liminary discussions pointed to the importance of the following factors: the view over the aircraft nose, the distance of the eye to the instrument-panel, the distance of the eye to the gun-sight, the crash distance of structures forward of the head, adequate clearance for the ejection seat, the controls to be easily within reach, the seat height and rudder-bar positions to be adjustable. From these early data a more elaborate mock-up model was then constructed, and the position and mode of operation of some two hundred instruments and controls determined. Certain principles are now common practice and are employed in all new aircraft built for the Royal Air Force, the Royal Navy and for civilian air lines. Standardization has also been agreed with the United States Services except for a few items. These important principles are (1) separation of controls into pre-flight and flight; (2) the separation of flight controls into throttle and control-column sides; (3) the distinction of controls by position, method of operation and knob-shape; (4) emergency and stand-by controls to be an over-action of the normal control or placed near the normal control; (5) controls to act in the expected direction, and the position of control surfaces to be indicated in the same way; (6) all controls to be set up forward for take-off; (7) standardization of the arrangement of flight instruments, and all engine-monitoring instruments to be arranged for rapid appreciation.

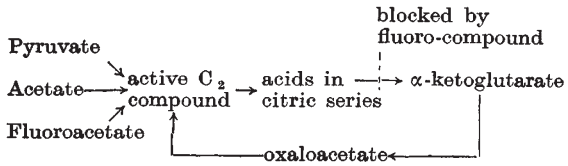
Much other work has been done on this problem of making man and aircraft a harmonious team; the tasks of other crew members are now being studied—those of the navigator, the flight engineer and the radar operator. New problems are, however, constantly being set by the swift evolution of aircraft and other equipment. These rapidly changing requirements stress once again the need for investigations directed towards discovering the principles of the subject, rather than for studies which are only *ad hoc* investigations. N. H. MACKWORTH

BIOCHEMISTRY AND PHYSIOLOGY OF THE CELL

AT the meeting in Newcastle upon Tyne of Section I (Physiology) of the British Association on September 6 the presidential address on "The Cell" by Prof. R. A. Peters was followed by a group of papers on particular aspects of cellular physiology. Prof. Peters emphasized that recent work upon organised enzyme systems has already produced therapeutic results. In illustration, he chose two poisonous substances, iodoacetic acid ($I:CH_2.COOH$) and fluoroacetic acid ($F.CH_2.COOH$), which have similar chemical structures but very different types of biochemical action. The iodine atom of the iodoacetic acid can easily take part in substitution reactions at neutral *p*H values, whereas the C—F group in fluoroacetic acid is very stable.

Iodoacetate owes its toxic properties to its ability to combine with —SH groups in certain enzymes, such as the triosephosphate dehydrogenase of muscle which is particularly sensitive, so that when muscle tissue is poisoned with this substance, lactic acid formation is completely stopped. The oxidation of pyruvate by the pyruvate oxidase system also depends upon —SH groups, but in this case a specific poison is to be found in the arsenical lewisite ($CH.Cl:CH.AsCl_2$), which attacks a specially arranged dithiol grouping. Its action can be reversed by British anti-lewisite (BAL) (dimercaptopropanol), which is now used clinically as an antidote in cases of arsenical dermatitis and other similar conditions. Since the pyruvate oxidase requires thiamin pyrophosphate as a co-enzyme, vitamin B_1 deficiency induces a biochemical lesion affecting the same enzyme system.

Fluoroacetate, which is the toxic principle of the South African plant known as 'gifblaar' (*Dichapetalum cymosum*), is very poisonous indeed, especially to mammals. Its toxic action is exerted on the central nervous system and on the heart, but is not due to the liberation of fluorine. Fluoroacetate has no action on any known isolated enzyme system, but it decreases the oxygen uptake of slices of kidney tissue and causes an accumulation of citrate. Such an accumulation of citrate is also found in the tissues, especially the heart and kidneys, of animals poisoned with fluoroacetate. Citric acid and related 6-carbon tribasic acids are formed in the operation of what is known as the citric acid cycle, being produced by the condensation of oxaloacetate with an active 2-carbon compound formed from pyruvate or even from acetate. The acids of the citric series, including *cis*-aconitate, then give rise to α-ketoglutarate, which in turn forms succinate and finally oxaloacetate, which starts the whole cycle again. Prof. Peters suggested that fluoroacetate does not compete with acetic acid for entry into the citric acid cycle, but that it is activated by the same enzyme as acetate and, in fact, enters the cycle. Since the foreign molecules so formed cannot be handled by one of the enzymes at the tricarboxylic acid stage, the foreign molecule jams the cycle and so leads to a gradual accumulation of citrate. Fluoroacetate is therefore poisonous, because it is so like a normal metabolite that the tissue enzyme concerned cannot distinguish between it and ordinary acetate.



The toxic actions of both iodoacetate and fluoroacetate can therefore now be explained on the basis of modern enzyme biochemistry.

Prof. Peters next turned to the question of the biochemical organisation of the cell and the location of the organised complexes of enzymes. Many such complexes are to be found in the granules in the cell cytoplasm where they may be arranged, not in a haphazard manner as if the granule were a mere bag of enzymes, but in a regular orientation of structurally related enzymes, spatially distributed in relation to each other in an appropriate pattern which can be upset by biochemical methods. In this arrangement, surface factors play a fundamental part even down to a molecular level, and the surfaces of separation in the cell may have an individual organised structure.

Any hypothesis of cell organisation has to explain the ability of the cell to conduct, at the same time, various chemical reactions which individually require quite different physico-chemical environments, that is, the cell has to act as a 'micro-kitchen' as postulated by Hofmeister, in which, among other things, enzymes with very different *p*H optima have to act har-

moniously together. Some apparent difficulties in relation to *p*H requirements for different enzymes can be eliminated if the site of enzyme action is confined to internal surfaces, and Prof. Peters stressed the dominant part played by surface structure, especially internal surface structure, where microheterogeneity may extend down to very fine limits.

It is also necessary that the cell should react as a whole to a stimulus applied to any one point on its surface. This may be related to the presence within the cell of a sub-microscopic organisation or mosaical three-dimensional structure capable of acting integratively. While the term 'cytoskeleton' may be applied to such an organisation, it does not indicate an inert structure so much as a co-ordinating mechanism which need not be many molecules thick.

Prof. Peters referred to recent suggestions that the gene might be considered as an enzyme, but suggested that enzymes themselves need not be regarded as the primary structure, which might rather be a protein or nucleoprotein groundwork characteristic of the individual cell, to which the enzymes are attached. Such a hypothesis is supported by recent work on paramecin, on plasmagenes and on skin grafting. While many of these problems may eventually be solved with the aid of the newer techniques of chemistry and physics, it will not be possible to dispense with scientific workers whose training is fundamentally biological. (See also *Nature*, Sept. 3, p. 393.)

The next speaker, Dr. R. Barer, emphasized that the concept of the microscope as a mere magnifying glass is being replaced by the realization that it can be used as a valuable physico-chemical tool. One of the major difficulties encountered in the study of the living cell is its great transparency to visible light; but this problem has been largely solved by the development of phase-contrast microscopy, which converts changes of refractivity into corresponding changes of intensity and thus enables living cells to be studied under excellent optical conditions. Considerable advances are being made in our knowledge of the structure and behaviour of cells and of the action of chemical and physical agents, such as fixatives, on living protoplasm.

The primary purpose of the electron microscope is to obtain very high resolution down to molecular level. The shadow-casting technique can produce very spectacular results when it is applied to biological material; for example, it can be used to demonstrate the presence of what are believed to be contractile molecular threads within muscle fibrils. In some cases it is possible to study the structure of cell membranes and the cytoplasm of cells grown in tissue culture. The reflecting microscope is completely achromatic and can therefore be used in the ultra-violet visible and infra-red regions of the spectrum without change of focus. This has enabled adsorption spectroscopy of cells, fibres, crystals and other materials to be carried out in a spectral range extending from 230 m to 14 μ. The use of ultra-violet and infra-red polarized light in conjunction with such spectroscopic methods has yielded particularly interesting information on the chemical organisation of crystals and orientated fibres. The reflecting microscope is a unique instrument for the correlation of chemical and structural organisation, and its possibilities are very far from being exhausted.

Prof. J. N. Davidson pointed out that the various components of the cell can now be separated by means of differential centrifugation which yields from the cytoplasm particles of two main sizes. The smaller particles, or microsomes, are ultra-microscopic in size, but the larger particles correspond to the mitochondria, or secretory granules, and a modern technique of homogenization and centrifugation in molar sucrose solution results in the isolation of morphologically intact mitochondria. These cytoplasmic particles contain protein, lipid and ribonucleic acid—the nucleic acid content being greater for the smaller particles. Certain enzyme systems are located in these cytoplasmic granules and the succinoxidase–cytochrome oxidase system, and the enzymes of the tricarboxylic acid cycle are to be found almost exclusively in the large particles. By virtue of their nucleic acid content, such particles can conveniently be studied by means of ultra-violet microscopy, which can also be made the basis for the photometric estimation of minute amounts of nucleic acid in different parts of the cell.

The cell nucleus contains a basic protein—either protamine or histone—a non-histone protein containing tryptophan (the chromosomin of Stedman) and both types of nucleic acid. Ribonucleic acid is present in only small amounts and appears to be located mainly in the nucleolus; deoxyribonucleic acid, on the other hand, is abundant in the cell nucleus, but the proportion found in dried nuclei depends largely upon the method of isolation, since modern techniques of preparing clean nuclei with the aid of citric acid tend to remove histone and so to cause an apparent increase in the deoxyribonucleic acid content when the nuclei are analysed in bulk. On the other hand, when the deoxyribonucleic content is expressed as an absolute amount per nucleus, very striking results are obtained. It has been shown that the deoxyribonucleic acid content of the cell nucleus is constant for the different organs and tissues in a given species, although there might be a big variation from one species to another. In general, the amount in the sperm cell nucleus is almost exactly half that found in the somatic cells. If the amount of deoxyribonucleic acid in the nucleus is, in fact, constant for a given species, it provides a standard of reference to which the other constituents and the biochemical activities of the cell might be related; and it also provides what is probably the most useful indication of cell growth, since an estimation of the deoxyribonucleic acid content of a sample of tissue will give a measure of the number of cells present.

A lipoprotein was defined by Prof. A. C. Frazer as a molecular complex of lipids and proteins possessing properties which are significantly different from the sum of the properties of its components. The linkage between lipid and protein molecules may be electrostatic, covalent or by secondary valencies. Methods used for lipoprotein studies include chemical methods, especially fractionation, microanalysis and the study of model systems; physical methods, of which X-ray diffraction techniques have proved valuable; physico-chemical methods, by which the inter-reactions of lipids and proteins at air/water or oil/water interfaces can be studied; cytological methods, which entail histochemical microanalysis or cell fractionation by ultra-centrifugation; and biological methods involving the study of cell structure and function under varying environmental conditions. The more these methods can be related to each other, the more rapidly will useful information on lipoproteins be obtained.

Using these methods, Cohn and his colleagues have separated a β-lipoprotein having spherical particles 185 A. in diameter and molecular weight of about 1,300,000, and an α-lipoprotein with particles about 300 A. long and 50 A. wide and molecular weight about 200,000. Many important lipids, such as œstrogens and carotenoids, appear to be associated with the β-lipoprotein. The chylomicrons in the blood are stabilized by a lipoprotein—the protein being linked to the non-reactant triglyceride core by lecithin. One conception of membrane structure is of a basic lipoprotein framework to which further lipid sub-units can be added to provide a lipid/protein mosaic. Mitochondria and other intracellular structures are said to be lipoproteins. The effects of solvents and dehydration on nerve myelin have been studied by combining X-ray diffraction and micro-analysis. The observations suggest the existence of lipid/protein and lipid/lipid subunits as part of a larger lipoprotein complex. Lipoproteins provide a structural medium which can accommodate both lipids and water. Association of lipid with protein may prevent oxidation—after separation, the lipid can oxidize rapidly. Fat transport in the blood is mainly as glyceride rather than lipoprotein. In general, a lipoprotein consists of a lipid/protein subunit largely dependent on electrostatic forces and particularly sensitive to *p*H changes and dehydration, and a lipid/lipid subunit in which van der Waals forces and the formation of hydrogen bonds might be more important.

Mitochondria were discussed by Dr. G. H. Bourne, who described them as rods, filaments or granules seen best by dark-ground illumination and phase-contrast microscopy, and often occupying a particular orientation in the cell as if they were arranged by currents of diffusion linked with the sub-microscopic structure of the protoplasm. They can be separated by differential centrifugation and shown to consist mainly of protein, lipid and ribonucleic acid, but they may also contain small amounts of vitamins, some pigments and certain enzymes. Most of the succin-oxidase of the cell is to be found in the mitochondria, which appear, therefore, to be intimately connected with the aerobic respiration of cells. Mitochondria are greatly reduced during starvation, but return on feeding. They are to be regarded not as semi-permanent self-reproducing cell organelles, but rather as temporary aggregates of complex composition and as a reserve store of metabolic substance for the cell.

Mr. M. M. Swann spoke of his researches with the polarizing microscope on cytoplasmic structure in the sea urchin egg, with particular reference to the changes occurring during the mitotic cycle. The highly oriented metaphase spindle and asters give way to a less oriented structure as mitosis progresses, and it appears that the agent controlling this change is liberated directly or indirectly by the chromosomes. This less oriented arrangement of protoplasmic material is normally so weakly birefringent as only to be visible with very refined methods. It consists apparently of form and intrinsic birefringences acting in opposition, and more or less cancelling out. This curious arrangement seems to obtain in rather different forms in both the fertilized and unfertilized eggs, and in other cells as well, and it is perhaps to be regarded as the 'cytoskeleton'. The asters and spindle are therefore not *de novo* structures, but modifications of a structure always present.

J. N. Davidson

FOLIC ACID, VITAMIN B_{12} AND ANÆMIA

THE programme for Section I (Physiology) of the British Association at the meeting this year at Newcastle upon Tyne included a symposium on folic acid, vitamin B_{12} and anæmia. In a brief introduction, the chairman, Prof. R. A. Peters, mentioned the importance of the topic and the intense interest aroused by the synthesis of folic acid and the isolation of vitamin B_{12}.

The first paper, on the chemical aspects, was read by Dr. E. Lester Smith. This contribution centred round the methods of treatment of the macrocytic anæmias, especially pernicious anæmia. The first effective treatment was discovered by Minot and Murphy in 1926. Their use of raw or lightly cooked liver by mouth was quickly superseded by liver extracts given at first orally and, later, by injection, made possible by more extensive purification through fractional precipitation with alcohol and other means. Some progress towards the isolation of the active principle was made by American, Norwegian, Swiss and British biochemists; but the problem proved exceptionally difficult, mainly on account of the lack of a satisfactory assay method. The final isolation of vitamin B_{12} was announced almost simultaneously in 1948 in America by Rickes and co-workers at Merck and Co., Inc., Rahway, N.J., and by Lester Smith of Glaxo Laboratories, Ltd., Greenford, Middlesex. This culmination of twenty-two years of research aroused great interest, which was increased by the announcement that the red crystalline substance had an extraordinarily high biological activity and contained cobalt in its molecule.

Some years previously, several American teams prepared, from liver, yeast and spinach, concentrates that promoted the growth of *L. casei* and other micro-organisms; they also promoted normal growth and prevented anæmias in chicks or monkeys on deficient diets. This series of researches culminated in the isolation of a crystalline substance known as folic acid or pteroylglutamic acid, which was synthesized by a large group of workers at Lederle Laboratories, Pearl River, N.Y., within a very short time of its isolation from natural sources. The great confusion that had existed over an apparent multiplicity of related factors was cleared up by the isolation of two conjugates of folic acid with an additional two and six molecules respectively of the glutamic acid radical. They have different activities towards micro-organisms, but can be converted into folic acid by specific conjugases.

It was only after synthetic folic acid became available that its efficacy in macrocytic anæmias was announced. From the high doses required, however, it quickly became apparent that folic acid could not be the effective agent in purified liver extracts. A little later it was shown that it is somewhat less effective hæmatologically than liver extract (both given at adequate dose-levels), while it is entirely ineffective against the neurological complications of pernicious anæmia.

The war-time scarcity of feeding stuffs focused attention on the fact that chicks and other farm animals need animal protein in their diet. Concentrates of an 'animal protein factor' were prepared from fish solubles and from cow manure, and gradually accumulating evidence indicated that this factor