mice into a very different environment, enclosing them in a small netted area and leaving them to breed. The offspring which appeared during the course of the experiment showed no tendency to approach the local races in their characters.

It may be accepted as a working hypothesis that the variable characters which separate one geographical race from another are produced under the influence of a number of genes, all independent, and all producing similar effects. As Prof. Karl Pearson pointed out in 1904, the effect of such multiple factors will be to produce an apparent blending inheritance; a view now very generally accepted. It follows that, in certain cases at any rate, if a small group of individuals phenotypically similar, though genotypically different, differing from the norm of a population, be isolated and left to breed freely, they will, when considered as a population, tend to vary still more from the original mode in the population from which they sprang and that they will do so in the direction in which the original isolated group differed. Prof. Pearson has reached the same conclusion from his own very different point of view and has evidence that the expected result does actually occur.

If, then, we can conceive of circumstances which will bring about such isolation in such a way that the individuals so separated are determined by an environmental condition, we shall have an explanation of the divergence of local races which will account for the appearance in them of individuals which lie outside the range of variation actually

observed in the small samples of the parent races which have been investigated.

There remains one type of adaptation which is perhaps of greater importance than those which we have been considering. Perhaps the most striking of all the phenomena of life is the power which all animals and plants possess of so regulating their functioning, and when necessary their morphology, that their life is continued in equilibrium with the conditions under which they find themselves.

How far such physiological adaptations are of the same nature as those internal morphological adaptations which alter the relative sizes of parts in ways determined by geometrical considerations of squares and cubes, and produce analogous modifications in other structural features, there is no evidence. What is certain, however, is that these, which are the fundamental things in evolution, lie open to experiment.

Thus the present position of zoology is unsatisfactory. We know as surely as we ever shall that evolution has occurred; but we do not know how this evolution has been brought about. The data which we have accumulated are inadequate, not in quantity but in their character, to allow us to determine which, if any, of the proposed explanations is a *vera causa*. But it appears that the experimental method rightly used will in the end give us, if not the solution of our problem, at least the power of analysing it and isolating the various factors which enter into it.

The Relation of Organic Chemistry to Biology.¹

By Prof. GEORGE BARGER, F.R.S.

SINCE, in the last resort, we are dependent on naturally occurring materials, which scarcely ever occur in a state of purity, it follows that the early chemists were even more concerned with separating one substance from another than many of us are to-day. Progress was at first limited to mineral substances capable of withstanding powerful reagents and a high temperature; much of the old chemistry is concerned with the heavy metals. The substances formed in such large numbers by living beings are much less stable, and their isolation demands a special technique. It is significant that, in spite of their knowledge of the smelting of ores, of the manufacture of glass, and of many other arts, the ancients failed to distil alcohol. Later, the chemical investigation of organic material was apt to consist in destructive distillation, naturally adding little to knowledge. Only the more volatile and stable substances could be isolated in this fashion.

An important systematic advance was made by K. W. Scheele (1742-1786), whose contributions to organic chemistry are almost as important as his discovery of oxygen. Scheele was a pharmacist, and most of the early chemists were trained as such, or as physicians, from the iatro-chemical period onwards. This old connexion between chemistry

and medicine was, however, scarcely a biological one. Joseph Black's work on fixed air and the mild alkalis indeed originated in medicine, from his M.D. dissertation, "*De humore acido a cibis orto et magnesia alba*", but the subsequent developments of Black's work were not biological in character. Again, although Berzelius was trained as a physician, his work had little connexion with biology.

The use of vegetable drugs, however, led pharmacists to examine the constituents of plants, and thus the foundations of descriptive biochemistry were laid. Scheele investigated a number of organic acids in the wet way. He obtained tartaric acid in 1769, and later benzoic acid by boiling gum benzoin with lime. He first prepared lactic acid (1780) from sour milk, and mucic acid by oxidation of milk sugar. When, soon afterwards, mucic acid was also obtained from gum tragacanth, it became evident that one and the same substance may be derived from both animal and vegetable sources. Oxalic acid was obtained from the acid potassium salt in *Oxalis acetosella*, and shown to be identical with an oxidation product of cane sugar. Scheele also obtained citric, malic, and even gallic acid by crystallisation from solution. Of more general biological interest is his discovery of uric acid, of glycerol, and of hydrocyanic acid; the last (acidum berolinense) by heating potassium ferrocyanide with dilute sulphuric acid.

¹ From the presidential address to Section B (Chemistry) of the British Association, delivered at Cape Town on July 23.

Scheele's discovery that esterification is greatly furthered by the presence of mineral acids later became important in connexion with catalysis, but theoretical speculations were foreign to his nature, and he was not greatly concerned with the essential character of acids. Such questions appealed more strongly to Lavoisier, who improved the nomenclature of organic acids and also investigated alcoholic fermentation, a biochemical process which early engaged the attention of chemists.

A knowledge of structure gave a great impetus to organic synthesis, not only in the laboratory for theoretical purposes, but also in the factory for practical uses; the manufacture of dyes, of synthetic drugs, of explosives became an important industry. The number of known carbon compounds grew at an enormous rate. Instead of being the chemistry of organised beings, organic chemistry became the chemistry of carbon compounds. Until the present century the proportion of chemists who, like Scheele, were interested in natural products steadily declined, and biology became of little interest to chemists as a whole, but physiologists have more and more realised the importance of chemistry for their subject and the intermediate subject of biochemistry has rapidly developed.

The systematic study of natural products, inaugurated by Scheele, was at first continued most successfully in France by Fourcroy, Vauquelin, and their pupils. Braconnet examined plants and discovered substances such as salicin and ellagic acid, of no particular importance to physiology, but also obtained glucose from cellulose (linen) and 'sucre de gélatine' or glycine from glue, thus making two fundamental observations in biochemistry. Kirchhoff, a German pharmacist, working at St. Petersburg, had already shown in 1811 that glucose is formed from starch, and investigated the process of malting. In 1833, Payen and Persoz discovered the first enzyme, diastase, and in 1827 a medical practitioner of London, W. Prout, better known to chemists in another connexion, could say in a paper "On the ultimate composition of simple alimentary substances" that they might be arranged in three classes, "the saccharine, the oily, and the albuminous".

By analysis Gay-Lussac was able to establish the fundamental equation for the fermentation of glucose into alcohol and carbon dioxide, and the first systematic advance in biochemistry, also due to analysis, was Chevreul's great work on the fats. In 1824, Wöhler obtained oxalic acid from cyanogen, the first synthesis of a vital product, if we except Scheele's production of cyanides from carbon, potassium carbonate, and ammonium chloride. Four years later, in 1828, Wöhler's synthesis of urea attracted universal attention, and since then much labour has been expended on the synthesis of vital products as an ultimate proof of their structure.

Wöhler had apparently no connexion with medicine or pharmacy, but Liebig was a pharmaceutical apprentice for one year, Frankland a druggist's assistant, Dumas, Schorlemmer, and even Wilhelmy, who investigated the kinetics of sugar hydrolysis, were pharmacists. Gmelin, Mitscherlich,

Wurtz, and Cannizzaro studied medicine; even in the present century medically qualified professors of general chemistry survived (Crum Brown, Emerson Reynolds). The pharmacists soon found a special field of research in alkaloids, essential oils, and other products of the *materia medica*. Within a few years of the recognition of the first organic base, morphine, by the German pharmacist Sertürner, a dozen alkaloids had been discovered, mostly in France, by Pelletier and Caventou, professors at the *École de Pharmacie*. It is presumably due to this institution, and to the high standard of pharmaceutical education in France, that the scientific output of French pharmacists has been so long maintained. For recent times we may refer to Bourquelot, professor at the *École de Pharmacie*, and to Charles and Georges Tanret, father and son, both practical pharmacists, who not only made important contributions to our knowledge of drugs but also to that of sugars. In Germany contributions of pharmacists to organic chemistry were of less importance, compared with the great developments in university research inaugurated by Liebig and fostered by the German States.

In Britain the State did very little for the universities and nothing for pharmaceutical teaching; although British pharmacists have the exclusive legal right to call themselves 'chemists', the State has not helped them to justify the title. At first the British themselves contributed little to organic chemistry; of the pioneers Faraday, Frankland, Perkin, and Williamson, only two were teachers. The sojourn of Hofmann in London, from 1845 to 1865, from the age of twenty-seven to that of forty-seven, was of the greatest influence on the development of organic chemistry in England, but it did not lead to biological applications. Particularly through the inauguration of the dye industry, by Hofmann's pupil, Perkin, and Mansfield, attention was directed to practical problems.

As a result of Emil Fischer's work, the new science of biochemistry was firmly established in the beginning of the present century. It should not be supposed that organic chemical theory is wholly unconnected with biology. Two examples out of many will show the contrary. When a protein is 'racemised' so far as possible, by Kossel's method, by leaving it for some weeks at 37° in half-normal alkali, it is found that certain amino-acids retain their optical activity, and these Dakin has assumed to be the ones with free carboxyl groups, situated at the ends of chains. The others undergo racemisation probably because in their case tautomerism is possible:

On subsequent acid hydrolysis the amino-acid $\text{NH}_2 \cdot \text{CR}^{\text{H}} \cdot \text{COOH}$ would be racemic, but $\text{NH}_2 \cdot \text{CR}^{\text{H}} \cdot \text{COOH}$ optically active. Dakin's views were first applied by Dudley and Woodman to show a structural difference between the caseinogens from cow's milk and sheep's milk, which had been considered by some to be identical.

Elementary analysis shows no difference, and individual amino-acids are obtained in the same amounts after hydrolysis. After racemisation, however, Dudley and Woodman found the tyrosine from cow's caseinogen to be wholly inactive, that from the sheep fully active. In the former animal the tyrosine is probably inside the molecule, in the latter it is on the periphery. We are thus able to discover differences in the intimate pattern of the molecule. Dakin and Dale connected these differences with antigenic specificity.

Crystallised albumins from the whites of hens' and ducks' eggs are very similar and seem to be composed of the same units in equal amounts, but Dakin found that three amino-acids, leucine, aspartic acid, and histidine, behave differently to alkali in the two molecules, and appear to occupy different places. Hen's albumin has some aspartic acid but no leucine or histidine on the periphery; duck's albumin, on the other hand, has no aspartic acid, but some leucine and histidine on the outside of the molecule. By the very sensitive anaphylactic reaction of the isolated guinea-pig's uterus, Dale showed that the two proteins are specifically different as antigens. Differences in arrangement, even of the same amino-acids, help to differentiate the proteins of various species. It is on the diversity of the proteins that the difference of species is based.

Another recent example of the application of organic chemical theory to biology is due to Stedman. Having traced the mitotic action of physostigmine to a urethane grouping, he synthesised a number of urethanes of simple dimethylamino-phenols, for example, $R.NH.CO.O.C_2H_4.N(CH_3)_2$. The physiological activities of the tertiary bases is generally in the order ortho and para > meta, but on conversion into quarternary salts the ortho and para become less active, the meta more so, and the order is meta > ortho or para. This recalls the reactivities of disubstituted benzene derivatives, which have of late been studied in connexion with the polarity theory.

Whilst organic chemists are often eager to investigate the constitution of animal and vegetable substances, they are less ready to undertake the preliminaries of purification and isolation, and are therefore less apt to discover new ones. By esterification and by the use of a high vacuum, Emil Fischer made the monoamino-acids amenable to fractional distillation, a standard operation of organic chemistry. He discovered several new members of the group. But most substances of physiological interest require a special technique, on the development of which the biochemist may spend much labour. Thus Kossel showed how to separate the purine and pyrimidine bases of the cell nucleus, and the important diamino-acids histidine, arginine, and lysine. Hopkins, by his special reagent, was able to isolate tryptophane, the parent substance of indigo, long after indigo itself was being manufactured synthetically. Dakin found that monoamino-acids can be extracted from aqueous solution by butyl alcohol, and using this new technique and Foreman's method of separating aspartic and glutamic acids by their calcium salts,

Dakin discovered hydroxyglutamic acid, an entirely unsuspected unit of protein.

A knowledge of the structure of amino-acids may throw light on how other nitrogenous constituents arise, particularly in plants. As an example the most recently discovered amino-acid may be quoted. The American bacteriologist Mueller found in casein and other proteins a new constituent containing sulphur, quite different from the well-known cystine. Dr. Coyne and I have recently established its constitution by synthesis. It turns out to be γ -methylthiol- α -amino- n -butyric acid, $CH_3.S.CH_2.CH(NH_2)COOH$, and we named it methionine. The methylthiol grouping at once indicates that it is the source of methylmercaptan, the occurrence of which in putrefaction was known, although not hitherto intelligible. Methionine is evidently also the parent substance of cheirolin occurring in the seeds of the wallflower and of other Cruciferae. Schneider had long ago established for this substance the remarkable constitution $CH_3.SO_2.CH_2.CH_2.CH_2.N.CS$. We now see at once that cheirolin is the thiocarbimide of oxidised and decarboxylated methionine. Similarly Perkin and Robinson connected the chemistry of harmine and harmaline with tryptophane when they showed that the mysterious base $C_{12}H_{10}N_2$, which Hopkins and Cole obtained by oxidising tryptophane, $C_{11}H_{12}O_2N_2$, with ferric chloride, is identical with harman. This observation not only settled the constitution of the alkaloids in question, but also explained the fitful yield of the oxidation product of tryptophane, which, after decarboxylation, had condensed with acetaldehyde.

Soon afterwards, Späth showed that harman itself occurs in Nature, as the alkaloid aribine, which had been given the erroneous formula $C_{23}H_{20}N_4$. It is becoming increasingly evident that many alkaloids arise by condensation of amino-acid residues. Mezcaline and other alkaloids of Cactaceae are closely connected with phenylalanine and tyrosine, as Späth has shown, and the mode of origin of isoquinoline alkaloids from aromatic amino-acids has also become clear. Harmine, harmaline, physostigmine, and rutæcarpine are all derived from tryptophane, and it looks as if the same is true of other alkaloids the constitution of which, like that of strychnine and of brucine, remains obscure.

The isolation of some natural substances, of great physiological interest, is beset with difficulties because they are present in minute amount and have not the convenient solubility relations which facilitate the separation of the alkaloids. This applies to the hormones present in animal tissues. Here the American slaughter-houses provide valuable facilities, and it is significant that adrenaline, thyroxine, and insulin were first crystallised in America, although the constitution of the two former hormones was later established in Europe, where also their synthesis was effected, that of thyroxine only a few years ago, through the brilliant work of Harington.

The difficulty of isolating vitamins is still more formidable; in the case of the antineuritic vitamin B, which is almost certainly a fairly simple sub-

stance, susceptible to attack by the methods of organic chemistry, much progress towards isolation has been achieved by selective adsorption and elution, the methods employed by Willstätter for enzymes. The discovery by Rosenheim and Windaus that vitamin D is formed by the irradiation of ergosterol has suddenly brought into prominence a substance which before was but a curiosity, chiefly known through the work of the French pharmacist, Tanret. At the same time the interest of biochemists in photochemistry has been stimulated, as well as in the extensive work of Windaus on the structure of cholesterol, which the latter had already shown to be connected with the bile acids, largely investigated by Wieland.

The sudden emergence of ergosterol into prominence does not stand alone; another of Tanret's ergot substances, ergothioneine, at first also an isolated curiosity, has acquired more general significance because it has been found in mammalian red corpuscles; it is likely that this will lead ultimately to the discovery in proteins of yet another sulphur-containing amino-acid, possibly a thiolhistidine. Altogether, ergot has yielded more substances of general biological interest than any other single plant.

The above examples of the relation between biological and organic chemical work relate to that division of biochemistry which may be termed descriptive. A knowledge of structure is also necessary in dynamic biochemistry, the study of the transformations which substances undergo in the living organism. The recognition of the fats as esters, and their behaviour to fat-splitting enzymes, the transformation of starch into sugar under the influence of diastase, the end-products of alcoholic fermentation; all these were early discoveries in dynamic biochemistry.

Just as the organic chemist may wish to know the mechanism of a reaction, for example of the Skraup synthesis of quinoline, so the biochemist wishes to know the intermediate steps in the transformation of, say, glucose into alcohol. The detection of these stages of metabolism is a matter of considerable difficulty, since under normal conditions the intermediate substances generally disappear as rapidly as they are formed. They have to be trapped by suitable means, as did Neuberg with acetaldehyde in alcoholic fermentation, or the metabolic process may sometimes be cut short, by using an isolated organ, such as the surviving liver, or the precursor of the intermediate substance may be administered in large excess.

Very little has been learned in this respect from the higher plants. The very process of photosynthesis is still beset with obscurity in spite of a plausible hypothesis; we know next to nothing about transformation of carbohydrate into fats, and vice versa, and in particular we are ignorant of the stages by which amino-acids are formed in plants from nitrates and carbohydrates; we simply do not know how the proteins of living beings originate. Nor have the higher plants given us much information of the way in which their fats, carbohydrates, and proteins are ultimately broken down.

Our knowledge of catabolism is principally derived from the animal world. It is found that the breakdown does not always occur in the manner in which the organic chemist would expect. Thus an organic chemist presented with the problem of transforming stearic acid into palmitic might brominate in the α position, and break down the corresponding α -hydroxy acid; or he might do a Hofmann degradation on the amide. In either case he would get an acid with 17 carbon atoms, and have to repeat the degradation in order to obtain palmitic acid. Knoop has shown, however, that in the animal organism the β -carbon atom is attacked so that the chain is shortened by two carbon atoms at a time, an acid with 18 carbon atoms being converted successively into one with 16, 14, 12, etc. In accordance with this scheme the principal fatty acids in Nature are those with an even number of carbon atoms. Knoop established this by feeding ω -phenyl fatty acids; those with an even number of methylene groups in the side chain were converted into benzoic acid and appeared in the urine as hippuric, those with an odd number of methylene groups yielded phenylacetic acid and were excreted as phenaceturic acid. Instead of using a resistant phenyl group and the whole animal, fatty acids themselves and the isolated liver may be used to establish the same result.

The degradation of amino-acids in the body also proceeds contrary to the expectations of the organic chemist. If he were asked to bring about the degradation by gentle stages he would doubtless first convert the α -amino into the α -hydroxy acid. The organism forms the α -keto acid, however, as shown by Neubauer and by Knoop. This biochemical result suggested to Knoop an interesting and unlooked-for synthesis of amino-acids *in vitro*, by reversing the normal breakdown. He shook solutions of α -keto acids, containing also ammonia and platinum black, in a hydrogen atmosphere, when the corresponding amino-acid resulted by the reduction of the hypothetical imino-compound. The transformation of tryptophane into kynurenic acid may be quoted as a particular problem of metabolism to which a good deal of organic chemistry has been applied.

The first stage in the degradation of fatty acids and of amino-acids seems pretty well established, and analogies *in vitro* have been found. Other problems are more obscure. Why is the benzene nucleus in phenylalanine oxidised, but not that in benzoic acid? What is the mechanism in the former case? Why is *p*-hydroxyphenylpyruvic acid easily oxidised and the corresponding lactic acid not? Why is *d*-phenylglycine easily oxidised and *l*-phenylglycine excreted almost unchanged? Altogether, the processes by which organic substances are burnt to carbon dioxide and water, by atmospheric molecular oxygen, at a low temperature, are still very puzzling, although Dakin, Hopkins, Knoop, Warburg, Wieland, and others have done much towards their elucidation. In the study of the chemical processes, as in that of the chemical constituents of living organisms, there is much scope for the application of organic chemistry,

and in addition, physical chemistry requires to be utilised.

Probably the most extensive attempt to use chemical constituents for botanical classification has been made by R. T. Baker and H. G. Smith, in the case of the Australian genus *Eucalyptus* with about two hundred species: the essential oils from well over half of these have been examined. Baker and Smith trace a relation between the venation of the mature leaves and the composition of their essential oil. The genus is thus divided into fairly well-marked groups, and it is possible to suggest the probable constituents of the oil of a given species by examining the venation of the leaves, and, conversely, by chemical investigation of the oil to gain a clue to the species. Maiden, the botanical expert on *Eucalyptus*, did not always agree with the classification of the chemists, but upon occasion he discovered morphological differences after a delimitation of species had been proposed on chemical grounds.

The main biological interest of alkaloids is not botanical in their distribution, but pharmacological in their action. This leads to a mention of the great developments in synthetic drugs, due to organic chemistry. In particular there is great scope for the organic chemist in chemotherapy, the combating of general infections of the host by synthetic drugs. The production of salvarsan, which has made such a great change to the treatment of syphilis and other protozoal diseases, and

the subsequent introduction of germanin (or Bayer 205) in the treatment of sleeping sickness, indicate great possibilities of applying organic chemistry to this particular department of medicine, and constitute a link between workers in very different fields.

I have directed attention to the many points of contact between organic chemistry and biology in the past and present, and if finally I am permitted to draw a conclusion it would be an educational one. I hold it to be desirable that biologists should have at least an elementary knowledge of organic chemistry, in spite of the difficulties imposed by ever-increasing specialisation in science. These difficulties are particularly felt in apportioning the time available for medical education among the many subjects of a crowded curriculum, and may to some extent be met by a careful consideration of what is really useful.

The chemical training of the physician (and of the biologist) should not be identical with the preliminary training of the professional chemist, although it still is so in many universities. In order to save time, much elementary chemistry, particularly inorganic, must be abandoned, thus making room for those aspects of the subject which have biological applications. This differentiation between the chemical needs of various groups of students requires special courses, and teachers who have a sympathetic understanding of the peculiar needs of their students, medical and biological.

Obituary.

PROF. CHARLES MOUREU.

NOT only the French but also chemists generally suffer a specially severe loss by the death of Charles Moureu, professor of organic chemistry in the Collège de France, the second to succeed Berthelot. In France, the leader in his subject, he was not merely a chemist of great achievement and high repute but also a man of outstanding personal character and social distinction. During the War he rendered inestimable service to his country by organising and directing the work—defensive and offensive—of the French chemists; in this connexion he was brought into close contact with our English workers. Since then he has been a familiar figure in England.

At the close of the War, Moureu entered upon a vigorous campaign in which he made clear to politicians and the public the importance of chemistry in the modern State and the great need of improving the status and financial position of the French scientific schools. His efforts to this end were in large measure successful. His success was in no slight degree due to the eloquence with which he stated his case in his book "*La Chimie et la Guerre*". Known throughout the world of chemistry, a shrewd man of affairs, a polished diplomat, in fact, Moureu was particularly endeared to the chemists of other nationalities, who met him during recent years at various international conferences, by his engaging manner and the obvious sincerity and breadth of his outlook. The

thesis developed in his book is that stated by his countryman Duclaux, which he quotes: "*La chimie est au fond de tout et rien ne lui échappe*". He expressed what to him was a profound truth when he said: "*Le Français le plus illettré a le sentiment, net ou confus, que sa patrie est grande et belle entre toutes. Fier, sans arrogance, d'être Français, il est profondément patriote.*" Patriotic to the core, at the same time he was so scientifically minded, so sane in his judgments, that he was not only willing but also able to deal with international problems broadly and dispassionately. He was the first president of the International Union of Pure and Applied Chemistry and contributed greatly to the foundation of the Union. At the conference at the Hague last summer, he rendered most important service in the very difficult discussion on the constitution of the Union which occupied the meeting.

Moureu was a son of the mountains, a native of the Basque region. He was born on April 19, 1863, at Moureux, a village in the Bearnese country, in which his family had lived during centuries; he died at Biarritz on June 13. An eloquent funeral discourse was delivered there, by his colleague and friend, Prof. Camille Matignon, on June 17; he was buried the following day at Oberon, in the Basses Pyrénées. The youngest of a large family, his father having died while he was an infant, he was cared for by an elder brother, Félix Moureu, who lavished upon him the affection of a father,