and France: the Fulbright and Smith–Mundt programmes in France, the technical assistance programme of E.C.A., the Point IV programme as it might apply to under-developed areas in French colonial possessions. Because of the fact that the secretariat of Unesco is located in Paris, the Paris Science Office might be expected to establish close working relations with that Organisation.

The initial proposals for the establishment of Science Offices in both Categories are as follows.

Category 1 (Area Offices): Western Europe, London; South Africa, Johannesburg; South America, Rio de Janeiro; Australasia, Sydney (or Canberra).

Category 2 (Single Country Offices): Paris, Brussels, The Hague, Rome, Berne, Stockholm, Oslo and/or Copenhagen, Lima, Ottawa.

The area office in London would have the dual function of geographical coverage of Western Europe in the various special disciplines of science and also the Category 2 functions as they pertain to matters of direct concern between the United States and the United Kingdom. The early establishment of area offices in Cairo and New Delhi is to be considered. The establishment of other Category 2 offices may be anticipated in South America, Africa, etc., after the area offices have been set up.

The establishment of Category 2 offices in Germany and Japan poses special problems which will be worked out in consultation with the United States High Commissioner for Germany and the Supreme Commander, Allied Powers in Japan.

The Category 2 offices which are to be established in capitals of various countries will, in general, consist of scientific staffs comprising one to three scientific workers. No general recommendation is made as to the size of the Category 1 or area offices; the present arrangement in the American Embassy, London, may give some clue as to the eventual size of these offices. At the present time the London Science Staff of the State Department consists of two men of science whose activities are essentially those of a Category 2 office. The Office of Naval Research, London, comprising ten to twelve men of science, exercises Category 1 or area office functions in its activities in Western Europe. The combined activities of the London Science Staff and U.S. Office of Naval Research, London, might furnish a pattern for the other area offices which are proposed in the report.

The functions to be performed by science staffs of both Categories 1 and 2 would cover the following: "reporting on significant trends and developments in foreign science; encouragement of collection and transmittal of foreign scientific and technical information to the United States by private individuals and organisations (public and private); actual collection and transmittal where the situation does not readily permit of direct access between such United States individuals and the foreign sources; advice to the chief of the United States mission and his staff on scientific matters; representation and maintenance of the interest of United States science and scientists abroad; response to the scientific requirements of all United States Government agencies; assistance to both United States and foreign scientists in the procurement of scientific apparatus, chemicals, biologicals, and other scientific tools and materials; arrangement, when appropriate and desirable, for collaborative research projects between United States and foreign scientists; the implementation of the flow of scientific information on a two-way basis; and the facilitation of arrangements for visits of United States scientists who may be travelling abroad".

It is fully realized by those who participated in the formulation of the report that the science staffs must encourage in every way two-way exchanges of scientific information and of scientific workers. As it states in the report, "experience clearly shows that the flow of information must be a cooperative enterprise".

The importance of science and technology in national affairs and international relations, particularly during the present period of rehabilitation, has been indicated in various ways. On the national scale one might point to the establishment of high-level scientific advisory groups in Great Britain, such as the Advisory Council on Scientific Policy, the Defence Research Policy Board, and the Committee on Industrial Productivity. On the international scale one could cite in the United States the work of the Division of International Relations of the National Research Council, the National Commission for Unesco, and the various educational exchange and technical assistance activities, such as the Fulbright, Smith-Mundt, Point IV, and E.C.A. programmes. The proposed Science Offices which would be established in various countries of the world could assist the agencies of the United States Government in such international programmes as are listed above.

The active participation of the National Academy of Sciences and the National Research Council in the work of the Science Office is expected after the last-named has been established. It is recommended in the Report that the State Department urge the National Academy of Sciences to appoint a committee of eminent United States men of science which would act as a top-level board in advising the Department concerning scientific and technological questions. The National Research Council has indicated that it would be glad to assist, through its Division of International Relations, and through appropriate organisational changes, in strengthening co-operation between the State Department and the scientific workers of the nation.

The Report submitted by Dr. Berkner has been accepted by the State Department. The selection and appointment of a science adviser may be expected in the very near future. Following his appointment, the establishment of the Science Office in the State Department and of the Category 1 and Category 2 Science Offices in other countries will follow in due course.

PHYSICAL CHEMISTRY OF DRUG ACTION

A SYMPOSIUM on "Physical Chemistry of Drug Action" was arranged jointly by the Royal Institute of Chemistry and the Society of Chemical Industry, and held in University College, London, on April 19.

In opening the symposium, Sir Cyril Hinshelwood pointed out that two distinct fields had to be explored: how the drug reaches the seat of action and what it does when it gets there. Various physico-chemical principles have been shown to govern the action of various drugs. The laws of physical

chemistry must apply to such reaction systems just as they apply to all non-living reaction systems.

Because of the elaborate nature of the mechanisms by which foreign substances become distributed in the higher animals, questions of access to the site of action are best studied in single-celled organisms. The question is often raised as to whether the permeability of the cell wall determines the action or whether equilibrium between the cell and the medium can be assumed. Arsenic-resistant trypanosomes, unlike sensitive trypanosomes, are unable to accumulate the arsenical from the medium, and penicillin is able to hinder the uptake of glutamic acid by cells. But penetration is by no means always the limiting factor. The time taken by proflavine to arrest the growth of *B. lactis aerogenes* is independent of the concentration gradient between the inside and outside of the cell. In fact, cells trained to be resistant to proflavine take up appreciably more of the drug than before the adaptation. Again, the influence of many inhibitors on the growth-rate of bacteria is independent of pre-treatment for periods amply sufficient for the establishment of even a sluggish equilibrium. Again, cells are freely permeable to sodium; but potassium is taken up preferentially and sodium scarcely at all. Hence penetration and accumulation are two very different things. When permeability is not the limiting factor, a further question arises: Is a simple partition between two phases involved, or an adsorption equilibrium? Perhaps, with the complex macromolecular networks involved in cells, something between solution and adsorption must be envisaged.

As to the mode of action of the drug at a given locus, various mechanisms have been demonstrated in different cases. In some cases, the effect is not directly dependent on the chemical constitution of the molecule. Ferguson has shown that numerous substances, from phenols to the rare gases, have approximately equal narcotic actions when present in the tissues at equal fractions of saturation.

However, the subtly differentiated kinds of physiological action involved in chemotherapy are usually highly dependent on structure. In some cases, ionization constants are determinative; in others it is the ability to form co-ordination compounds with trace-metals. In yet others, covalent bonds may be formed with specific groups such as —SH; in others the action depends upon a steric resemblance between the drug and some essential metabolite.

In the matter of predicting relations between structure and biological action, too much should not be expected of physical chemistry. Nevertheless, its value for supplying rational interpretations is considerable, and knowledge of these can be used for modifying the drug molecule so as to improve its action.

The network of normal metabolic reactions taking place in a cell is often cyclically linked and contains many competing reactions. The kinetics of these processes are being intensively studied in the presence and absence of inhibitors, and the results are likely to make a distinct contribution to our knowledge of drug-action.

In conclusion, physico-chemical principles provide a rational system in terms of which we may, and indeed should, envisage the relations of cells to those foreign substances that gain access to them: but we must not look for a simple all-embracing formula.

Prof. F. A. Paneth spoke on the use of tracer elements in pharmacology. Because any element and its isotope can be relied upon to remain together during chemical reactions, the use of isotopes as indicators in tracing the distribution of a drug may offer advantages over other methods. Actually, it is often the only feasible method. The more complicated the system to be studied, the clearer is the superiority of this indicator method. This explains why the most extensive use of isotopes is found in the biological sciences.

In studying biological processes, it is safer to use inactive (rather than radioactive) tracers. Even small activities have been known to exert a marked effect on biological processes. Unfortunately, mass-spectrographs which will measure small, practicable amounts of inactive tracers (such as 0·001 c.c. of nitrogen-15) still remain to be developed. The measurement of such quantities of radioactive material is, on the other hand, quite simple. In Britain we have very few kinds of inactive isotopes, principally carbon-13 in the form of barium carbonate and oxygen-18 in the form of water. However, other kinds would be available before long, as in the United States.

The radiochemist has an exacting task in preparing substances for studies of drug action (cf. *Quart. Rev. Chem. Soc.*, 2, 93; 1948; *Nature*, 163, 388; 1949) and for analyses by the isotopic dilution method. First of all, a drug must be chosen which can be recovered from biological material in a pure state, either as such or as a well-defined breakdown product. The synthesis of an isotopic form of this drug must then be undertaken. If the isotope has a short life-time, it is better to choose the most rapid synthesis even though a lower weight of pure product can be obtained by this route. It is usually the chemist's duty to work with the strongest obtainable concentrations of isotopic material and to present the biologist with substances of the highest possible specific activity. In support of this statement, it has been shown that, in one case, a sample of iodine of low specific activity had to be used in such a high dosage that a strong pharmacological effect was elicited and the experiment completely spoilt.

It is not always convenient to set up an isotopic chemical department in a medical school. Hence it is worth noting that the Radiochemical Centre at Amersham is willing to consider the synthesis of isotopic substances to order. 'Isotope farming' provides a very useful method for synthesizing isotopic specimens of the more complex molecules associated with living processes. This is accomplished by supplying the desired fungus, animal or higher plant with isotopically charged foodstuffs or gaseous carbon dioxide from which it then synthesizes isotopically labelled material. In this way, isotopic casein, sugars, digitalin and penicillin have been obtained. Isotopic farming can also provide a useful means of disposing of residues of carbon-14.

Because iodine becomes concentrated in the thyroid gland, cancer of the thyroid can be treated orally by radioactive iodine. This is not yet a method of general utility for treating other forms of cancer because no organic or inorganic substance that will concentrate in cancerous tissues is known. When such a substance is found, it can readily be made radioactive and hence should prove specifically destructive to the cancer. For the present, the principal value of artificial radioactive substances in pharmacology lies in their use not as drugs but as indicators of the mode of action of drugs.

Dr. H. R. Ing discussed the effect of size and shape of drug molecules upon drug action. The idea of

'fit' between biologically active molecules and the biological structures upon which they act goes back to Pasteur and was used by him to explain the stereo-specificity of enzymes. It has since been extended by Landsteiner to give a satisfactory explanation of the antigen-antibody reaction and by Michaelis to develop his postulate of an enzyme-substrate complex, a hypothesis now widely accepted. Studies of the interaction between a drug and its biological receptor have much to gain from this concept of 'fit'. A good physical basis for it exists in the Van der Waals forces and in hydrogen-bonding. Van der Waals forces, being both weak and of short range, are consistent with what is known of the stereo-specificity (as well as the ready reversibility) of drug-receptor bonding. To be held by these forces, molecules must come into intimate contact at numerous points: thus the drug molecule must be of such a shape and size as to accommodate itself closely to the biological structure (for example, enzyme or cytoplasmic membrane) on which it is to exert its disturbing effect. The experimental approach to spatial relationships must be confined, at first, to fairly simple molecules.

The best approach to the function of shape, in isolation, can be found in the study of isomeric drugs. The usual lack of competitive antagonism between optical isomers is informative, as is the lack of competition between sulphanilamide and the *o*- and *m*-isomerides of the highly competitive *p*-amino-benzoic acid. Two isomeric cations which have approximately the same volumes but very different shapes are $(C_2H_5)_4N^{\oplus}$ and $(CH_3)_3N^{\oplus}C_6H_{11}$; the former, but not the latter, exerts a strong paralysing action on the neuromuscular junction.

Some of the simplest examples of the importance of shape are provided by pairs of optical enantiomorphs. *l*-Adrenaline is ten to twenty times as active as *d*-adrenaline in increasing arterial blood pressure. Clearly, the low activity of the *d*-isomer is due to its low affinity for receptor sites. By a systematic stepwise modification of the adrenaline molecule, it can be shown that the *l*-isomer forms three attachments to the receptor, using three groups (phenolic —OH, alcoholic —OH and —NH) which are capable of forming hydrogen bonds (or the —NH group may be engaged by an ionic bond). *d*-Adrenaline is able to form only two of these bonds, and further evidence indicates that the alcoholic —OH of this isomer is too remote from the appropriate group on the receptor to make effective contact with it.

By continuing these stepwise variations, it has been shown that the *m*-OH group is more important than the *p*-OH, because omission of the latter gives a substance, 'neosynephrin', the *l*-form of which has one-third of the activity of adrenaline.

The effect of shape can be followed in acetylcholine

$$CH_3COOCH_2CH_2X^{\oplus}Me_3 \qquad (I)$$

(I, $X = N$) and its analogues where $X = P$ or As. When nitrogen is replaced by phosphorus, the activity falls to one-twelfth, and replacement by arsenic lowers activity to one-eightieth. These differences in pharmacological effect can be shown to be due to the size of the cationic head, namely, the hetero-atom plus the methyl groups which it carries. The larger the hetero-atom the more the methyl groups are extended into space to occupy the volume which three ethyl groups on a nitrogen atom (a combination with only feeble activity) would normally occupy. From these and other experiments in varying the shape of the acetylcholine molecule, it would appear that two methyl groups of this hormone have to fit on to fixed receptors in the effector-cells. Any change in the distance between them will be reflected in the lowered activity of the molecule.

Both shape and size have been varied, independently and together, in a stepwise exploration of the antibacterial properties of certain planar cations of the acridine, benzacridine, quinoline and benzquinoline series and their non-planar hydrogenated analogues (cf. *Brit. J. Exper. Path.*, 30, 159; 1949). This work has led to a clear understanding of the minimal spatial requirements for activity in this series of drugs.

These intimations of the importance and nature of 'fit' between drug molecule and biological structure are beginning to illuminate otherwise puzzling structure-action relationships.

Prof. Adrien Albert spoke on ionization—an important factor which is sometimes critical. Many biologically active substances respond to a change in *p*H by a change in their degree of ionization. Conversely, if the *p*H is held constant, closely related substances, even isomers, ionize to widely different extents. The importance of these data lies in the fact that the ion and the neutral molecule of a given substance have different degrees of biological activity in all cases that have been investigated. Sometimes these differences even partake of an all-or-nothing character. Chemistry provides many examples that help us understand how an ion and a molecule of the same substance can elicit different biological responses.

(i) Chemical reactivity in the bulk phase is often dependent on the degree of ionization. Dimethyl-aniline becomes nitrated in the *para* position, but its ion undergoes *meta* nitration. Again, the uncatalysed autoxidation of ascorbic acid proceeds through the divalent anion, but not when catalysed by copper, which permits only the monovalent anion to be attacked.

(ii) Adsorption at surfaces is not indifferent to ionization. In non-specific adsorption (where the molecule has a highly polar/non-polar structure) the neutral molecule is the more highly adsorbed; but in the specific adsorption from water of well-hydrated molecules, the ion is frequently preferred.

(iii) The penetration of membranes is effected much more readily by a molecule than by its corresponding ion, principally because of the surface-charge on the membrane. However, ions can be made to penetrate natural membranes by increasing the proportion of lipophilic to hydrophilic groups.

Ionization is an essential condition for the action of certain drugs. The cationic antibacterials of the acridine, phenanthridine and benzquinoline series are cases in point. Regardless of the type of substituent (for example, amino-, diamino-, methyl-, chloro-) present, the important condition is that these substances should be ionized at *p*H 7. Hence, in these series, one can make numerous pairs of isomers, of which one is ionized and the other is not; the ionized one is always found to have high antibacterial activity, whereas the non-ionized substance has little or none.

For some other drugs, particularly weak acids, ionization is highly disadvantageous. The action of phenylarsenoxides on the spirochæte of syphilis (Eagle, 1945), of barbiturates and local anæsthetics on *Arenicola* worms (Clowes and Keltch, 1931), of

salicylic acid on echinoderm division (Smith, 1925) are examples where the ion is entirely or almost entirely inactive.

A number of drugs, particularly the alkaloids and local anæsthetics, have pK values between 6 and 8. This means that at physiological values of hydrogen ion concentration (around pH 7), both ions and neutral molecules are present in a ratio lying between 1 to 1 and 1 to 9. Such drugs can pass through membranes which would exclude ions and yet can regenerate some ions (by mass action) on the far side of the membrane.

From these and other examples, it is clearly important to know the ionization constants of all biologically active substances under investigation. Such knowledge should then be used to decide whether ion or molecule is the more active. This is done in two complementary ways: (i) by varying the pK of the drug through appropriate substitution, keeping the pH of the biological medium constant; (ii) by keeping the composition of the drug constant and varying the pH. Such information can materially shorten the time taken to find the most active substance in a given series, because it brings one of the commoner variables completely under control.

Drs. H. J. Barber, F. Bergel, T. McLachlan, B. A. Pethica, M. A. Phillips, D. Ridge, J. H. Schulman, R. Slack and H. I. Stonehill took part in the discussion.

ADRIEN ALBERT

OPERATIONAL ANALYSIS AND THE NATURE OF SOME PHYSICAL CONCEPTS

THE Philosophy of Science Group of the British Society for the History of Science, under the chairmanship of Prof. J. H. Woodger, held a meeting on May 5 at University College, London. A general discussion took place on questions arising out of Prof. P. W. Bridgman's three lectures on "The Nature of Some of our Physical Concepts" delivered at University College during April 24–28. (These lectures are to be published in the *British Journal for the Philosophy of Science*.) The meeting was attended by about forty members of the Group and visitors.

Prof. Bridgman opened the discussion with a brief summary of his lectures. He thought that their most important feature was the detailed analysis of how the operational technique can be applied to specific physical concepts and problems. In the first lecture, he had discussed general concepts such as field, action at a distance, and empty space; in the second, thermodynamical phenomena, in particular the laws relating to energy and entropy; and in the third, some situations presented by thermo-electric phenomena. Prof. Bridgman believed that the particular novelty of his analysis in these lectures was the self-conscious separation of physical operations into those of an instrumental character and those of a 'paper-and-pencil'—that is, mental—character. He had been aware of this distinction for a long time, but only recently had he seen how it applied to what physicists actually do. With regard to this, there are two points of view, as follows.

Instrumental operations correspond most nearly to what used to be called 'physical reality'. This aspect of physics can be illustrated by an analysis of the field concept. Instrumentally, the existence of a field at a certain place means that, if you go there with the appropriate type of instrument, it will record a certain 'reading'. Similarly, in applying the first law of thermodynamics, one must specify the elements of space, and in particular their boundaries, on which one operates, so that the fluxes over these boundaries correspond to the actual instrumental readings.

The other aspect relates to the way in which our verbal demands interlock with our instrumental operations. For example, we accept the typical conservation laws of physics as verbal guides with rational implications, but we also find that there exist instrumental operations corresponding to our verbal demands.

It is Prof. Bridgman's belief that, in general, no sharp dividing line can be drawn in physics between the purely instrumental and the purely mental. He regards the whole operational approach as part of a larger programme, according to which we regard the world about us in terms of 'activity' rather than picturing it statically. From this point of view, it is preferable to describe our theories in terms of what we 'do' rather than in terms of 'things'.

Prof. H. Dingle said that, although he is in general agreement with the operational point of view, he attaches less importance than Prof. Bridgman to the distinction between instrumental and paper-and-pencil operations. He prefers to emphasize instead the distinction between those concepts which are associated with measurements, usually denoted by symbols in our equations, and those, such as action at a distance, empty space, etc, which we employ 'pictorially'. He thought that this differentiation is important because we should confine our operational analysis to concepts of the former type, as he has already explained in some detail in his presidential address to the Group in March 1949 (*Brit. J. Phil. Sci.*, 1, 5; 1950). Prof. Dingle considered that one of the most important applications of the operational principle concerns the separation of the actual experimental results from the theoretical concepts used in visualizing them. As an example, he directed attention to a well-known method of determining the wave-length of monochromatic light by means of a diffraction grating. The fundamental equation can be written as $d \sin\theta = m\lambda$, as explained in standard text-books. Operationally, the numbers d, θ and m (spectrum number) can be directly determined; but the fourth number λ, the wave-length, is never measured directly, that is, from crest to crest. Hence, the operational content of this equation is confined to the invariance of the quantity $d \sin\theta/m$ for different values of d, θ and m. If we wish, we can denote this invariant by the symbol λ. So far, no picture of this invariance need be formed. If, however, we appeal now to theory and regard light as consisting of trains of waves, we can give a theoretical interpretation to λ as a length; whereas, if we regard light as consisting of corpuscles, we can interpret λ as a constant of the dimensions of action divided by momentum. We are at liberty to use any picture we find satisfactory, provided that λ has the correct physical dimensions. The function of such pictures is to stimulate and guide research, to facilitate the mental grasp of the situation, and ultimately to disappear in favour of better ones. These functions are not assisted but rather hindered by the demand that the details of the pictures must satisfy the operational criterion.