Address of the President
Sir Robert Robinson, at the
Anniversary Meeting, 30 November 1946

The grievous losses sustained by the Society during the past year have just been announced. Our *Obituary Notices* are the appropriate medium for the appreciation of the services to science and the Society of the deceased Fellows but, before following the example set by Sir Henry Dale last year and proceeding to the presentation of Medals, I will make a few very brief comments. First that Sir James Hopwood Jeans, O.M. was awarded a Royal Medal in 1919 for his distinguished contributions to astronomy and he was the ‘A’ Secretary for the next ten years. We pay a tribute to the memory of an active and conscientious former officer of the Society whose eminence in the scientific field has received world-wide recognition.

Professor Percy Faraday Frankland, C.B.E., was elected a Fellow sixty-five years ago. He was awarded the Davy Medal in 1919 and served as Vice-President in 1917–18.

During the past year Council nominated the late John Maynard Keynes, first Baron of Tilton, for election as a Fellow of the Society under Statute 12. His untimely death robbed the Society of the opportunity to add the lustre of his name to the records.

Mr H. G. Wells was a friend of science whose imaginative writings and popular expositions have had an influence which it would be hard to overestimate. Though he was not a Fellow of the Society I think it right that we should ‘praise him as a famous man’ and add our voices to the general acclaim of his achievement.

*Awards of Medals, 1946*

The *Copley Medal* is awarded to Professor Edgar Douglas Adrian, O.M., for his outstanding contributions to nerve physiology.

During the last thirty years Professor Adrian has been engaged on a series of systematic investigations of the essential functions of the nervous system which have been extended from a study of the activity of single nerve fibres to the reaction of the cortex of the forebrain of man to impulses that reach it from the periphery. The advance of our knowledge of the working of the nervous system is largely the result of his researches into the nature of the fundamental process of individual cells and combinations of cells.

His early work with Keith Lucas provided important observations on conduction by nerve fibres and on the reactions of muscles. This was followed by a series of independent researches by the combination of a valve amplifier with a capillary electrometer which made possible an analysis of the behaviour of individual sensory receptors and of single motor units. Among many important discoveries...
these investigations revealed how the frequency of impulses conveyed by each fibre is used in the central nervous system to signal the intensity of peripheral and central events.

By the same methods he undertook a detailed analysis of the activity of many types of sense organs and of simpler reflex actions in terms of the activity of single nerve fibres, and in some cases demonstrated that the same principles underlie all nervous activity throughout the animal kingdom. Other investigations dealt with the nature of the fundamental process in nerve cells and in synaptic regions of the central nervous system.

During the past ten years he has been mainly concerned with the interpretation of the potential waves in the cortex of the forebrain. Hans Berger had drawn attention to the existence of these in man, but the subject was neglected until Adrian and Matthews reinvestigated it. Adrian's subsequent studies included, in the first place, an examination of the electrical activity of the brain and its reaction to messages from the periphery, and in the second place a mapping out of the regions of the cortex which serve as receiving centres for such messages. His aim has been to analyse these phenomena in terms of activity of simple nervous units, and the results of his work are the basis of the subsequent development of electroencephalography, which has attained an important place in both physiological and clinical investigations.

By his researches on the exposed brains of animals he determined the laws of spread of activity in the cortex, its reactions to natural and artificial stimuli that reach it, and showed that the interaction between a local excitation and the background of spontaneous activity is the essential feature of a cortical response.

By a study of the comparative physiology of the sensory areas of the brain he has also shown how their development and to some extent their reactions to peripheral stimuli depend on the structure and mode of life of the animal.

After determining the representation in the brain of receiving stations for superficial and proprioceptive stimuli he investigated that of vision and hearing. He has even succeeded in demonstrating the different features of impulses that reach the visual cortex from the rods and cones of the retina; he has also dealt with the distribution and significance of certain non-sensory afferent impulses, as those that reach the cerebellum.

Adrian has blazed many trails in his exploration of the territory of nerve physiology. It is certain that for many years to come his lead will be followed and the new knowledge will be consolidated along the lines of his pioneering work.

The Rumford Medal is awarded to Sir Alfred Charles Glyn Egerton for his distinguished researches on combustion.

The Rumford Medal founded in 1800 is awarded once every second year 'to the author of the most important discovery or useful improvement which shall be made and published by printing or in any way made known to the public in any part of Europe during the preceding two years on Heat or on Light, the preference
always being given to such discoveries as, in the opinion of the President and Council of the Royal Society, tend most to promote the good of mankind'.

Sir Alfred Egerton admirably fulfils the requirements of these terms of award. He is a physical chemist whose researches have always been directed towards the application of physico-chemical principles to the process of combustion of hydrocarbons in all its ramifications. For some time the approach to combustion problems has been empirical because there was no satisfactory physico-chemical basis of the theoretical or practical aspects to make further significant progress possible. This background has now been partly provided by Egerton who was one of the first to see clearly how necessary it was to apply the new conceptions of combustion to the complex processes occurring under the conditions obtaining in internal combustion engines. One of the great obstacles to achieving greater efficiency is the difficulty of preventing premature detonation. This phenomenon is essentially a chemical one in the sense that organic peroxides, produced during combustion, are known to be responsible for the pre-ignition. Thus the chemical behaviour of peroxides might provide a key to the solution of the problem and much of Egerton's work has been devoted to this enquiry. The investigation involved the elaboration of special physical techniques since ordinary chemical methods were inapplicable to this type of research.

During the war Egerton has directed his attention to the vital problem of ensuring that combustion appliances should be devised and operated with the maximum possible efficiency. This can only be achieved by a thorough scientific analysis, hitherto lacking, mainly because the problem had hardly been considered worthy of serious study. The result of his labours cannot fail to be of great benefit to the country during the period of very low fuel production and will lead to considerable economies under all circumstances.

The characteristic of Egerton's work has been the application of modern physico-chemical methods to current scientific and technical problems of great moment, combined with experimental researches developed with great ingenuity.

A Royal Medal is awarded to Sir William Lawrence Bragg for his investigations of the structure of solids.

The diffraction of X-rays by crystals was observed in 1912 by Laue, Friedrich and Knipping, but the pioneers of the present-day development are the late Sir William Bragg and his son Sir Lawrence. It was W. L. Bragg who formulated the law \( n = 2d \sin \theta \) that is now so familiar in all studies concerned with the structure of molecules and their states of aggregation. Soon after Laue's discovery there followed, from father and son, a series of papers on the phenomena of X-ray 'reflection' on the one hand and the determination of fundamental crystal structures on the other, the far-reaching consequences of which could hardly have been foreseen, even by their authors. At the present time crystal analysis by X-rays is an established technique, a sharp tool of research that lays bare the complexities of organic and mineral matter alike.
The inspiration and genius of Bragg are seen in so many of the modern developments of X-ray diffraction to structural analysis that it is possible to select only a few outstanding illustrations. His principal interest has always lain in the interpretation of diffraction phenomena with the view of making the actual methods of analysis more precise, more simple, and more extended. In developing such methods he and his collaborators have elucidated the atomic arrangement in a great number of fundamental types of inorganic crystal structures. Chief among these are those of the diamond and the elementary salts and oxides, in the study of which the subject found its first beginnings. After these perhaps his greatest analytical success is shown in the field of the silicates. A chemical riddle has been transformed into a system of simple and elegant architecture. He has also contributed greatly to our knowledge of the structure of metals and alloys and their phase changes, and of the relations between their physical properties and atomic arrangement in the crystalline state. Latterly he has brought to a still clearer focus the concept of X-ray diffraction as a branch of optics and has thus initiated methods that have already gone far towards replacing the earlier laborious calculations by rapid devices based on the analogy of the diffraction of visible light.

The implications and applications of the principles and methods of X-ray spectroscopy and X-ray structure analysis are one of the wonders of modern science, and with this manifold triumph the name of Sir Lawrence Bragg is inseparably associated.

A ROYAL MEDAL is awarded to Dr Cyril Dean Darlington in recognition of his distinguished contributions to cytology.

The importance of Darlington’s work lies not so much in the discovery of isolated new phenomena—although he has discovered many of these—but rather in the achievement of a synthesis which brings together a highly diversified body of apparently disconnected facts into an integrated system.

Darlington’s first major achievement was the clarification of the relations between the two main forms of nuclear division—mitosis and meiosis. Out of the confused mass of available observations, he singled out as fundamentally significant two facts, first, that chromonemata attract one another specifically, by an attraction which is satisfied when two similar threads are associated; and second, that in the earliest stage of mitosis each chromosome is already split into two halves, while at the beginning of meiosis they are still single. On the basis of these two facts, he showed that the relation between the two forms of division could be understood as the result of a temporal shift in the operation of a single physiological process. His so-called ‘precocity’ theory of meiosis was then supported by a whole series of new observations, in which the resources of comparative study and of new techniques were used for the specific purpose of obtaining answers to critically formulated questions.

Starting from the basis of the relation between the two major forms of nuclear division, Darlington has pursued his enquiry in two directions. On the one hand,
he has accumulated a very large body of facts concerning the detailed mechanics of cell division in many different groups of plants and animals. The comparative method enabled him to reach important new conclusions as to the mechanism of crossing-over, the cycles of spiralization and contraction of chromosomes, the nature of the mitotic spindle and the forces exerted by it and within it, the role of the centromeres and so on. These results have laid a broad foundation of observation and deduction which appears, for the first time, firm enough to bear a superstructure of physico-chemical interpretation. Proceeding in quite another direction, Darlington discussed the implication of his cytological ideas on evolutionary theory. The existence of the mitotic and meiotic modes of division had been explained as the result of different modalities in the application of a single set of physiological principles; Darlington showed that further, slighter modifications could produce many of the widely diverse series of reproductive mechanisms met with in the animal and plant kingdoms. He emphasized the fact that the mechanism of evolution is itself subject to evolutionary changes.

More recently Darlington’s work has led him to the investigation of the general problems of gene action, of the physiological action of the two major types of nucleic acid, and the relation between the gene and other similar bodies in the cytoplasm. Darlington was one of the first to enter this highly speculative field and he has contributed not only his full quota of stimulating speculation, but also a large share of the still scanty facts. It is not too much to say that Darlington’s results and theories are recognized as the basis of modern nuclear cytology.

The Davy Medal is awarded to Professor Christopher Kelk Ingold for his outstanding researches in physico-organic chemistry.

Progress in one of the most active fields of chemical science during the present century has resulted from attempts to elucidate the detailed mechanism of organic reactions in terms of modern physical concepts. Throughout this development Ingold’s contributions are especially distinguished. Possessing detailed knowledge and understanding of both the physical and organic branches of the science he has been in a position to effect the synthesis of the two modes of approach without which a successful attack on the difficult, yet fundamental, problems involved could not be achieved. It is not possible in short compass even to outline the range of investigations with which Ingold has been concerned, but brief mention may be made of the work on stereochemistry dealing with ring strain and the effect of gem dimethyl groups on the valency angles of carbon. A further application of underlying physical principles is evident in his investigations of tautomerism in triad systems, and in the development of our ideas on ring-chain tautomerism. This work led on to more general studies of the mechanism of reactions, including the difficult question of substitution in the benzene ring, in addition to the ordinary reactions of organic chemistry, such as hydrolysis and substitution, which despite their apparent simplicity have proved to be complicated and difficult to interpret. The success which Ingold has achieved in interpreting these phenomena in terms
of the electron theory of valency is striking but in addition he has played the most prominent part in the experimental investigations which have led to our present knowledge of the kinetics and mechanism of organic chemical reactions. Ingold always has been interested in the elucidation of the course of chemical change by application of physico-chemical methods based on reaction velocities and in this field may be cited the extensive work on the mechanism of substitution at an aliphatic carbon atom, leading to the recognition of the uni- and bi-molecular processes, by means of which so much has been done to solve the difficult problems raised by the Walden inversion and the phenomena of racemization. In these intractable regions the contribution of Ingold and his flourishing school are of fundamental importance. Another aspect of his work involves a still deeper concern with physical principles as applied to organic chemical problems. His interest in the chemistry of benzene has led him to investigate in the fullest detail, using infra-red and Raman spectra, and indeed all available physical methods of approach, the fine structure of the benzene molecule. In order to provide the necessary data it was necessary to devise methods for the preparation of the various deuterium substituted benzenes—no mean feat of organic chemistry in itself—and the interpretation of the experimental results in terms of quantum mechanical principles has recently been published in an issue of the Journal of the Chemical Society, which he monopolized. Although his theoretical contributions have attracted more attention, the originality of his experimental technique is equally noteworthy and his happy selection of crucial tests amounts to genius.

The Darwin Medal is awarded to Sir D'Arcy Wentworth Thompson, in recognition of his distinction as a zoologist.

Sir D'Arcy Thompson is now in his 62nd year as a Professor of Biology and Natural History. He published his first scientific paper in 1879. His most distinguished work, *On growth and form*, appeared in 1917 and was republished in a new and enlarged edition in 1942. He is still writing, but mainly in the field of the classics where he is a considerable scholar, and a great authority on all animals that have appeared in classical texts.

D'Arcy Thompson's scientific work ranges over a wide field of general zoology and marine biology. He is an expert on the subject of fisheries, and for a considerable period did tireless work both for the Conseil International pour l' Exploration de la Mer and the Fishery Board for Scotland, carrying out hydrographical observations and being responsible for a great deal of fishery statistics. In the main, however, D'Arcy Thompson's scientific reputation rests on his work on growth, and the dimensional relationships of animal forms. The better part of the foundation of modern research into these subjects is his demonstration of methods by which the shape of the living organism can be brought into the field of controlled mathematical enquiry.

D'Arcy Thompson's work springs essentially from an enquiry into the relationships of animal forms, and from an attempt to introduce a degree of mathematical
precision into the otherwise purely descriptive language of systematic evolution. He was able to show, for example, that the evolution of one form from another could often be illuminated by the use of Cartesian transformations. By making clear the formal unity and coherence in the relationship of animals which apparently differ in a multitude of ways, his studies made possible the quantitative demonstration of steps in the evolution of different forms, and more so, the orderly process of change in the development of the same form. In his own words, growth can be studied as a systematic deformation of form at an earlier stage. He showed, for example, that relative growth rates in different parts of the body are distributed according to an ordered system of growth-gradients. This concept can be applied to certain types of evolutionary transformation, since it helps to explain how a single genetic change can automatically affect both the size and the growth interrelations of several organs. The development and illustration of the theory of allometry is another extension of D'Arcy Thompson's ideas.

The wide variety of problems to the solution of which D'Arcy Thompson has opened the door is well indicated in the 'Festschrift' presented to him last year. In introducing his classic *On growth and form*, D'Arcy Thompson declared that it required no preface, since it was all preface. His elaboration of the subject covers so wide a field, however, that, until such time as some different and all-embracing set of general propositions is put forward to take the place of those he propounded, individual contributions to study of growth and bodily transformation must necessarily represent isolated developments of the structure which he has presented to us. D'Arcy Thompson's work will always be regarded as a necessary step in the development of biological knowledge.

The *Sylvester Medal* is awarded to Professor George Neville Watson in recognition of his distinguished contributions to mathematical analysis.

Watson is a mathematician of outstanding perseverance and analytical skill. For forty years he has devoted his energies to pure mathematics, and has made many important and exhaustive contributions, particularly in the field of analysis. The most important researches of Watson's earlier period are those on asymptotic expansions: his great memoir 'A theory of asymptotic series' appeared in the *Philosophical Transactions* of 1911 and was followed by a stream of other writings dealing with the characteristics and transformations of these series, and with their applications to several well-known functions of importance in mathematical physics. This group of discoveries has enriched the region of mathematics in which Stirling was the pioneer two centuries ago, and where the methods of approximation are reduced to a precise science. These include the method of 'steepest descent' and any account of asymptotic series to-day must be based to a great extent upon Watson's discoveries.

About that time many of the ablest pure mathematicians were trying to sum a difficult oscillating series involving Bessel and Legendre functions, which had presented itself in the theory of the diffraction of wireless waves round the earth.
Watson solved the problem by a new method (1918), and went on to study the more difficult case of the transmission of electric waves when it was assumed that the earth is surrounded by a concentric conducting layer, as suggested by Heaviside. Watson's powerful analysis made possible a great advance in the physical theory.

Another example of his capacity for providing a brilliant solution of a problem which had been attempted by many of his predecessors is furnished by his paper on the Rogers-Ramanujan identities. Following this came his work on general transforms in which he solved a problem which many celebrated mathematicians had attempted without success. This is probably Watson's greatest achievement, and ranks as one of the most important contributions to the subject made in recent years. In addition it has had the great merit of inspiring a large amount of work by other mathematicians. Among the more notable papers of the next years, were those on 'Generating functions of class-numbers', on Ramanujan's continued fraction, and one that gave the proof of Ramanujan's assertion about the number 691 which occurs in 'almost all' the terms of a certain infinite product when expressed as a series. The series of papers on singular moduli, during the period 1932–36, are deservedly celebrated.

His great book on Bessel functions is perhaps the most impressive single work that has ever been written on the analysis of functions. In collaborating with Professor E. T. Whittaker in the second and later editions of *Modern analysis*, he has shown the same breadth and power and has influenced the course of higher analytical mathematical teaching throughout the world.

The Hughes Medal is awarded to Professor John Turton Randall in recognition of his distinguished contributions to applied physics, and especially of his development of the magnetron.

In 1940 Randall, while working in the laboratory of Professor Oliphant, at Birmingham, agreed to join H. A. H. Boot in an endeavour to utilize the magnetron principle for the production of electromagnetic waves of frequency greater than 3000 Mcyc. Previous work in the laboratory had shown that satisfactory circuits for these wave-lengths must be an integral part of the internal structure of the valve itself. Randall and Boot together put forward the suggestions that such a circuit, for a multi-segment magnetron, should consist of a revolver-like arrangement of holes, spaced evenly about a circle, each hole communicating by means of a slot with a central cavity in which the cathode was mounted. The first trials with demountable valves using tungsten cathodes were immediately successful, and it was shown that the suggested form of valve can generate continuously oscillations of the required wave-length.

With the assistance of S. M. Duke, Randall and Boot were able to develop methods of construction of the magnetron which enabled oxide-coated cathodes to be used, and which therefore gave high powers when the valve was subjected to pulsed operation. Empirical investigation fixed the best coupling arrangement by which
the power could be fed into an external circuit. Careful investigation of the operation of a valve showed that it was subject to sudden changes of wave-length, a condition which limited its applicability to Service equipment. This difficulty was overcome by the 'strapping' methods developed by Dr J. Sayers.

There is little doubt that the magnetron valve was the prime factor in the improvements made in Radar during the war, and Randall deserves a very large share of the credit for this development.

He contributed also to the problem of crystal detection of centimetre waves.

Randall's studies of fluorescence and phosphorescence were of a high standard and his careful and painstaking experimental work did much to establish on a firm basis the theories of semi-conductors developed by Wilson and others, and especially the assumptions about the existence of 'electron traps'. His work on practicable phosphors has been of importance in the development of fluorescent lamps, and of the screens of cathode-ray tubes.

Randall has also made contributions to the X-ray investigation of the structures of glasses and of liquids, and he developed satisfactory forms of oxide cathodes for the fluorescent lamps.

I am greatly obliged to colleagues in the Council for their assistance in the preparation of notes on the Medallists.

It would certainly be convenient for me, but neither fitting nor necessary, to traverse from this Chair the ground covered by the Report of Council for the past year. His Majesty the King, accompanied by Her Majesty the Queen, opened the British Empire Scientific Conference on 17 June and each of the Delegates from the Dominions, the Colonies, and the United Kingdom was presented to their Majesties.

The Conference, and the Official Conference that followed, provided the opportunity for a veritable ferment of discussion and many wise and timely suggestions were made.

His Majesty the King drew attention to the desirability of holding similar conferences in the future in other cities of the Empire. Fellows will be glad to know that the Society is represented on the continuing body which will watch the progress of implementation of the resolutions that emerged from the Conferences.

The culmination of our activities was the tribute, I think we may claim, the worthy tribute, paid to the greatest of natural philosophers in our celebrations of the Isaac Newton Tercentenary.

The resounding success of these memorable occasions was made possible by the hard work and devotion of a few, by the willing co-operation of many, and by generous financial assistance. To all, the Officers, Council and Fellows of the Society are most deeply indebted. Many of our distinguished foreign guests have written letters expressing their pleasure in the visit and their satisfaction in meeting us in a truly international gathering. It was most unfortunate that exigencies of space, and other matters of which you will be cognisant, imposed a limitation on
the desired full participation of all Fellows in these Conferences. The necessity for appointed delegations from the United Kingdom was realized from the outset to be a necessary corollary, under present conditions, of the invitation to a large number of guests from abroad.

Professor Hill has served the Society as Biological Secretary for ten years and now as Foreign Secretary during the past year, always with the greatest zeal and efficiency. We shall sorely miss his wisdom in counsel, his occasionally puckish delight in giving the new idea a chance, and our ability to draw so often in the future as in the past on his unequalled store of knowledge of scientific matters and scientific men. We wish him all happiness and success in the experimental enquiries to which he now proposes to devote himself. You have just appointed his successor in the Foreign Secretariaship. The Society is indeed fortunate, that Professor Adrian, after a little natural hesitation, accepted the nomination of Council.

His world-wide fame as an investigator and discoverer and his extensive knowledge of scientific affairs overseas render the appointment peculiarly appropriate and one that will maintain the reputation, and sustain the prestige, of the Society in foreign lands. But the Foreign Secretary, as an Officer and member of Council, shares our general work and responsibilities. We look forward with keen anticipatory pleasure to his co-operation, and assure him of ours.

The Council has received with great regret the resignation of Mr Griffith Davies as Assistant Secretary. He was appointed in September 1937 and though I have only had one year's experience of his willing and able help, it has been amply sufficient to enable me to realize the extent of the loss that the Society has sustained. Mr Davies has become an authority on the records and history of the Society and is prepared, indeed is anxious, to continue his studies in those directions. Council has appointed him a member of the Library Committee and, subject to the concurrence of that Committee, he will be Chairman of a sub-committee charged with the duty of preparing for the celebration of the Tercentenary of the Society.

The inspired address that Sir Henry Dale delivered a year ago is fresh in our memory and his thesis that scientific knowledge should be a free gift to mankind found a ready response in all our hearts.

The warning of the possible danger to scientific ideals and integrity inherent in the conception of 'total war' must be heeded. We are, however, presented with some difficult practical problems that call for immediate solution and some of us may be on the horns of a dilemma. It is analogous to that which faces the leaders of religion in times of war and it was clearly felt quite recently in Parliament during the debate on conscription. This dilemma can only be resolved by real friendship and concord among the nations and is ever present in an armed peace. A definition courts inaccuracy and undue simplification but, very roughly, it is a question of a conflict between our ideals and conception of service to humanity on the one hand, and our duty as citizens and units of a democratic community on
the other hand. As Sir Henry rightly observed, the individual scientist must obey the dictates of his conscience.

Opinion is in a formative condition and before proceeding to the rather more congenial task of discussing certain recent scientific advances, I will offer some propositions for consideration. I need not remind you that the Royal Society as a body has no views on political questions, and therefore I speak for myself alone.

In the first place all scientists should strive to promote international amity and the outlawry of all methods of warfare which by their nature involve ‘total war’. These include aerial bombardment of cities, chemical warfare, biological warfare, the use of atom bombs, and any similar devilries that may be devised. This is not an empty dream because the universal brotherhood of scientists has a real existence. Understanding between the nations will resolve such dubieties and what follows is set down on the assumption that agreement will unhappily not be reached, or will be inadequate to justify a relaxation of defensive measures.

My second point is that the clear-cut distinction between war and peace is fallacious in the present connexion. Under modern conditions a nation must prepare, in peacetime, its defences against a possible attack.

Thirdly, it is inconsistent to praise our scientists for their outstanding contributions to the war effort and at the same time to suggest that they offend against our ethical code if they serve the country in a similar fashion during an uneasy peace. It is useless to attempt to disguise the fact that such service implies some sacrifice of freedom. During the war the scientific effort was nation-wide and control extended to many university departments. Nevertheless the universities have preserved intact their precious liberty of action, and I see no signs of any attempt to curtail it. Surely this suggests a feasible line of demarcation in that extra-mural contracts, placed by Service Departments with the universities, need not, and should not, contain any clauses restricting free publication of the results. Although it has sometimes been irksome, the refusal of many universities to accept theses that cannot be published is a step in the right direction.

The future historian of science will certainly characterize the first half of the twentieth century as an age of unsurpassed progress of discovery in physics. He will also note the crescendo in the elaboration of physical techniques and the decisive part they played in the dramatic developments of the sister sciences. Examples are the commonplaces of our scientific practice and could be culled from almost any active region of investigation. That almost self-evident fact is well illustrated by the record of the Medallists of 1946 and I invite you to reflect on the extent to which their distinguished experimental contributions have been rendered possible by a quick appreciation of the potentialities of new physical methods. The thermionic value, the photoelectric cell, high-vacuum technique, high-pressure technique, production and management of very low and very high temperatures, X-rays, and the use of isotopic and radioactive tracers, are but a few of the tools which modern physics has placed at our disposal.
The vastness of the subject is very significant and even if, as is necessary, I confine myself to organic chemistry, only a small part of it can be mentioned.

The forty years of my own experience have seen a revolution in the methods of experiment and unquestionably the great waves of advance are clearly identified with the introduction of new techniques. The improvement of balances and the pioneering work of Pregl brought in microanalysis and, following in its wake, microchemical manipulation. It is safe to say that this has increased the output of a given laboratory man-power by at least 100% because of the saving of time and energy expended previously on pure routine. But even more important is the fact that microchemistry has made possible the successful attack of problems, especially in the field of biochemistry, which could not even be attempted thirty years ago.

Many of the more spectacular researches concerned substances of high biological activity and a vital part was played by the co-operation of botanists, zoologists, physiologists and bacteriologists. But equally necessary was the help of physicists in the provision of methods of investigation of 1 or 2 mg. of material.

Among the more valuable of these new resources are ultra-violet and infra-red spectroscopy and X-ray crystal analysis. The triumphs of the latter are well known and I will only add that the last details of the constitution of penicillin were revealed by the X-rays in the hands of Crowfoot and Rogers at Oxford and Bunn and Turner-Jones at Northwich. The laborious Fourier analysis which the complete mapping of electronic densities still demands, will soon be carried out by machines and it is not at all improbable that molecular structures will eventually be ascertained with ease, and almost by inspection. That will not close the organic chemical and biochemical laboratories but, on the contrary, will give impetus to their work in many fascinating directions.

Ultra-violet spectroscopy, once the concern of specialists, is now practised universally; for many purposes, however, the study of infra-red absorption promises even greater usefulness.

Although subject to constitutive influences, the bands in the infra-red are far less so than those in the ultra-violet and the method provides a kind of elementary analysis of the simpler groups contained in the molecule. It has been used inter alia to follow the course of polymerization, for the analysis and characterization of hydrocarbons, such as the isomeric octanes or butanes, and in the everyday control of industrial processes.

We were very impressed by, and grateful for, a recent demonstration of the power of infra-red spectroscopic analysis. A crucial test was devised in order to establish a detail of the constitution of strychnine and the outcome depended on the unequivocal identification of a degradation product obtained in very small quantity. Our own work indicated that it was carbazole mixed with one of the four C-methylcarbazoles, and probably with 3-methylcarbazole. But we could not be quite certain.

Mr Pausacker made the four methylcarbazoles, of which one was new, and Mr Richards kindly studied their infra-red spectra. They were characteristic and
differed also from that of carbazole. Using only 1.5 mg. and a novel technique, Richards showed conclusively that the specimen was essentially carbazole containing about 10% of 3-methyl carbazole. The probable course of events recalls the stages through which mountains have been said to pass—an inaccessible peak, an easy day for a lady.

In many directions there have been notable advances in the processes of purification and analysis, but I will merely mention in passing the so-called molecular still, the ultra-centrifuge, polarography and electrophoresis.

I would however like to draw your attention to a recent series of researches which foreshadow a leap forward in our knowledge of the proteins, again because of the introduction of a new technique. In doing this I hope to make some amends for having recently bemoaned in another place the relatively small contribution of British scientists to protein research. The equipment for those who venture to follow the pioneers is not elaborate. I gather that the chief requirements are a lead tray, an earthenware drain pipe and a sheet of paper.

Although the use of animal charcoal for the removal of coloured impurities from solutions has a respectable antiquity and the separation of dyes in solution on filter paper has long been employed as a method of analysis, modern chromatography was introduced by Tswett forty years ago. He showed that coloured substances are selectively adsorbed from suitable solutions and that distinct bands are formed in a vertical column when the solution of a mixture is poured in at the top and allowed to fall through the adsorbant. In this way Tswett showed that leaf-green chlorophyll consists of two substances, later investigated by Willstätter and Stoll.

The many developments have included various devices for applying the method to colourless substances. A coloured group may be added to the molecule, the fluorescence of the bands may be observed instead of the colour, the adsorbent may be pre-coated with a fluorescent substance (Brockmann), or the column may be streaked with a reagent to produce a visible effect.

Chromatography is now a standard laboratory procedure and in this country Sir Ian Heilbron was the first to perceive its advantages.

Another well-known method of separation of substances depends on their partition between immiscible or partially immiscible solvents and an apparatus for carrying out a large number of successive partitions has been devised by L. C. Craig at the Rockefeller Institute of Medical Research.

A still more ingenious idea is that of the partition chromatography which A. J. P. Martin and R. L. M. Synge (1941) worked out in the laboratories of the Wool Industries Research Association. It makes use of a Tswett column but is based on the principles of partition rather than on that of adsorption. This distinction is evidently valid in reference to the phases concerned but it is not so certain that the two processes are not basically similar at the molecular level. As an example particles of silica gel can be impregnated with a buffer solution on the alkaline side and placed in a column through which the substances to be separated, dissolved in a suitable immiscible solvent, are passed. The effect is obviously that of a large number
of successive extractions and bands analogous to those of a chromatogram are produced; the order of the bands from top to bottom will be one of decreasing acidity of the components of the mixture. Ceteris paribus the most acid constituent will be found in the top layer. This technique has been found to be well adapted for the separation of the penicillins on the laboratory scale. In 1944, Martin in collaboration with R. Consden and A. H. Gordon made a further step forward by the use of water-saturated cellulose as the stationary phase and a mobile phase consisting of a solvent such as phenol or collidine, partially miscible with water. Gordon, Martin and Synge had already shown in 1943 that strips of filter paper could be used to separate amino-acids and the later work is an extension of this observation for the same purpose. The development may be one-dimensional or, preferably, two-dimensional in which procedure the first solvent is removed by drying and a second solvent is allowed to ascend the paper at right angles to the direction taken by the first. A drop of protein hydrolysate suffices and its constituent amino-acids become segregated in definite areas the position of which is dependent on the nature of the amino-acid and the solvents used. The well-known colour reaction with ninhydrin is used to show up the spots. Thus a rapid qualitative analysis of protein bausteine is achieved and moreover the presence of a new amino-acid will be indicated and a rough idea of its constitution will perhaps be obtained. Furthermore the simpler peptides are separated and by subsequent hydrolysis and repartition their amino-acids can be recognized.

These researches will I believe be recognized as the greatest contribution to the study of the structure of the proteins made since the classical work of Emil Fischer.

How the method can be used is well shown by an outstanding investigation of the molecular structure of gramicidin-S by Consden, Gordon, Martin and Synge (1946). A partial hydrolysate was fractionated on two-dimensional paper chromatograms. The location of dipeptides and tripeptides having been determined these were taken from a duplicate paper, hydrolyzed, both before and after deamination, and the amino-acids identified by means of further chromatograms. The dipeptides so recognized were synthesized and their behaviour on partition paper chromatography was found to be identical with that of the respective constituents of the partial hydrolysate. The method of ionophoresis was also used and the findings were consistent. From the chain ABCDE, AB, BC, CD, DE, ABC and DEA were obtained and identified.

Hence, not only is the order of the five amino-acids established but it is rendered very probable that the substance is a cyclic polypeptide. The crystallographic results of Crowfoot and Schmidt are compatible with the hypothesis that the ring contains ten amino-acid groups.

At the Liverpool meeting of the British Association for the Advancement of Science (Section B, 1923) I mooted the idea that many high molecular weight substances of repeating pattern type should be regarded as mammoth rings, basing this speculation mainly on the absence of end-groups required on the open-chain hypothesis. A cyclic decapptide would include a ring of thirty members.
I will now refer to a subject pursued in my own laboratory in collaboration with biologists, namely Dr C. E. Coulthard of the Research Department of Boots Pure Drug Company, Limited and Dr J. Ungar of Glaxo Laboratories, Limited.

The tubercle bacilli are characterized by the possession of a waxy envelope which has often been considered to confer some degree of immunity against the attack of chemotherapeutic agents. Consequently it has been sought to endow the latter with fat-soluble groups in the hope of penetrating the supposed protective covering. Actually it may be doubted whether this scheme, which has brought little success, is based on a sound conception, for it may be argued that all that could be achieved would be the establishment of a reservoir of the agent in the lipins. On these lines it would seem necessary to link the fatty part of the molecule to the water-soluble part, which it is hoped will attack the organism, by a readily hydrolyzable linkage. Several variations of this theme can be envisaged. Be this as it may, it is obvious that the chemical nature of the lipins of the bacteria deserve close attention and the first chemist to attack the problem, and with important results, was R. J. Anderson (1929 and later). The fatty acids obtained by hydrolysis of the waxes from the bacterial bodies were fractionated and one of them, tuberculostearic acid, was found by Spielman, a colleague of Anderson's to be 10-methylstearic acid.

Important constituents of the mixture were acids of the formulae $C_{26}H_{52}O_2$ and $C_{30}H_{60}O_2$; the former termed phthioic acid has been the more closely studied. Anderson was of the opinion that it was a branched-chain acid similar in constitution to tuberculostearic acid but the evidence garnered by him and his collaborators and by Wagner-Jauregg, was insufficient to establish the details.

E. Stenhagen and S. Stallberg then studied the behaviour of phthioic acid in monomolecular films and also the X-ray reflexions from barium phthioate. They came to the conclusion that the acid is ethyldecyldodecylacetic acid, or something very similar, but the synthesis of this substance by N. Polgar showed that this was an error probably due to the unusual degree of tilt of the molecules.

I will not burden you with the organic chemical details of Polgar's further work but combined analytic and synthetic attack of the degradation products made it very probable that phthioic acid is $3:13:19$-trimethyltricosanoic acid, a straight chain of twenty-three carbon atoms with three methyl branches. Phthioic acid is feebly optically active but the optically inactive, synthetic $3:13:19$-trimethyltricosanoic acid closely resembles phthioic acid in respect of its physical properties, including the behaviour of monomolecular films on water, and in the melting-points of its derivatives. We thus returned to the original general hypothesis of Anderson.

It has been known for some years that phthioic acid possesses toxic properties (F. Sabin of the Rockefeller Institute for Medical Research, New York, and others) and that it produces lesions when suitably injected into experimental animals, for example, the guinea-pig. But the observations of Coulthard and Ungar are new in that they have been able to reproduce, by a single intraperitoneal injection of synthetic acids of known constitution, a pathological picture which is almost
identical with that of tuberculosis, in respect of the particular manifestations observed. There is no doubt whatever of the reality of the phenomenon and it is highly significant.

The study of a range of synthetic branched long-chain fatty acids from this point of view is in its infancy but the following results can be cited.

The acids have been synthesized by N. Polgar, partly with the collaboration of S. David and E. Seijo.

3:12:15-Trimethyldocosanoic acid is even more active than phthioic acid, or synthetical 3:13:19-tricosanoic acid, which are equal within the limits of the method. On the other hand 2:13:17:21-tetramethyldocosanoic acid is inactive.

13:17:31-Tricosanoic acid is inactive, and so is 2:13-dimethylpentacosanoic acid.

13:16-Tricosanoic acid is active but it was suspected that the specimen contained a 3-methyl-substituted impurity. A purified specimen exhibited greatly diminished activity.

4:13:16-Tricosanoic acid is very active and though here again the presence of some 3-methyl substituent is not excluded the activity is such that it can hardly be due to an impurity.

3:13:19-Δ^{13:19}-Tricosadienic acid is active but less so than the related saturated substance. It is probable that the specimen contains several geometrical isomerides. The syntheses are very laborious and the biological tests are prolonged, so that progress is necessarily slow.

At present it looks as if a methyl substituent in the 3- or 4-position is necessary.

The biological property is evidently highly constitutive but it is too early to attempt an identification of all the requisite structural features. A working hypothesis is that the methyl groups block β-oxidation and some relation to physiologically active unsaturated substances may well be brought to light in the future.

An extremely interesting discovery, quite unrelated to this work in its origin, has been announced by R. P. Cook from the Biochemistry Laboratory, Cambridge University. He has obtained an acid, or a mixture of acids, C_{25}H_{50}O_{2} by feeding cholesterol to rats. This is very suggestive of an extraordinary process of unwinding of the tetracyclic nucleus of the sterinoid by breaks at the points where the rings are fused, and also at some peripheral point, and in the side-chain. For example, one possible degradation is illustrated below:

\[
\text{CH}_2(CH_3)_4 \cdot \text{CHMe(CH}_2)_12 \cdot \text{CHMe(CH}_2)_3 \cdot \text{CO}_2\text{H}
\]

5:18-dimethyltricosanoic acid
We are unable to equate the constitution of any substance that could be obtained in this way with that of phthioic acid but such a direct relation was hardly to be anticipated. If Cook's acid is really derived from the cholesterol molecule by some transformation, it must be a branched-chain acid and the determination of its structure is a most urgent problem, the solution of which must surely shed some light on an aspect of the biochemistry of phthioic acid.

The temptation to carry speculation a little further cannot be resisted. In 1926 Professor L. Ruzicka, For.Mem.R.S., elucidated the constitution of civetone, the odoriferous principle of the civet cat, and made the dramatic discovery of the existence of large carbocyclic rings in nature. He also noted the structural relation of civetone with oleic acid. Since the ketone has one less carbon atom than the acid and the latter is widely distributed, the degradation of oleic acid to civetone is more probable than the reverse synthesis. It may be suggested that oleic acid suffers \( \omega \)-oxidation, a biochemical process to which Verkade has paid attention, and that this is followed by a familiar ketonization.

\[
\begin{align*}
\text{Oleic acid} & \quad \text{Civetone} \\
(CH_2)_7.CH_3 & \quad \text{CH} \\
CH & \quad \text{CH} \\
CH & \quad \text{CH} \\
(CH_2)_7.C_0_2.H & \quad \text{CH} \\
& \quad \text{CH} \\
& \quad \text{CH} \\
& \quad \text{CO} \\
& \quad \text{CH} \\
& \quad \text{Me} \\
& \quad \text{C_0_2.H} \\
& \quad \text{C_0_2.H} \\
\end{align*}
\]

But analogy then leads us to assume a similar mechanism for muscone from the musk-rat, which was also studied by Ruzicka. We find that its progenitor should be a 3-methylpalmitic acid.

\[
\begin{align*}
\text{3-Methylpalmitic acid} & \quad \text{Muscone} \\
(CH_2)_{12}.CH_3 & \quad \text{CHMe.CH_2.C_0_2.H} \\
& \quad \text{CHMe.CH_2.C_0_2.H} \\
& \quad \text{CHMe.CH_2.C_0_2.H} \\
& \quad \text{CHMe.CH_2.C_0_2.H} \\
\end{align*}
\]

The occurrence of the 3-methyl-substituent is interesting in relation to phthioic acid. Further Professor Hans T. Clarke and his collaborators at Columbia University, New York, have shown by the use of C\( ^{13} \) that the fatty acids are produced in the organism from acetic acid only. In parenthesis, this is a remarkable experimental justification of J. N. Collie's speculations on the role of keto-methylene chains in bio-synthesis. An additional molecule of acetic acid could be used to introduce methyl substituents by the mechanism.

\[
R.C_0_2.H + CH_3.C_0_2.H \rightarrow R.C_0 .CH_2.C_0_2.H \rightarrow R.C_0 .CH_2 \\
R.C_0 .CH_2 + CH_3.C_0_2.H \rightarrow R.CHMe.CH_2.C_0_2.H
\]

3:13:19-Tricosanoic acid is not a possible product of this scheme of bio-synthesis. It would therefore not be surprising to find that phthioic acid, as at present known, is a mixture of a trimethylicosanoic acid and a trimethyltetracosanoic acid. On this hypothesis the chain should in any case be even-numbered and the methyl groups can only be attached to the odd-numbered carbon atoms. The constitution
proposed for tuberculostearic acid conforms to the first condition, but not to the second. It could, however, be 9-methylstearic acid, if oxidation occurs at carbon atoms 9 and 10 and is accompanied by a pinacol-pinacolone migration. Alternative views to that already mentioned involve the intervention of molecules of propionic acid or formaldehyde (or an equivalent) in order to provide the methyl substituents. These, however, fix the methyls on even-numbered carbon atoms and, though tuberculostearic acid then falls into line, they are at variance with our own deductions in regard to the constitution of phthioic acid.

Following the clue afforded by chaulmoogric and hydnocarpic acids in the treatment of leprosy, Roger Adams, Davy Medallist of 1945, prepared a range of substituted fatty acids, some of which had considerable action on \textit{B. leprae} (or possibly an analogous organism) \textit{in vitro}. The irritating action of these substances precluded their use in practice.

Our first efforts in the field of tubercle fatty acids had a similar objective, but we have now abandoned the idea of a frontal attack on the organism in favour of an attempt to alleviate the symptoms of the disease. If this can be achieved by an immunity method it is probable that the body resistance will be strengthened. That investigation has not gone beyond the planning stage but we are glad to know that it will be in the capable hands of Professor M. Stacey at Birmingham University.

There are indications that the pathological role of abnormal lipins may not be confined to tuberculosis. Thus Novak and Grey (1938) found tuberculous tissue, with lesions, associated with granulosa cell tumours, and suggested that these effects were due to lipins produced by the malignant growths. These observations have very recently been confirmed and extended in America.