 87.
Asthenia, 87.
Astigmatism, 141.
Ataxia, 76, 87.
Atmospheric air, 280.
Atonia, 87.
Atrium, 198, 275.
Atropine, effect on heart, 252.
on pupil, 144.
on salivary gland, 334.
Atwater-Benedict calorimeter, 384.
Auditory area, 101.
nerve, 102.
radiation, 94, 103.
tract, 102, 164.
tube, 157, 158.
Auerbach's plexus, 350, 368.
Auricles, 198.
Auricular diastole, 201.
pressure, 222.
systole, 201.
Auriculo-ventricular bundle, 200, 240.
ganglia, 235.
node, 240.
valves, 199.
Autacoid substances, 457.
Autolysis, 408.
Autonomic afferent fibres, 117
ganglia, functions of, 116.
nervous system, 111.
Axis-cylinder, 44.
Axon, 41, 44.
reflex, 116, 258.

Bacterial action in intestine, 378, 441.
Bacterium lactis, 429.
Barcroft's blood-gas apparatus, 283.
tonometer, 288.
Basilar membrane, 159, 163.
Basket-cells, 85.
Basiphile cells, 175.
Beats, 162.
Benedict's test, 7, 442.
Beri-beri, 425.
Betz-cells, 60, 91.
Beverages, 431
Bile, 360.
absorption of bile-salts, 362.
analysis of, 361.
capillaries, 411.
functions of, 363.
influence on fat absorption, 364, 376.
mucin, 361.
pigments, 362, 437.
quantity of, 364.
salts, 361.
secretion of, 364.
Bilirubin, 179, 181, 362.
Biliverdin, 362.
Binocular vision, 153, 155.
Bipolar nerve-cells, 40.
Biuret reaction, 438.
Bladder, urinary, 454.
Blind spot, 146.
Block, heart-, 241, 304.
Blood, 174.
amino-acids in, 374.
arterial and venous, 202.
carbonic acid in, 291.
circulation of, 201.
in fœtus, 478.
coagulation of, 190.
defibrinated, 190.
fibrin, 186, 190.
flow, rate of, 209.
gases of, 282.
nitrogen in, 282, 316.
oxalated, 191.
oxygen in, 282.
plasma, 185.
proteins of, 186.
quantity of, 195.
reaction of, 189.
salts of, 186.
serum, 186.
specific gravity of, 174.
venous, 202.
Blood-corpuscles, red, 174, 176.
chemistry of, 177.
fate of, 184.
function of, 178.
number of, 175.

Blood-corpuscles, red,
origin of, 183.
stroma of, 176.
Blood-corpuscles, white, 175, 184.
amœboid movements of, 184.
chemistry of, 185.
functions of, 184.
origin of, 185.
varieties of, 175.
Blood-flow through an organ, 253.
Blood-platelets, 175.
Blood-pressure, 202.
in arteries, 202.
in capillaries, 204, 209.
in veins, 204, 209.
influence of gravity on, 261.
influence of respiratory movements on, 317.
measurement of, in man, 207.
Blood-vessels, structure of, 200.
Bomb-calorimeter, 383.
Bone-marrow, 184, 185.
Boundary zone, 434.
Bowman's capsule, 434.
glands, 126.
β-oxybutyric acid, 392, 400, 443.
Brachium conjunctivum, 86.
pontis, 86.
Brain, 77.
stem, 77.
Bread, 430.
Broca's area, 105.
Bronchi, 275.
Bundle of His, 200, 240.
Burdach's column, 62.

Calcium salts, 5.
effect on heart, 244.
excretion in large intestine, 378.
in coagulation of blood, 191.
of milk, 343.
phosphate in urine, 441.
Calorie-value of diet, 420.
of food-stuffs, 384, 422.
Calorimeter, 383, 384.
Canal of cochlea, 159.
of Schlemm, 128.
Cane-sugar, 7.
digestion of, 366.
Capillary circulation, 212.
electrometer, 29.
pressure, 204, 209.
wall, diffusion through, 272, 293.
Capillaries, dilatation of, 266.
Carbohydrates, 6.
absorption of, 375.
action of pancreatic juice on, 356.
of saliva on, 328.
metabolism, 393.
Carbonic acid:
excretion of, 280.
Carbonic acid:
in alveolar air, 282.
in atmosphere, 280.
in blood, 291, 298.
tension in alveoli, 295.
in blood, 291.
in tissues, 313.
Carbon monoxide poisoning, 317.
Carboxyhæmoglobin, 179.
Cardiac cycle, 215.
impulse, 215.
murmurs, 218.
muscle, 199.
influence of salts on, 244.
of temperature on, 245.
of tension on, 226.
physiological properties of, 238.
nerves, 246.
output, 222, 268.
reflexes, 248.
sounds, 217.
Cardiogram, 216.
Cardiograph, 216.
Cardio-inhibitory centre, 248.
Cardiometer, 222.
Casein, 342.
Caseinogen, 12, 15.
action of gastric juice on, 342.
in milk, 428.
Castration, 480.
Catalysts, 324.
Cells, 2.
Central nervous system, 39.
Centres in medulla oblongata, 79.
Centriole, 475.
Cephalin, 9.
Cerebellar ataxia, 87.
Cerebello-spinal tract of Löwenthal, 62.
Cerebellum, 84.
functions of, 87.
inferior peduncle, 86.
middle peduncle, 86.
removal of, 87.
structure of, 84.
superior peduncle, 86.
tracts of, 86.
vermis, 84.
Cerebral circulation, 266.
Cerebral hemispheres, removal of, 95.
association-fibres in, 94.
associative functions, 96.
commissural fibres in, 95.
cortex of, 89.
excitability of, 99.
function of layers, 91.
motor and sensory areas (*see* Areas).
projection-fibres in, 94.
Cerebral peduncles, 82.
Cerebro-cerebellar fibres, 94.
Cerebro-spinal fasciculi, 60, 107.
fluid, 109.
Chalones, 457.

Chemiotaxis, 184.
Chemistry of the body, 5.
Cheyne-Stokes breathing, 311.
Cholesterol, 9, 362.
Choline, 9.
Chorda tympani, 333.
  taste-fibres, 126.
  vaso-dilator fibres of, 256, 334.
Chordæ tendineæ, 199, 214.
Chorion, 478.
Choroid coat, 128.
  plexus, 110.
Chromaffine material, 458, 460.
Chromatic aberration, 141.
Chromatin, 13, 475.
Chromatolysis, 42.
Chromoproteins, 13.
Chromosomes, 475.
Chyle, 375.
Ciliary ganglion, 114, 143.
  movement, 37.
  muscle, 129, 138.
  nerves, 143.
  processes, 129.
Circulation of blood, 201.
  cerebral, 266.
  essential features of, 268.
  in the capillaries, 212.
  scheme, 205.
  time, 213.
Clarke's column, 56.
Climbing fibres, 86.
Coagulation of blood, 190.
    time of, 195.
  of colloids, 19.
  of milk, 342.
  of proteins, 11.
Coagulometer, 195.
Cochlea, 158.
Cochlear nerve nucleus, 81.
Coefficient of solubility of a gas, 285.
Cold, effect of, on muscular contraction, 25.
  sensations, 121.
  spots, 121.
Collagen, 12, 342.
Collaterals in spinal cord, 41, 58.
Collecting tubules of kidney, 434
Colloids, 18.
Colon, movements of, 379.
Colour-blindness, 150.
  contrast, 152.
  vision, 150.
Comma tract, 62.
Commissural fibres of cerebrum, 95.
Compensation, 227.
Compensatory pause, 239.
Complement, 177, 188.
Complemental air, 279.
Complementary colours, 151.
Compressor urethræ, 455.
Conduction, in nerve, 45, 48.
  loss of heat by, 416.
Cones, 130, 145.
  functions of, 146.
Conjugate deviation, 153.
Conjugated proteins, 12.
Conjunctival reflex, 2, 69.
Consonance, 162.
Consonants, 167.
Constrictor fibres to arteries, 112, 252
Contraction of muscle, 22.
  of pupil, 142, 144.
  voluntary, 36.
  wave, 24.
Contrast in visual sensation, 152.
Convection, loss of heat by, 416.
Convoluted tubules, 434.
  secretion by, 449.
Co-ordinated movements, 88, 170.
Cord, spinal, 55.
Cornea, 128
  nerve-endings in, 120.
Coronary arteries, 245.
Corpora quadrigemina, 82.
Corpus Arantii, 199.
  callosum, 95.
  luteum, 474.
  striatum, 89, 418.
Corpuscles of blood, 174.
  of Golgi and Mazzoni, 121.
  of Meissner, 121.
  of Pacini, 121.
  of Ruffini, 121.
Corresponding points, 153.
Cortex cerebri (*see* Cerebral hemispheres).
Corti's organ, 160.
Costal respiration, 277.
Cranial autonomic fibres, 114.
Creatine, 22, 408, 439.
Creatinine, 402, 439.
Cretinism, 469.
Crico-arytenoid muscles, 166.
Cricoid cartilage, 165.
Crico-thyroid muscle, 166.
Crista acustica, 169.
Crura cerebri (*see* Cerebral peduncles).
Crusta, 82
Crystalline lens, 132.
Crystalloids, 18.
Curare, action of, 23.
Current, electric, in eye, 146.
    heart, 242.
    muscle, 29.
    salivary gland, 336.
  of action, 32.
  of injury, 32.
  of rest, 32.
Cushny's theory, 453.
Cutaneous end-organs, 120.
  impulses, conduction of, 121.
  sensations, 121.

Cystine, 14, 15, 442, 443.
Cyton, 40.

D : N ratio (*see* G : N ratio).
Dark-adapted eye, 119, 147.
Dead space, 281.
Deamination, 400.
Decerebrate dog, 96.
  frog, 95.
  pigeon, 95.
  rigidity, 96.
Decidua, formation of, 478.
Decussation of fillet, 78.
  of pyramids, 78.
Deep reflexes, 74.
  sensibility, 124.
Defects of eye, 140.
Defibrinated blood, 190.
Deficiency diseases, 427.
Degeneration of nerve, 52.
Deglutition, 336.
  nervous mechanism of, 338.
Deiters' nucleus, 78, 81.
Denaturation of proteins, 11.
Dendrons, 40, 42.
Dental consonants, 167.
Depressor nerve, 248, 259, 268.
Descending tracts, 60.
Dextrin, 8, 329.
Diabetes, experimental, 398.
  in man, 399.
Diabetic puncture, 396.
Diacetic acid, 392, 393.
  in urine, 400, 443.
Diamino-acids, 14.
Diapedesis, 213.
Diaphragm, 276.
Diastole, 201.
Diastolic arterial pressure, 207.
Dicrotic wave, 231, 233.
Diet, 420.
  accessory factors in, 424.
Dietaries, 433.
Differential blood-gas manometer, 283.
Diffusion, 16.
Digestion, 322.
  gastric, 341.
  intestinal, 366.
  pancreatic, 354.
  salivary, 328.
  stages of, 325.
Dilatation of pupil, 144.
Dilator pupillæ, 129.
Dioptre, 141.
Diphasic variation, 31.
Direct cerebellar tract, 63.
Disaccharides, 6.
Discord, 162.
Discus proligerus, 473.
Dissociation of oxyhæmoglobin, 287.
Dissonance, 162.
Diuretics, 452.
Dobie's line, 20.
Dorsal nucleus, 56.
  spino-cerebellar fasciculus, 63.
Ductless glands, 457.
Ductus cochlearis, 159.
  endolymphaticus, 168.
Dudgeon's sphygmograph, 231.
Dyslysin, 362.
Dyspnœa, 280.

Ear, 156.
Eck's fistula, 401.
Effector organ, 68.
Efferent fibres of cerebellum, 86.
  nerves, 52.
  path of reflex, 68.
  projection-fibres, 94.
Egg-albumin, 9, 15.
Eighth nerve, nucleus, 81.
Elasticity of arteries, 206.
  of muscle, 22, 25.
Elastin, 12, 342.
Electrical changes in eye, 146.
  in heart, 242.
  in muscle, 29.
  in salivary gland, 336.
  stimulation, 23.
  variations, 32.
Electrocardiogram, 243.
Electrolytes, 16.
Electrolytic dissociation, 15.
Electrometers, 29.
Electrotonus, 47.
Embryo, 477.
Emmetropic eye, 136, 139.
Emulsion, 9.
End-bulbs, 121.
Endocardiac pressure, 219.
Endocardium, 199.
Endocrine organs, 457.
Endolymph, 158.
Endoneurium, 44.
End-organs in skin, 120.
End-plate, fatigue in, 51.
End-products, effect on enzymes, 323.
Energy, sources of, 420.
  total daily output of, 421.
Enteroceptive nervous system, 118.
Enterokinase, 354, 366.
Enzymes, 322.
  mode of action of, 324.
  source of, 323.
Eosinophile leucocytes, 175.
Epicardium, 200.
Epicritic sensibility, 124.
Epidermis, 415.
Epididymis, 472.
Epiglottis, 166.
Epineurium, 44.

Equilibration, 88, 170.
functions of labyrinth in, 172.
Erectile tissue, 473.
Erepsin, 366.
Ergastoplasm, 328.
Ergotoxin, action of, 259.
Errors of refraction, 140.
Erythroblasts, 183.
Erythrocytes, 174.
Erythrodextrin, 8, 329.
Ethereal sulphates, excretion of, 441.
Eupnœa, 280.
Eustachian tube, 157, 158.
Excitatory state in nerve, 45.
Exophthalmic goitre, 469.
Expired air, 280.
Extensibility of muscle, 22, 25.
Extensor reflex, 70.
External auditory meatus, 156.
geniculate body, 101.
Exteroceptive nervous system, 118.
Extra systole, 239.
Eye, dark-adapted, 119, 147.
electrical changes in, 146.
filtration angle of, 128.
formation of image in, 134.
movements of, 152.
nutrition of, 133.
optical defects of, 140.
structure of, 128.
Eye-muscles, extrinsic, 153.

Facial nerve, nucleus of, 79.
Facilitation of reflexes, 72.
Fæces, 379.
Fallopian tube, 473.
False vocal cords, 166.
Far point of vision, 139.
Fasciculus cuneatus, 62.
Fasciculus gracilis, 62.
Fasting, metabolism in, 408.
Fat, absorption of, 375.
composition of, 8.
depots, 389.
formation from carbohydrates, 389.
functions of, 391.
in intestinal epithelium, 376.
metabolism in starvation, 391, 408.
oxidation of, 392.
Fatigue, cause of, 35, 108.
of olfactory mechanism, 126
of visual mechanism, 152.
Fats, 8.
digestion in stomach, 343.
in intestine, 356.
heat-equivalent, 384.
Fat-soluble A, 424.
Fatty acids, 8.
degeneration, 391.
infiltration, 391.
Fehling's test, 7, 442.
Fenestra ovalis or vestibuli, 157, 160.
rotunda or cochleæ, 157, 160.
Fermentation test, 7.
Ferments (*see* Enzymes).
Fertilisation, 477.
Fibrin, 186, 190.
Fibrinogen, 186, 190.
Field of vision, 153.
Fifth nerve, nucleus of, 80.
Fillet, 78, 82.
lateral, 82, 103.
Final common path, 71.
Flexion reflex, 69.
Flicker, 149.
Fluid, cerebro-spinal, 109.
Fluoride, effect on clotting of blood, 194.
Focus of lens, 135.
Food, amount necessary, 422.
Food-stuffs, 427.
calorie-values of, 384, 422.
Foramen of Majendie, 109.
Forced movements, 88.
Fore-brain, 77, 89.
Fourth nerve, nucleus of, 80.
Fovea centralis, 132.
Free nerve-endings, 120.
Free-weighted muscle, 26.
Freezing-point, depression of, 17.
Frog, heart of, 235.
muscle-nerve preparation, 22.
Fronto-pontine fibres, 107.
Fructose, 6, 366, 375.
Fundamental tone, 162.
Funiculus cuneatus, 62.
gracilis, 62.

Galactose, 7, 366, 375.
Gall-bladder, 364.
Galvanometer, 29.
Ganglia, spinal, 57.
sympathetic, 112.
Gaseous exchange in lungs, 293.
metabolism of organs, 313.
Gases, tension of, 285.
Gastric digestion, 341.
fistula, 340.
hormone, 345.
juice, 340.
action on fats, 343.
milk, 342
proteins, 341.
secretion of, 343.
Gastrin, 345.
Gastro-colic reflex, 379.
-ileac reflex, 371.
Gelatin, composition of, 15, 431.
food-value of, 431.
Gels, 19.
Geniculate body, external or lateral, 101.
internal or medial, 103.

Germ-cells, 473.
chromosomes in, 476.
division of, 477.
Germinal vesicle, 473.
Gigantism, 465.
Glaucoma, 134.
Gliadin, 15, 430.
Globin, 178.
Globulin, 11.
Glomerulus, function of, 446.
pressure of blood in, 446.
Glosso-pharyngeal nerve, 126, 310, 331, 339.
nucleus of, 79.
Glottis, 165.
Glucoproteins, 13.
Glucosamine, 13.
Glucosazone, 7.
Glucose, 6.
in blood, 393.
in urine, 442.
Glutamic acid, 15, 404.
Gluten, 430.
Glycerol, 8.
Glycine, 14, 15.
Glycocholic acid, 361.
Glycogen, 8, 394.
formation of, 394.
preparation of, 394.
Glycosuria, 396.
Glycuronic acid, 443.
G : N ratio, 397, 399.
Golgi and Mazzoni, corpuscles of, 121.
Goll's column, 62.
Gowers' tract, 63.
Graafian follicles, 473.
Gram-molecule, 17.
Granule-layer, 89.
Gravity, effect of, on circulation, 261.
Green-blindness, 151.
Grey matter of cerebral cortex, 89.
Grey rami communicantes, 112.
Growth, effect of diet, 404, 424.
Guanine, 13, 406.
Gustatory area, 103.
sensations, 125.
Guttural consonants, 167.

Hæmatin, 178.
Hæmatoidin, 181.
Hæmatoporphyrin, 181.
in urine, 437.
Hæmin, 181.
Hæmochromogen, 180.
Hæmocytometer, 175.
Hæmoglobin, 13, 176, 178.
absorption spectrum of, 178.
affinity for carbon monoxide, 179, 317.
composition of, 178.
crystals of, 178.
Hæmoglobin,
decomposition products of, 180.
dissociation-curve of, 287.
estimation of, 181.
iron in, 178.
oxygen capacity of, 283.
Hæmoglobinometer, 182.
Hæmolysis, 176.
Hæmolytic sera, 177.
Hair-follicles, 120, 415.
Harmony, 162.
Hay's test, 362.
Head's diaphragm slip, 298.
Head's views on cutaneous sensation, 124.
Hearing, 156.
end-organ of, 160.
Heart, 198.
accelerator nerves to, 248.
changes in form of, 214.
diastolic filling of, 215, 227.
effect of atropine on the, 252.
electrical changes in the, 242.
inhibitory nerve of, 246
innervation of the, 246.
nerve-ganglia in, 235, 246.
nutrition of, 243.
of frog, 235.
of mammal, 240.
output of, 222, 225, 268.
sequence of events in, 214.
sounds, 217.
work of, 222.
Heart-beat, 214, 235.
causation of, 235.
effect of calcium on, 244.
of carbonic acid on, 245.
of hydrogen ion concentration on, 244.
of drugs on, 252.
of potassium on, 244.
influence of temperature on rate of, 245.
myogenic hypothesis, 236, 240.
neurogenic hypothesis, 236.
propagation of, 237.
rate in exercise, 251, 320.
reversal of rhythm of, 237.
Heart-block, 241.
Heart-lung preparation, 223.
Heart-muscle, 199.
influence of tension on, 225, 239.
physiological properties of, 238.
refractory period of, 238.
Heat-loss, 414.
production, 414.
in muscle, 34.
regulation, 417.
sensations, 120.
spots, 121.
stroke, 419.
Helicotrema, 160.

Heller's test, 442.
Helmholtz's theory of hearing, 163
Hemianæsthesia, 64.
Henle's loop, 434.
Hensen's line, 20.
Hering's theory of colour-vision, 151.
Heterotypical mitosis, 477.
Hexone bases, 14.
Hexoses, 6.
Hibernation, 393.
Hind-brain, 77.
Hippocampus, 103.
Hippuric acid, 440.
Hirudin, 195.
His' bundle, 200, 240.
Histidine, 14, 404, 406.
Histones, 11.
Homogentisic acid, 443.
Homoiothermic animals, 414.
Homotypical mitosis, 477.
Hopkins' test for lactic acid, 33.
  for tryptophane, 10.
Hormones, 2, 345.
  gastric, 345.
  genital, 480.
  intestinal, 367.
  mammary, 479.
  pancreatic, 357.
Hürthle's manometer, 214.
Hyaloid membrane, 130.
Hydræmic plethora, 270, 447, 452.
Hydrated proteins, 10.
Hydrazine hydrate, 180.
Hydrogen-ion concentration, 189, 244, 300.
Hydrolysis of starch, 8.
  of proteins, 10, 13.
Hyperglycæmia, 396.
Hypermetropia, 140.
Hyperpnœa, 280.
Hypertonic solutions, 18.
Hypogastric nerves, 116, 381, 455.
Hypoglossal nucleus, 80.
Hypophysis cerebri (*see* Pituitary body).
Hypotonic solutions, 18.
Hypoxanthine, 22, 406, 413.

Ileo-colic sphincter, 370, 371.
Illusions, optical, 156.
Image, retinal, 144.
Immunity, 188.
Incus, 158.
Indirect vision, 153.
Indol, 378, 441.
Induction, retinal, 152.
Infantilism, 465.
Inferior cervical ganglion, 112.
  colliculi, 82.
  mesenteric ganglion, 115.
  peduncles of cerebellum, 86.
Inflammation, 213.
Infundibula of lung, 275.
Inhibition of heart, 246.
  of reflexes, 69.
Inner cell-lamina, 89.
  fibre-lamina, 89.
Inorganic constituents of the body, 5.
Inosite, 8, 21.
Intercostal muscles, action of, 277.
Internal capsule, 106.
  ear, 158.
  geniculate body, 103.
  respiration, 274, 312.
  secretions, 457.
Intestine, large, 377.
  small, absorption in, 371.
  movements of small, 367.
    of large, 379.
Intestinal digestion, 366.
  juice, 365.
Intra-ocular fluid, 133.
  tension, 133.
Intra-thoracic pressure, 278.
Intra-vascular coagulation, 194.
Invertase, 366.
Involuntary muscle, 36.
Involution, 478.
Iodine in thyroid gland, 468.
Ions, 15.
Iris, 129.
  functions of, 142.
  local stimulation of, 143.
  nerve-supply of, 143.
Iron, 5, 178, 181, 378, 431.
Irradiation, 69.
Island of Reil, 93, 104.
Islets of Langerhans, 398.
Isoleucine, 14.
Isometric contractions, 28.
Isotonic contractions, 28.
  solutions, 18.
Isotropic substance, 20.

Jacksonian epilepsy, 99.
Jaffé's test, 439.

Karyomitosis, 475.
Karyoplasm, 475.
Katabolism, 382.
Katacrotic pulse, 231.
Kathelectrotonus, 47.
Kathode, 28.
Keratin, 12, 415.
Ketoses, 7.
Kidney, blood-supply of, 435.
  function of glomeruli of, 446.
  nerves of, 446.
  secretion in frog, 449.
    mammal, 444.
  structure of, 434.

Kidney tubules, 434.
absorption in, 450.
function of the, 448.
secretion in, 449.
work of, 449.
Kinæsthetic impulses, 65.
Knee-jerk, 74.
Krause's membrane, 20.
Krogh's microtonometer, 293.
Kymograph, 203.

Labial consonants, 167.
Labyrinth, 168.
Lachrymal secretion, 127.
Lactalbumin, 428.
Lactase, 366.
Lactation, 479.
Lacteals, 269, 372.
Lactic acid,
effect on respiratory centre, 300.
on vaso-motor centre, 260, 304
in blood, 33, 260, 320.
in muscle, 32.
in urine, 33, 320.
Lactose, 7, 428.
in urine, 442.
Lævulose, 7, 442.
Langerhans' islets in pancreas, 398
Langley's ganglion, 331.
Large intestine, 377.
functions of, 377.
movements of, 379.
Laryngoscope, 167.
Larynx, 165.
movements of, in deglutition, 337.
Lateral cerebro-spinal fasciculus, 60.
columns of cord, 55.
fillet, 82, 103.
geniculate body, 101.
Law, Marey's, 249.
of forward direction, 43.
of specific irritability, 119.
of the heart, 227.
Weber's, 120.
Lecithin, 9, 53, 353.
Lens, crystalline, 132.
changes in shape of, 138.
variations with age, 139.
Lenses, formation of images by, 135.
Leucine, 14, 355, 443.
Leucocytes, 175, 184.
number of, 176.
origin of, 185.
varieties of, 175.
Leucocytosis, 185.
Ligamentum pectinatum iridis, 128.
Light-reflex, 142.
Limbus laminæ spiralis, 159.
Lipase, gastric, 343.
pancreatic, 356.
Lipoids, 9.
Lissauer's tract, 62.
Liver, 410.
bile-formation in, 360, 364.
functions of, 411.
glycogen of, 394.
lymph-production in, 271.
structure of, 410.
urea-formation in, 401.
uric acid formation in, 407.
Load, effect on contraction, 26.
Local reflexes, 352, 368.
sign, 123, 155.
Localisation of function in cerebral hemisphere, 97.
Locke's fluid, 244.
Locomotor ataxia, 75.
Long ciliary nerves, 143.
Longitudinal inferior fasciculus, 95.
superior fasciculus, 95.
Loudness of sound, 162.
Ludwig's stromuhr, 210.
Lungs, 274.
exchange of gases in, 293.
Lutein, 474.
Lymph, composition of, 269.
flow of, 272.
formation of, 270.
function of, 269.
Lymphagogues, 271.
Lymphocytes, 175.
Lysine, 14.
influence on growth, 404.
Lysins, 176.

Macula acustica, 169.
lutea, 132.
Malleus, 157.
Malpighian bodies of spleen, 412.
Maltase, 323, 366.
Maltose, 7, 329.
Mammary gland, 478.
hormone, 479.
Manometer, 203.
Hürthle's, 219.
Piper's, 220.
Marchi's fluid, 53.
Marey's law, 249.
tambour, 219.
Marrow, 184.
Medial fillet, 82.
geniculate body, 103.
longitudinal fasciculus, 78.
Medulla oblongata, 81.
Meissner's corpuscles, 121.
Membrana granulosa, 473.
tectoria, 161.
tympani, 157.
Membranes, permeability of, 16.
semipermeable, 16.
Membranous labyrinth, 158, 168.
Menière's disease, 171.

Menopause, 474.
Menstruation, 474.
Mercurial manometer, 203.
Metabolism, 382.
  during starvation, 408.
  endogenous, 403.
  end-products of, 388.
  exogenous, 403.
  methods, 382.
  of carbohydrates, 393.
  of fats, 389.
  of muscular work, 409.
  of nucleo-proteins, 405.
  of protein, 400.
  relation of, to body-surface, 387, 418.
Metabolites, action on blood-vessels, 266.
Metaproteins, 10, 341, 354.
Methæmoglobin, 180.
Microtonometer, 293.
Micturition, 454.
Mid-brain, 77, 82.
Middle cell-lamina, 89, 91.
  peduncles of cerebellum, 86.
Milk, 427.
  as a diet for infants, 428.
  composition of, 428.
  secretion of, 463.
Milk-sugar, 7, 428.
Millon's reaction, 10.
Mitosis, 475.
Mitral cells, 103.
  valve, 199.
Modality, 119.
Molecular layer, 85, 89.
  of retina, 129.
Monoamino-acids, 14.
Monophasic variation, 32.
Monosaccharides, 6.
Moss-fibres, 84.
Motor aphasia, 105.
  area, 97.
  path, 78, 107.
Mountain sickness, 315.
Movement, co-ordination of, 88, 170.
  sensation of, 172.
Movements of deglutition, 336.
  of large intestine, 379.
  of small intestine, 367.
  of stomach, 347.
Mucins, 13.
Müller's fibres, 130.
Multipolar nerve-cells, 40.
Murexide test, 440.
Muscarine, action on heart, 252.
Muscle, 20.
  afferent nerves of, 21, 172.
  anisotropic substance of, 20.
  chemical changes in, 32.
  chemical characters of, 21.
  clotting of, 22.
  elasticity of, 22, 25.
  electrical changes in, 29.
Muscle,
  excitation of, 22.
  extensibility of, 22, 25.
  cardiac, 199.
  heat-production in, 34.
  independent excitability of, 23.
  injury-current of, 32.
  involuntary, 36.
  isotropic substance of, 20.
  metabolism of, 409.
  plasma, 22.
  production of carbonic acid in, 32.
  reciprocal innervation of, 70.
  red, 21.
  spindle, 172.
  stimulation by constant current, 28.
  twitch, 23.
  voluntary, 20.
Muscular contraction, 22.
  "all or none" phenomenon, 24.
  effect of fatigue, 25.
    of load, 26.
    of temperature, 25.
  efficiency of, 35.
  electrical changes in, 29.
  heat-production during, 34.
  histological changes in, 21.
  isometric, 28.
  isotonic, 28.
  latent period of, 23.
  physical changes in, 23.
  respiratory quotient during, 410.
  time-relations of, 23.
  voluntary, 36.
Muscular contractions, summation of, 28.
    source of energy for, 34, 410.
  exercise, 319.
  movements, co-ordination of, 88, 170.
  relaxation, 24.
  sense, 172.
    paths for impulses of, 65.
  tone, 75, 171.
  work, 27.
    effect on metabolism, 410.
Musculi papillares, 199.
Musical sounds, 162.
Myelin-sheath, 44.
Myelination, 59.
Myelocytes, 185.
Myenteric plexus, 350, 368.
Myocardium, 199.
Myogenic theory, 236.
Myopia, 141.
Myosin, 22.
Myosinogen, 22.
Myxœdema, 468.

Near point, 139.
Negative after-image, 152.
  variation, 32.
  ventilation, 306.

Nerve, 44.
chemical constituents of, 45.
conductivity of, 45, 48.
degeneration of, 52.
double conduction in, 51.
endings in skin, 120.
excitability of, 45.
excitatory state, 45.
effect of gases, etc.. on, 48.
of constant current, 46.
of oxygen, 48.
of temperature, 46.
function of, 52.
medullated, 44.
non-fatiguability of, 51.
non-medullated, 45.
physiological properties of, 45.
propagated impulse in, 48.
effect of constant current, etc., on, 51.
refractory period of, 46.
regeneration of, 54.
structure of, 44.
Nerve-cell, 40.
function of, 43.
Golgi's second type, 41, 57.
Nervi erigentes, 256, 380, 455.
Nervous system, 39.
Neurolemma, 44.
Neurogenic theory, 236.
Neuroglia, 40.
Neuron, 40.
function of, 42.
Neutrophile leucocytes, 175.
Nicotine, effect on heart, 252.
on synapse, 114.
Ninth nerve, nucleus of, 79.
Nissl's granules, 40.
Nitrogen, endogenous, in urine, 402.
estimation, 438.
excretion in starvation, 408.
exogenous, in urine, 402.
in protein, 9.
requirements of body, 422.
Nitrogenous constituents of urine, 402.
equilibrium, 409.
Nocuous stimuli, 69.
Nodal point, 135.
Nodes of Ranvier, 44.
Nuclease, 406.
Nuclei pontis, 82.
Nucleic acid, 13, 405.
Nuclein, 13.
metabolism of, 405.
Nucleoprotein, 12, 405.
digestion of, 342.
Nucleotides, 406.
Nucleus, 2.
ambiguus, 79, 81.
Bechterew's, 170.
caudatus, 106.
cuneatus, 78, 81.
Nucleus,
Deiters', 81, 170.
dentatus, 84.
emboliformis, 84.
fastigii, 84.
globosus, 84.
gracilis, 78, 81.
lenticularis, 105, 106.
red, 83.

Occipital lobe, 100.
Oculo-motor nucleus, 80, 83, 101, 140 143.
Odours, 126.
Œsophagus, 338.
Œstrus, 475.
Oleic acid, 8.
Olfactometer, 127.
Olfactory apparatus, 126.
area, 103.
glomeruli, 103.
lobe, 103, 126.
mucous membrane, 126.
sensations, 126.
tract, 104.
Olivary nucleus, 81.
Olivo-spinal tract, 62.
Oncometer, 248.
Optic chiasma, 101.
decussation, 101.
disc, 130.
nerve, efferent fibres in, 129.
radiation, 94, 101, 106.
tract, 101.
Optical axis of lens, 135.
centre of lens, 135.
defects of eye, 140.
illusions, 156.
Optimal temperature for ferments, 324.
Optogram, 145.
Ora serrata, 132.
Organ of Corti, 160
Osazones, 7.
Osmometer, 17.
Osmosis, 16.
Osmotic pressure, 16.
measurement of, 16.
of colloids, 18.
of electrolytes, 16.
of plasma, 187.
of proteins, 272, 447.
Osseous labyrinth, 168.
Otic ganglion, 331.
Otoliths, 169.
function of, 171.
Outer cell-lamina, 89.
fibre-lamina, 89.
Output of heart, 222, 225, 268.
Ovary, 473.

Overtones, 162.
Ovulation, 473.
Ovum, 473.
  maturation of, 475.
Oxalate blood, 191.
  crystals, 441.
Oxidases, 322.
Oxyacids, 400.
Oxygen, avidity of tissues for, 315.
  capacity of blood, 283.
  effect of changes in tension of, 301.
  exchange in lungs, 293.
  lack in asphyxia, 260, 303.
    production of lactic acid in, 301.
  tension in alveoli, 290.
    in blood, 286, 301.
Oxyhæmoglobin, 178, 286.
  absorption spectrum of, 178.
  dissociation of, 287.
    influence of acids on, 289.
      of temperature on, 289.
  reduction of, 178.

Pacinian corpuscles, 120, 121.
Pain impulses, path of, in cord, 66.
  sense, 121.
  spots, 121.
Palmitic acid, 8.
Pancreas, changes during secretion, 360.
  internal secretion of, 398.
  islets of, 360, 398.
Pancreatic diabetes, 398.
  fistula, 353.
  juice, 353.
    action on carbohydrates, 356.
      on fats, 356.
      on milk, 357.
      on proteins, 354.
    activation of, 354.
    secretion of, 357.
      effect of acids in duodenum, 357.
  secretin, 357.
Paraganglia, 458.
Paramyosinogen, 22.
Parasympathetic system, 111.
Parathyroids, 470.
Parotid gland, 326.
  nerves of, 331.
Pars ciliaris retinæ, 129.
Partial pressure, 285.
Parturition, 478.
Pawlow's gastric fistula, 340.
Pelvic visceral nerves, 115, 256.
  to bladder, 455.
  to colon and rectum, 380.
Pendular movements of intestine, 370.
Pentoses, 6, 405, 442.
Pepsin, action of, 341.
Peptones, 10, 341, 354.
  effect on coagulation of blood, 195.
Pericardium, 200.
Perilymph, 158.
Perimeter, 154.
Perineurium, 44.
Peripheral ganglia, effect of nicotine on, 114.
Peristalsis, 368.
Permeability of membranes, 16.
Pes, 82.
Pettenkofer's test, 362.
Phagocytes, 185.
Phakoscope, 137.
Phenylalanine, 13, 404, 431, 444.
Phenylglucosazone, 7.
Phenylhydrazine test, 7, 443.
Phloridzin glycosuria, 397.
Phosphates, excretion by large intestine, 378.
  in urine, 437, 441.
Phospholipines, 9.
Phosphoproteins, 12.
Photochemical substance in retina, 150.
Photohæmatachometer, 212.
Pilocarpine, effect on heart, 246.
Pineal gland, 89, 457.
Piper's manometer, 220.
Piston recorder, 222.
Pitch, 162.
Pituitary body, 463.
  functions of, 464.
Placenta, 478.
Plain muscle, 37.
Plasma, blood, 185.
  osmotic pressure of, 187.
Plethora, hydræmic, 270, 447, 452.
Plethysmograph, 254.
Pleura, 276.
  cavity, pressure in, 278.
Poikilothermic animals, 414.
Polar bodies, 477.
Polarisation, 29.
Polygraph, 232.
Polymorphic layer, 89.
Polymorphonuclear leucocytes, 175.
Polyneuritis, 426.
Polypeptides, 10, 355.
Polysaccharides, 8.
Pons, 81.
Portal vein, 202, 401, 410.
Position, sensations of, 171.
Positive after-images, 149.
Posterior columns of cord, 55, 61.
  funiculi, 55, 61.
  longitudinal bundle, 78.
  root ganglia, 57.
Post-ganglionic fibre, 111.
Postural reflexes, 171.
Precipitins, 188.
Predicrotic wave, 231.
Prefrontal region, 93, 104.
Preganglionic fibre, 111.
Pregnancy, 477.

Prepotent reflex, 72.
Presbyopia, 140.
Pressure-sense, 122.
  paths in cord, 65.
  spots, 121.
Primary colour sensations, 150.
Primordial follicle, 473.
Principal focus of lens, 135.
Projection-fibres, 94.
Proline, 15.
Propagated impulse in nerve, 45, 48.
Proprioceptive senses, 168.
  system, 88, 118.
Prosecretin, 358.
Prostate, 472.
Prosthetic group, 12.
Protamines, 11.
Proteins, 9.
  absorption of, 374.
  ammonia-nitrogen in, 14.
  conjugated, 12.
  derivatives of, 13.
  gastric digestion of, 341.
  hydrated, 10.
  hydrolysis of, 10, 13.
  pancreatic digestion of, 354.
Proteose, 10, 341.
Prothrombin, 187.
Protopathic sensibility, 124.
Protoplasm, 2.
Psychical secretion of gastric juice, 344.
  of saliva, 333.
Ptyalin, 323.
Puberty, changes at, 474, 480.
Pulmonary circulation, 202.
  ventilation, 300.
Pulse, 230.
  anacrotic, 231.
  katacrotic, 231.
  rate of, in man, 251.
  velocity of wave, 233.
  venous, 234.
Pupil, 129.
  contraction of, 143.
  dilatation of, 143.
Purine bases, 13, 406.
  metabolism of, 406.
Purkinje cells, 84.
  fibres, 240.
  images, 146.
Pyloric canal, 348.
  sphincter, 348.
  vestibule, 348.
Pyramidal cells, 91.
  decussation, 78.
  tracts, 60, 94, 107.
Pyruvic acid, 390.

Rami communicantes, 112.
Reaction-time, 149.
Reactions, reversible, 323.
Receptive substance, 461.
Receptor organ, 68.
Reciprocal innervation, 70.
Red-blindness, 151.
Red corpuscles, 174, 176.
  marrow, 184.
  nucleus, 83.
Reduced eye, 135.
Referred pain, 117.
Reflex action, 66.
  facilitation of, 72.
  inhibition of, 69.
  in spinal animal, 68.
  reinforcement of, 75.
Reflex arc, 68.
  scratch, 70.
  time, 68.
Reflexes, 68.
  axon, 116, 258.
  deep, 74.
  prepotent, 72.
  visceral, 76.
Refraction, 134.
  in reduced eye, 135.
Refractory period, 46, 238.
Regeneration of nerve, 54.
Reissner's membrane, 159.
Renal excretion (*see* Kidney).
Rennin, 342.
Reproduction, 472.
  female organs of, 473.
  male organs of, 472.
Residual air, 279.
Resonance, 163.
Respiration, 274.
  apparatus, Atwater-Benedict, 384.
    Haldane and Pembrey, 386.
  chemical regulation of, 298.
  chemistry of, 280.
  Cheyne-Stokes, 311.
  effect of lack of oxygen on, 301.
    of changes in barometric pressure on, 315.
    of division of vagi on, 306.
    of exercise on, 308, 319.
  nervous regulation of, 304.
  rate of, 280.
Respiratory centre, 296.
    action of vagus on, 306.
    automaticity of, 297.
  exchange, 385.
  movements, 276.
    Head's method, 298.
  muscles, 277.
  passages, 274.
  quotient, 280, 385.
    effect of foods on, 388.
    in diabetes, 398.
    in hibernation, 393.
    in muscular work, 387, 410
  sounds, 280.
Restiform body, 86.

Rete mucosum, 415.
Retina, 129.
  chemical changes in, 145.
  electrical changes in, 146.
  histological changes in, 145.
Retinal image, 134.
  induction, 152.
Reversibility of ferment action, 323.
Rhodopsin, 130, 145.
Rhythm of heart, 236, 240.
Ribs, movement of, 276.
Rigor mortis, 22, 36.
Rima glottidis, 165.
Ringer's fluid, 244.
Riva-Rocci sphygmomanometer, 207.
Rods of Corti, 160.
  of retina, 130.
Rubro-spinal tract, 62, 78.
Ruffini, corpuscles of, 121.

Saccule, 168.
Saccus endolymphaticus, 168.
Sacral autonomic fibres, 115.
Saliva, composition of, 326.
  functions of, 328.
  secretion of, 330.
    changes in blood-supply during, 333.
    effect of nerves on, 332.
    electrical changes during, 336.
    histological changes in, 327.
    pressure of, 334.
Salivary digestion, 328.
  in stomach, 330.
Salivary glands, 326.
  nerves of, 330.
Salmin, 15.
Salts, absorption of, 373.
Sanson's images, 137.
Saponification, 9.
Sarcolemma, 20.
Sarcomere, 21.
Sarcoplasm, 21.
Sarcostyle, 21.
Scala tympani, 159.
  vestibuli, 159.
Schafer's theory of contraction, 21.
Schematic eye, 135.
Schlemm, canal of, 128.
Sclera, 128.
Scleroproteins, 12.
Scratch-reflex, 70.
Sebaceous glands, 415.
Second wind, 321.
Secretin, 357.
  effect on intestine, 367.
    on liver, 364.
    on pancreas, 357.
Secretory process, 334.
Segmentation, 369.
Semicircular canals (ducts), 168.
  functions of, 170.
Semilunar ganglion, 114.
  valves, 199.
Semipermeable membrane, 16.
Sensations, 118.
Sensory adaptation, 119.
  aphasia, 105.
  areas of cortex, 99.
  decussation, 78.
  path, 65, 106.
Septum transversum, 169.
Serine, 14, 15.
Serous salivary glands, 328.
Serum-albumin, 15, 186.
  globulin, 186.
  osmotic pressure of, 187.
  protein, 187.
Seventh nerve, nucleus of, 79.
Sham feeding, 344.
Shock, 264.
  spinal, 76.
Short ciliary nerves, 143.
Sight-testing, 136.
Simultaneous contrast, 152.
Sino-auricular ganglion, 235.
  node, 240.
Sinus venosus scleræ, 128.
Sinusoids, 411.
Sixth nerve, nucleus of, 80
Skatol, 378, 441.
Skin, 415.
  functions of, 416.
Sleep, 108.
Small intestine, 366.
  absorption from, 371.
  movements of, 367.
  nerves of, 370.
  progress of digestion in, 367.
Smell, sense of, 126.
  area for, 103.
Sols, 19.
Sound-waves, 162.
Speech, 105, 167.
Spermatids, 472.
Spermatocytes, 472.
Spermatogonia, 472.
Spermatozoa, 472.
Spherical aberration, 141.
Sphincter, ileo-colic, 370, 371.
  pupillæ, 129.
  pyloric, 348.
  trigonal, 455.
Sphingo-myelin, 9.
Sphygmograph, 231.
Sphygmomanometer, 207.
Spinal accessory nerve, nucleus of, 79.
  animal, 68.
  cord, 55.
    ascending tracts, 62.
    cells of, 57.
    collaterals of, 58.
    conduction in, 59.
    descending tracts, 60.

Spinal cord,
effect of strychnine, 69.
endogenous and exogenous fibres of, 62.
hemisection of, 64.
path of impulses in, 63.
regions of, 56.
structure of, 55.
tracts, methods of tracing, 59.
ganglia, 57.
medulla (*see* Spinal cord).
nerve-roots, 57.
shock, 76.
Spino-cerebellar tracts, 63.
Spino-tectal tract, 63.
Spino-thalamic tract, 63.
Spiral ganglion, 102, 161.
lamina, 159.
Spirometer, 279.
Splanchnic area, 260.
nerve, 114, 261.
Spleen, 412.
Staircase phenomenon, 238.
Stannius ligature, 237.
Stapedius muscle, 158.
Stapes, 158.
Starch, 8.
digestion by saliva, 329.
hydrolysis of, 8.
soluble, 329.
Starvation, 408.
Stearic acid, 8.
Stellate ganglion, 112.
Stercobilin, 363.
Stethograph, 297.
Stimuli, summation of, 28.
Stimulus, adequate, 118.
threshold, 119.
Stomach, 339.
movements of, 347.
nerves to, 350.
Stratum corneum, 415.
granulosum, 415.
lucidum, 415.
opticum, 129.
Striæ acusticæ, or medullares, 102.
Striated muscle, 20.
String galvanometer, 30, 242.
Stromuhr, 210.
Structural basis of body, 2.
Strychnine, effect on cord, 69.
Subliminal stimuli, 119.
Sublingual gland, 326, 327, 331.
Submaxillary ganglion, 331.
gland, 326, 327, 331.
Substantia nigra, 82.
Successive contrast, 152.
Succus entericus (*see* Intestinal juice).
Sugar in blood, 393.
in urine, 442.
utilisation of, in body, 395.
Sugars, 6.
Sulphocyanate in saliva, 326.
Summation of contractions, 28.
of stimuli in reflex action, 72.
in sensation, 119.
Superior cerebellar peduncles, 86.
cervical ganglion, 112, 114.
colliculi of corpora quadrigemina, 82, 84.
Superior oblique muscle, 153.
Supplemental air, 279.
Suprarenal glands, 458.
nerve-supply of, 264, 462.
Surface tension, 2.
Suspensory ligament, 132, 138.
Swallowing (*see* Deglutition).
Sweat, 416.
Symes' cannula, 243.
Sympathetic ganglia, 112.
nerves of heart, 248.
system, 111.
Synapse, 42.
Systole, 201.
Systolic pressure, 207.

Tactile discrimination, 64, 123.
localisation, 66, 123.
sensations, 120.
path of impulses, 65.
spots, 121.
Tambour, 219.
Taste, 125.
area, 103.
bulbs, 125.
nerves, 103, 125.
sensations, 125.
Taurocholic acid, 361.
Tears, 127.
Tegmentum, 82.
Temperature, effect on heart, 245.
on metabolism, 419.
on muscle, 25.
sense, 120.
Temporal lobe, 101.
Tendon-reflexes, 74.
Tendril-fibres, 86.
Tension, effect of, on bladder, 455.
on heart, 226, 239.
on muscle, 27, 35.
of gases in liquids, 285.
Tensor tympani muscle, 158.
Test-types, 136.
Testis, 472.
Tetanus, 28.
Thalamo-cortical fibres, 94.
Thalamus, 89, 106.
Thermopile, 34.
Third nerve, functions of, 143, 153.
nucleus of, 80, 83, 101, 140, 143.
Threshold stimulus, 119.
Thrombin, 191.

Thrombogen, 191.
Thrombokinase, 192.
Thymus, 471.
Thyroid cartilage, 165.
Thyroid gland, 468.
Thyro-arytenoid muscle, 166.
Thyroxin, 468.
Tidal air, 279.
Timbre, 162.
Tissue-respiration, 312.
Tone in arteries, 252.
  in muscle, 37, 75, 171.
Tonometer, 288.
Tortoise heart, 236.
Touch (*see* Tactile).
Touch-corpuscles, 121.
  spots, 121.
Trachea, 274.
Trapezium, 103.
Traube-Hering curves, 260.
Tricuspid valve, 199.
Trigeminal nerve, nucleus of, 80.
Triolein, 8.
Tripalmitin, 8.
Triple phosphate, 442.
Tristearin, 8.
Trommer's test, 7.
Trypsin, 354.
  action on proteins, 354.
Trypsinogen, 354.
Tryptophane, 11, 14, 15, 355, 404, 431
Tuberculum acusticum, 81, 102.
Tympanic membrane, 157.
  movements of, 161.
Tyrosine, 11, 14, 15, 404, 431, 444.
  crystals, 355.
  in urine, 443.
  test for, 355.

Umbilical cord, 478.
Unipolar nerve-cells, 40, 42.
Unstriated muscle, 36.
Urate deposit, 441.
Urea, 438.
  bacterial action on, 438.
  effect of hypobromite on, 438.
  formation of, 401.
  nitrate, 438.
  output on protein diet, 402.
  oxalate, 438.
  preparation from urine, 438.
Ureter, contractions of, 454.
Uric acid, 406, 440.
  in spleen, 413.
  origin of, 406.
  production in birds, 406.
  tests for, 440.
Urinary constituents, 436.
  daily amount of, 436.
  deposits, 441.
Urine, 436.
  abnormal constituents in, 442.
  acetone in, 392, 443.
  ammonia in, 439.
  chlorides of, 441, 450.
  composition of, 436.
  formation of, 444.
  lactose in, 442.
  neutral sulphur in, 441.
  phosphates in, 441.
  pigments of, 437.
  pressure of, in ureter, 448.
  reaction of, 437.
  salts of, 436.
  specific gravity of, 436.
  sugar in, 442.
  sulphates of, 441.
Uriniferous tubule, 434.
  functions of, 448.
Urobilin, 363, 427.
Urochrome, 437.
Uroerythrin, 437.
Uterine tube, 474.
Uterus, 474.
  changes in, during pregnancy, 477.
Utricle, 168.
Uveal layer, 129.

Vagus nerve, 115.
  action on heart, 246.
    on intestine, 370.
    on œsophagus, 338.
    on respiration, 306.
    on stomach, 344, 350.
  apnœa, 306, 310.
  escape, 247.
  expiratory fibres in, 306.
  nucleus of, 79.
  tonic action on heart, 247.
Valves of heart, 199, 214, 217.
Variation, diphasic, 31.
  monophasic, 32.
Vascular mechanism, 198.
  tone, 252.
Vaso-constrictor nerves, course of, 252.
Vaso-dilator fibres, 256.
  in mixed nerve, 257.
  in sympathetic nerves, 259.
Vaso-motor centre, 255.
    effect of C_H on, 260.
  centres in cord, 256.
  impulses, path of, 112.
  nerves, 252.
  reflexes, 259.
Vegetable food, utilisation of, 432.
Veins, 201.
  rate of flow in, 209.
  valves in, 201.
Venous blood-pressure, 204, 209.
  pulse, 234.
Ventral spino-cerebellar fasciculus, 63.

Ventricles, capacity of, 200.
pressure in, 219.
Ventricular diastole, 201.
folds in larynx, 166.
systole, 201.
Vermiform appendix (process), 381.
Vesicular murmur, 280.
Vestibular nerve, 80, 169.
nucleus of, 81.
Vestibule, 168.
Vestibulo-spinal tract, 62.
Villus, 372.
changes in, during fat absorption, 376.
Visceral nerves, 114.
spinal reflexes, 76.
Vision, 134.
binocular, 153, 155.
colour, 150.
direct, 153.
field of, 153.
indirect, 153.
Visual acuity, 136.
adaptation, 147.
angle, 136.
area, 100.
fatigue, 152.
judgments, 149, 154.
path, 101.
purple, 130, 145.
sensations, 148.
Weber's law, 120.
stimuli, time-relations of, 149.
Visuo-psychic area, 100, 149.
Visuo-sensory area, 100, 149.
Vital capacity, 279.
Vitamines, 424.
Vitreous humor, 133.
Vocal cords (folds), 165, 166.
Voice, pitch of, 167.
production of, 166.
Volume of an organ, 254.
of contracted muscle, 23.
Voluntary contraction, 36.
electrical changes in, 36.
muscle, 20.
Vowel-sounds, 167.

Warm points, 121.
Water, absorption of, 373, 378.
Water-soluble B, 424.
C, 427.
Weber's law, 120.
Weigert-Pal method, 54.
White blood-corpuscles (*see* Leucocytes).
White rami communicantes, 112.
White, sensation of, 148.
Word-blindness, 105.
Word-deafness, 105.
Work done by heart, 222.
by muscle, 27, 35.
Wrightson's theory of hearing, 164.

Xanthine, 22, 406.
Xanthoproteic reaction, 10.

Yeast, action on glucose, 7.
Yellow spot, 132.
Young-Helmholtz theory, 150.

Zein, food-value of, 404.
Zona fasciculata, 458.
glomerulosa, 458.
pellucida, 473.
reticularis, 458.
Zonula ciliaris, 133.
Zymogenic granules, 323.
in pancreas, 360.
in salivary glands, 328.

WELLCOME LIBRARY INSTITUTE

Printed by SPOTTISWOODE, BALLANTYNE & Co. LTD.
Colchester, London & Eton, England