COMMITTEE OF THE PRIVY COUNCIL
FOR MEDICAL RESEARCH

REPORT OF THE MEDICAL RESEARCH COUNCIL FOR THE YEAR 1934–1935

Presented by the Lord President of the Council to Parliament
by Command of His Majesty
January 1936

LONDON
HIS MAJESTY'S STATIONERY OFFICE
1936

Cmd. 5079.

THE COMMITTEE OF THE PRIVY COUNCIL FOR MEDICAL RESEARCH

(Ex Officiis)

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THE MINISTER OF HEALTH (*Vice-Chairman*).
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THE SECRETARY OF STATE FOR HOME AFFAIRS.
THE SECRETARY OF STATE FOR DOMINION AFFAIRS.
THE SECRETARY OF STATE FOR THE COLONIES.
THE SECRETARY OF THE MEDICAL RESEARCH COUNCIL (*Secretary*).

THE MEDICAL RESEARCH COUNCIL

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*Appointed during the period covered by this report, or at its close, to succeed—
The Rt. Hon. LORD DAWSON OF PENN, P.C., G.C.V.O., K.C.B., M.D., P.R.C.P.
Professor A. E. BOYCOTT, D.M., F.R.C.P., F.R.S.

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REPORT

OF THE

COMMITTEE OF THE PRIVY COUNCIL FOR MEDICAL RESEARCH

FOR THE YEAR 1934-1935

TO THE KING'S MOST EXCELLENT MAJESTY IN COUNCIL

MAY IT PLEASE YOUR MAJESTY,

We, the Lords of the Committee for Medical Research of your Majesty's Privy Council, humbly submit to your Majesty a report of our proceedings during the year ending on 30th September 1935.

1. A supplementary grant-in-aid of £1,500 was provided by Parliament at the end of the last financial year to meet the cost of the partial restoration, in 1934, of abatements which had been made in the remuneration of persons paid from public funds. We have since directed that the restoration should be made complete, in accordance with the arrangements approved for the public services generally in 1935.

2. A grant-in-aid of £165,000 was provided by Parliament for the expenditure of the Medical Research Council during the present financial year, as compared with £139,000 in each of the three previous years, and with £148,000 in the years preceding the financial crisis of 1931. This increase has made it possible to proceed with plans for new research work which had been temporarily in abeyance, and to undertake additional investigations required for the purposes of administrative Departments.

3. The estimates of the Council for the present financial year are being met by our provisional allocation of funds under the following heads:

For administration, including expenses of the Council, of the administrative offices and staff, and of travelling, we have provided £9,500.

For the expenses of the National Institute for Medical Research at Hampstead and of the farm laboratories at Mill Hill in association with it, for the salaries of the scientific staff and the expenses of research work done by them or by other workers temporarily attached, we have provided £58,500.

For research grants to scientific workers, and for the expenses of their researches at the Universities and at other centres in the

United Kingdom, for research work in clinical medicine, for various statistical inquiries, and for investigations of the Industrial Health Research Board, we have provided in all £97,000.

4. In accordance with the provisions of the Royal Charter, as amended in 1926, we determined, by an Order dated 22nd July 1935, that the Right Hon. Lord Dawson of Penn, P.C., G.C.V.O., K.C.B., M.D., P.R.C.P., and Professor H. S. Raper, C.B.E., D.Sc., M.B., F.R.S., should be the members of the Medical Research Council to retire on 30th September 1935.

By the same Order, made after statutory consultation with the Medical Research Council and with the President of the Royal Society, we reappointed Professor H. S. Raper and appointed Professor J. A. Ryle, M.D., F.R.C.P., now Regius Professor of Physic in the University of Cambridge, to be members of the Medical Research Council from 1st October 1935.

5. On 30th September 1935, Professor A. E. Boycott, D.M., F.R.C.P., F.R.S., resigned his membership of the Medical Research Council for reasons of health. By an order dated 2nd October 1935, made after consultation as aforesaid, we appointed Professor Matthew J. Stewart, M.B., F.R.C.P., Professor of Pathology in the University of Leeds, in this vacancy.

6. We have received from the Medical Research Council a report, which is submitted herewith, upon the progress of their work during the year ending 30th September 1935. This is the twenty-first annual report upon the research work falling now to their duty and formerly to that of their predecessors, the Medical Research Committee.

7. The public moneys available for the work of the Medical Research Council have again received important augmentations from other sources. Funds for the promotion of particular schemes of research have been provided by the Dental Board of the United Kingdom, the British Empire Cancer Campaign, the Trustees of the late Viscount Leverhulme, the Sir Halley Stewart Trust, the Rockefeller Foundation of New York, the Nitrate Corporation of Chile, Ltd., and the Stock Exchange Dramatic and Operatic Society. The parts of the Council's programme which have received assistance in this way are mentioned under the appropriate headings in the report. Acknowledgement is also made in the report of new private benefactions made to the Council for special purposes of research.

8. The Medical Research Council have continued to maintain close touch, at relevant points in their work, with the chief administrative Government Departments concerned with questions of health. They have in particular, as in previous years, co-operated with the Ministry of Health and the Department of Health for Scotland, and, as regards the health of industrial workers, with

the Home Office and the Mines Department, while in problems of tropical medicine they have acted in consultation with the Colonial Office. The Council have again, also, been closely concerned with international health work under the League of Nations, and especially with that of the permanent International Commission on Biological Standards, upon which they are directly represented.

9. Effective consultation on all scientific and financial questions of common interest has been maintained between the Medical Research Council and the sister organizations working under the Committees of the Privy Council for Industrial Research and for Agricultural Research respectively. With the Department of Scientific and Industrial Research there has been co-operation in such directions of work as the ventilation of buildings, the production of synthetic chemical products of possible therapeutic value, and the effects of transport and storage upon the qualities of foodstuffs. With the Agricultural Research Council there has been joint action in the furtherance of work upon questions of health and disease which concern both man and animals. The Medical Research Council have also continued to have the benefit of free intercourse with organizations and institutions overseas, in the Dominions and in India, having scientific interests equivalent to their own.

J. RAMSAY MACDONALD,
Lord President.

EDWARD MELLANBY
Secretary to the Committee of the Privy Council for Medical Research.

29th January 1936.

REPORT

OF THE

MEDICAL RESEARCH COUNCIL FOR THE YEAR 1934–1935

TO THE LORDS OF THE COMMITTEE OF THE PRIVY COUNCIL FOR MEDICAL RESEARCH

May it please Your Lordships,

The Medical Research Council beg leave to submit the following report upon their proceedings during the year from 1st October 1934 to 30th September 1935.

I. INTRODUCTION

Towards the close of the period under review the Council learnt with regret of the impending retirement of their Chairman, the Marquess of Linlithgow. They have expressed to him, and wish here to record, their congratulations on his appointment to the high office of Viceroy of India, and their warm appreciation of the sympathetic and effective way in which he has presided over their own proceedings.

Nutrition: the Application of Modern Knowledge

Few annual reports have been published by the Council without reference being made in the Introduction to the progress of investigations on nutrition. Sometimes the new facts described have been of academic interest only, but more often they have borne implications of great practical importance for the health of the community. As year by year has passed, however, the absence of any notable influence on public health has suggested that the new knowledge has failed to find effect in the life of the people. Closer examination would no doubt reveal that this is not entirely the case, but the general situation indicates that, until recently, the public was unaware of the importance of proper feeding as a factor in preventive medicine.

There is now, fortunately, clear evidence that these times are passing, and the Council have been able to welcome many recent indications of greater public interest in nutrition. They recognize that this interest has been aroused not solely nor even primarily because of the intrinsic practical importance of proper feeding in its relation to health, but largely because of the probable economic effects on agriculture and industry. Nevertheless, whatever may have given the opportunity, the Council are happy to

know that the discoveries of their own and other investigators of nutritional problems are likely in the near future to play their due part in advancing human welfare. Among practical measures, the Council are particularly pleased to note the extension of cheap milk facilities to large numbers of schoolchildren in this country. That the tendency is not merely national, moreover, is shown by the great interest taken in the Assembly of the League of Nations in the recent discussion on nutrition, largely centring round what has been called 'the marriage of health to agriculture'. This has already been followed by the appointment of an international Technical Commission by the Health Committee of the League, and by a meeting of this Commission in London (under the chairmanship of the Secretary of the Medical Research Council) at which a statement of human nutritional requirements was agreed upon: the report has since been published.

In view of this change in attitude, it may be useful here broadly to survey the subject of nutrition, and to enumerate some of the more practical discoveries which the Council have assisted during the period of their existence. In the first year of their work they initiated research on rickets which led to the elucidation of its nutritional aetiology, and in particular to the discovery of a calcifying vitamin, now known as vitamin D, a substance which was ultimately prepared in its pure form by workers at the National Institute. In addition to laboratory investigations on rickets, they promoted, in association with the Lister Institute, clinical investigations on rachitic children at Vienna, which confirmed the laboratory investigations and placed the methods for the prevention and cure of the disease on a firm basis. Later they supported work arising from the rickets investigations, on the dietetic factors which determined the production of perfect or imperfect teeth, as a result of which it is now practicable to improve greatly the structure of the teeth of the rising generation by proper feeding in infancy and childhood. They are also responsible for the clinical investigations made at Sheffield and Birmingham which demonstrated that, apart from dental structure, decay of the teeth can be slowed down by diet. This work has led to a new outlook on what is probably the commonest disability of civilized man, namely, dental decay, and has supplied facts ready and feasible for widespread translation into practice.

One of the most important practical investigations initiated by the Council demonstrated the effects of supplementing the diet of growing children with milk and other substances. It may be remembered that in a carefully controlled test on children in institutions the addition of a pint of milk daily, to what had been regarded as an adequate diet, produced surprising benefits in height, weight, mental activity, and general health. The large-

scale investigation now being made on schoolchildren by the Milk Marketing Board will no doubt confirm these earlier results.

For a number of years the Council, working through their Accessory Food Factors Committee, have initiated and financially supported investigations made with the object of standardizing the different vitamins. Through this work, vitamin D was first standardized in this country, and the whole series of investigations later made it possible for International Conferences, convened by the Health Organization of the League of Nations in 1931 and 1934, to establish international standards and units for vitamins A, B_1, C, and D. Thus people throughout the world can now discuss these vitamins in terms of units, in the same way as they can discuss time and distance in units of hours and metres.

Other investigations supported by the Council, and described more fully in recent reports, are those concerned with nutritional anaemia. This work called attention to the high incidence and significance of anaemia both in pregnant and lactating women and in their infants in this country, and showed how the condition could be avoided or mitigated. Certain nutritional investigations sponsored by the Council, also, have been directed to the study of goitre. Others, again, have had as their object the determination and close analysis of the usual dietaries of different sections of the community.

These are only a few of the more important contributions to knowledge in nutrition for which the Council have been responsible: the list could be greatly extended. It would indeed be fair to claim that throughout their existence the Council have realized the fundamental importance of this rapidly developing subject, and have placed it in the foreground of their programme. Research on nutritional problems is costly, and it is difficult to believe that many of these important contributions to knowledge could have been made without the strong financial support of a public department such as the Medical Research Council.

Many of the modern discoveries have been adopted by individual people, by institutions, and by local authorities, to the lasting benefit of the health of some sections of the population of this and other countries, and, no doubt, with the passage of time, the new teachings will gradually permeate all sections of the community. It can hardly be claimed, however, that at the present time more than a small fraction of the people have reaped the benefits that modern knowledge of nutrition can offer. It is clearly outside the duty and capacity of a body such as the Council to conduct a crusade of conversion to the acceptance of newly acquired knowledge, even when it affects the general health of the community. Their duty is to discover, by promoting and assisting investigation, and not to educate the public or to introduce legislation. They

must, nevertheless, be intensely interested in the application of knowledge gained by medical science, especially where its utility is in the field of preventive medicine. In general, any curative form of therapy can be readily adopted by practising doctors, whereas discoveries in preventive medicine stand in another category and usually require great public interest and legislation before they can become effective, especially when they touch, as they usually do, the economic interests of the country. It can be readily understood, therefore, how warmly the Council welcome the awakening of the public to the importance of proper feeding.

It is most fortunate that, in spite of the large number of new facts discovered in recent years bearing on nutrition, the essential teachings which will help the community so greatly can be reduced to a few simple statements. The first is that the younger the child the more essential is correct feeding for proper growth and health. It is thus necessary to apply the new teachings of nutrition to the case of the pregnant and lactating mother, so that the sustenance she supplies to the developing offspring shall be the best possible: and, despite the great importance of improvement in the dietary of schoolchildren, proper feeding of the infant and child of preschool age is an even greater need. Breast feeding is of even higher value than has been previously believed, and ought to be more extensively adopted and continued for longer periods.

On the dietary side, the broad requirements can be simply stated to the public—without mention of calories, vitamins, or other technicalities necessary to the investigator—by saying that much more milk ('safe' milk), cheese, butter, eggs (especially egg-yolk), and vegetables (especially green vegetables) ought to be consumed. In particular, milk ought to be the chief drink for children, and especially in the first years, while bread and other cereals should in these early years be greatly reduced.

Ergot in Childbirth: The Isolation of Ergometrine

For many years the value of ergot as a drug in obstetrics has been empirically known, its important effect being that of inducing powerful contractions of the uterus. Ergot is not a simple substance, however, being in fact a fungus found as a parasite on rye and other grasses, and different preparations of it vary considerably in the nature and strength of their pharmacological actions. It has thus been a matter both of scientific interest and of practical importance to isolate and identify the effective constituent. The result of work undertaken with this object has been to reveal not a single active principle but a whole series of alkaloids, each with its particular pharmacological properties. These substances have been successively discovered by different workers during a period

of more than thirty years, and it is only during the last year that what appears to be the chief one of them has been recognized.

Early in 1935, this new alkaloid, to which the name ergometrine has been given, was isolated as the result of a joint investigation, in which the late Dr. H. W. Dudley, at the National Institute for Medical Research, had co-operated for nearly three years with Dr. J. Chassar Moir, at the Obstetric Unit of University College Hospital, London. The investigation had started in 1932 with Dr. Moir's demonstration that a watery extract of ergot, when administered by the mouth, had a stimulant action on the contractile activity of the human puerperal uterus which could not be attributed to any of the active principles hitherto known to exist in ergot. As the result of this combination of chemical with directly clinical research, ergometrine has now been identified as the principle mainly responsible for the value of ergot in obstetrics; and, although its identification has been achieved after so many other active substances in ergot had been found by laboratory researches, its isolation and purification, now that it has once been identified, prove to be much easier than those of the more complex ergot alkaloids which the earlier work had revealed. A brief survey of the course of the earlier investigations may throw some light on the cause of this long delay.

The crystalline alkaloid, ergotinine, isolated by Tanret in 1875, had proved to be almost if not quite inactive; and it was not till 1906 that Barger and Carr isolated the alkaloid ergotoxine, as the substance responsible for a highly characteristic activity of ergot preparations which Dale had observed a year earlier. These two alkaloids are closely related substances, easily convertible the one into the other, but differing in that the crystalline ergotinine is almost inactive, while ergotoxine has an intense and highly characteristic action: this action includes a strong stimulant action on the plain muscle of the arteries and the uterus, but also a highly characteristic paralysis of the motor effects of sympathetic nerve impulses and of adrenalin.

In the succeeding twenty-seven years other active alkaloids were obtained from ergot, chemically distinguishable from ergotoxine, but practically identical with it in pharmacological action. The best known of these, ergotamine, was described by Stoll in 1920; and in this case also there is an almost inactive isomer, ergotaminine. Sensibamine, described in 1932, is stated by Stoll to be only a molecular mixture of ergotamine and ergotaminine; while the relation of ergoclavine, described in 1933, to the other alkaloids is not yet clear. For practical purposes, however, these alkaloids may all be regarded as closely similar in action to ergotoxine.

It has never been completely accepted that either ergotoxine or

any other of these alkaloids would account for the activity of many ergot preparations which were regularly used, with apparent success and satisfaction, in medical practice. The watery extracts which figured in many pharmacopoeias, as well as a number of widely used proprietary extracts, showed practically none of the highly specific and easily recognized action which ergotoxine has on sympathetic nerve effects; and the absence of this action showed them to be free not only from ergotoxine, but from all the other alkaloids subsequently discovered until last year. There was the further difficulty that neither ergotoxine nor any of the similarly acting alkaloids produced their effects at all readily when given by the mouth, the customary mode of administering the most widely used preparations of ergot: so that, even if they had been present, these alkaloids would hardly have come into action when ergot extracts were given under the usual conditions of practical therapeutics.

Barger and Dale were led, by an early recognition of these anomalies, to look for active substances of other kinds in watery extracts of ergot. The special activities of tyramine and of histamine were thus discovered; and the further investigation of these has opened up interesting fields of physiology and pathology. Later, Dale and Ewins similarly found acetylcholine in certain ergot extracts; and, again, the resulting detailed investigation of its action and its properties has had important developments in recent physiology. But, although all these substances proved to be of physiological interest and could be shown to have some stimulant action on the uterus, none of them was significantly active when given by the mouth, even in doses much larger than those present in apparently effective doses of ergot extracts.

The apparent disparity between pharmacological evidence and clinical practice remained, and a certain scepticism arose as to the basis of the clinical reputation of these watery ergot extracts. There was a lack of such objective records as would give convincing evidence of their activity, and a measure of its intensity and its duration. When, in 1932, Chassar Moir used a method for obtaining a quantitative record of the contractions of the human uterus in the puerperium, it was at once made clear that a watery extract of ergot, administered in ordinary doses by the mouth, evoked a vigorous contractile activity of a uterus which had previously been quiescent, or had exhibited relatively weak and rare contractions. This stimulant effect, lasting for some hours, was not produced by any of the known constituents of ergot, nor by any other known substance, when similarly administered. On the other hand, no form of laboratory experiment on the lower animals would enable this unknown principle to be recognized and estimated, in a complex ergot extract, with a preci-

sion approaching that which could be attained with oral administration to the passive and co-operating human subject. An investigation was promptly begun, in which Dr. Dudley's chemical fractionation of the ergot extract was checked, at every stage, by Dr. Chassar Moir's direct, clinical tests; and last March they were able jointly to announce the isolation of ergometrine, as the substance in ergot responsible for this most familiar of all the actions of that complex drug.

The combined investigations of chemist and pharmacologist on ergot, extending over the past thirty years, make a fascinating story. Again and again new constituents have been isolated from ergot which, although of great physiological interest, have not solved the particular problem of the obstetrician, which was the chief object in view. At last, the drug has given up its secret, and the practising doctor can now administer pure ergometrine to his patients. These researches, while illustrating how results of equal or even greater importance may be attained by the laboratory as by-products of the chase, also illustrate in no uncertain way how vital to the solution of a problem, originating in and concerning clinical practice, may be the guidance provided by continued investigation upon the clinical material itself.

The Curative Agent of Pernicious Anaemia

Since the discovery by Minot and Murphy, in 1926, of the successful treatment of pernicious anaemia by liver, several references to further advances in knowledge have been made in these reports. Thus, in the report for 1927–8 mention was made of the possibility, which was then being opened up, of obtaining powerful preparations of the anti-anaemic principle of liver in watery extracts that could be injected into patients suffering from this disease. Preparations of this kind, indeed, became the usual means of treatment, especially after it had been established that one injection exerted its action over a period of days and was often as effective as, say, half a pound of liver by the mouth daily. Besides being simpler and more convenient for the patient, a given amount of active principle is apparently more effective when injected, probably because, when liver or its extracts are taken by the mouth, a large proportion is destroyed in the alimentary canal.

It is now possible to refer to a further development in this important therapeutic problem. During the past year Dr. H. D. Dakin, F.R.S., and Dr. West have published, in America, a method for preparing the active haemopoietic agent from liver in a much purer state than has hitherto been possible. This substance is apparently not a simple chemical body, as is met with in the case of some hormones such as adrenalin and thyroxin, but is

probably a complex protein structure made up of amino-acid and other groups, and comparable in this respect to insulin.

During the summer Dr. Dakin came to England and supervised the preparation on a manufacturing scale of haemopoietic liver principle, according to the published method, by a British firm, a member of whose staff had previously discovered an important stage of the chemical procedure. At the invitation of the Council, three investigators—Professor Stanley Davidson of Aberdeen, Professor E. J. Wayne of Sheffield, and Dr. C. C. Ungley of Newcastle-on-Tyne—undertook to test the effect of this substance on cases of pernicious anaemia. The results of these tests have now been published in a conjoint paper, and show that the substance thus prepared is extremely potent. Injections of from 0·1 to 0·2 grammes of the active preparation, once weekly, brought about a large increase in the red blood corpuscles of the patients, and in the course of a few weeks restored them to health. To any one mindful of the almost certain death that followed the development of pernicious anaemia, even so recently as ten years ago, the recovery that follows these minute injections of anti-anaemic principle seems little short of miraculous.

No doubt, as in the case of insulin, improvements in technical procedure will rapidly bring about increases in yield of the haemopoietic principle from the liver, and possibly also further purification of the substance. The problem is, however, still one of great difficulty, because it is as yet impossible to foretell whether any particular preparation will be active until it has been tested on patients suffering from pernicious anaemia. No effective laboratory test of activity has yet been established, in spite of world-wide endeavours, while the chemical complexity of the liver principle has prevented the discovery of any chemical or physical property which can be regarded as a measure of its therapeutic influence. Discoveries along these lines will, no doubt, be forthcoming in the future, but in the meantime it is a pleasure to note this present milestone in the advancement of knowledge of this great problem, and to congratulate Dr. Dakin and Dr. West on their important discovery. The Council are glad to have had the opportunity of forwarding the clinical trials of the new potent active principle.

The treatment of pernicious anaemia by liver therapy in general has now been established sufficiently long to allow some examination of its effect on the death-rate due to this disease. The effect, as revealed by statistical analysis of relevant figures given by the Registrar-General, is interesting: as might be expected, two results are outstanding. There has been a large fall in the death-rate from this disease up to the age of 65, but after this age, and especially by the age of 75, the recorded death-rate has greatly increased. Taking the figures of the years 1931–3, for the particularly

important age-group 35–45, death-rates due to pernicious anaemia were only 48 per cent. in males, and 58 per cent. in females, of the corresponding death-rates in 1921–6, i.e., the pre-liver period of treatment. The figures in general show that the lives of patients suffering from pernicious anaemia have already been appreciably extended by this form of therapy.

The Prevention of Childbed Fever

Puerperal sepsis, an infective condition due to the invasion of the body by harmful micro-organisms during childbirth, is not only a heavy cause of maternal mortality but also one of the great enigmas of medical science at the present time. On the one hand, medical practitioners have for fifty years or more been living in an atmosphere permeated by teaching of the fundamental importance of antisepsis and asepsis. On the other hand, here is an infective state which still remains common in spite of greater precautions and better technical methods. These circumstances make the situation particularly challenging; and the challenge is not the less impressive because the condition occurs in what ought to be a normal physiological process, and often when there has, in fact, been little or no obstetrical interference. One thing is certain: a situation such as this must mean that knowledge of the problem of infection in general, and of this special aspect of the problem in particular, is imperfect, and that a solution can be attained only through better information about the factors at work.

It was in view of these considerations that the Council were glad to give their support, in 1930, to the establishment of a 'unit' of research in the subject at Queen Charlotte's Hospital, London, in the Bernhard Baron Memorial Research Laboratories attached to the new Isolation Block at Hammersmith. The funds which the Council were themselves able to provide for this purpose, in addition to the resources which the Hospital had available, were largely augmented by a generous subvention from the Rockefeller Foundation of New York, granted for a period of seven years. Particular inquiries also received some financial and other assistance from the Ministry of Health.

A report by Dr. Dora Colebrook, which the Council have just issued, is one of a number of valuable accounts describing the work done in the unit. Whereas it has long been known that the morbid agent responsible for most cases of puerperal sepsis is a streptococcus characterized by its ability to haemolyse red blood corpuscles, it has been realized only in the last few years that the cocci having this property in common really comprise several groups, and a number of sub-groups, of which only certain members are harmful to human beings. At first sight this would appear

to complicate the problem from the point of view of the investigator, but in reality it does not: indeed, the recognition of these different groups and sub-groups promises to throw much light upon the aetiological problems, not only of puerperal fever, but of a wide range of infections for which haemolytic streptococci are wholly or in part responsible. In human pathology, that range includes scarlet fever, acute tonsillitis and epidemic sore throat, erysipelas, whitlow, impetigo, wound infections, 'hospital sepsis', and perhaps acute rheumatism: in animal pathology, bovine mastitis, equine strangles, and other conditions.

The new technical procedures developed at the Rockefeller Institute in New York for the differentiation of the haemolytic streptococci, have enabled workers at Queen Charlotte's Hospital to reach an important conclusion in respect of puerperal fever. It is that the haemolytic streptococci which are occasionally found in the genital tract of healthy parturient women are not, as was formerly supposed, identical with those causing puerperal fever, and are indeed usually harmless to their human hosts. As a corollary it would seem to follow that when the pathogenic types of haemolytic streptococci do invade the genital tract they have been conveyed to it from some outside source. That conclusion finds much indirect support from the present report.

It has been the task of Dr. Dora Colebrook to develop the work of other investigators and to track down these outside sources in a large series of cases of puerperal fever. Her results will be of considerable interest to bacteriologists, as showing that it is now possible, by a judicious application of various technical improvements, to obtain reliable and clear-cut results of definite epidemiological value. And to epidemiologists, as well as to obstetricians concerned with puerperal fever, they should also be of great interest, as indicating with a very high degree of probability what are the usual sources, outside the genital tract, from which haemolytic streptococci are conveyed to the woman in labour. The multiplicity of these sources will at once attract attention, although it need occasion no surprise in view of the great variety of infections caused by the haemolytic streptococci. Ample confirmation of the view that the streptococci of the respiratory tract bear an intimate relation to puerperal fever is contained in Dr. Colebrook's results; but these results suggest that the respiratory tract of the mother must be taken into account as well as that of her attendants; and familial sources of infection have been incriminated in not a few instances.

In the nature of the case, it would be scarcely possible to obtain stronger evidence than is given by Dr. Colebrook's report, and by other work from Queen Charlotte's Hospital, and elsewhere, as to the responsibility of the throat and nose-carried streptococci on

the one hand, and of those of various septic infections on the other, in the causation of puerperal fever. Until methods are known for ensuring a high resistance of the maternal body to these pathogenic agents, it should be recognized that it is undesirable—and, indeed, dangerous—for any person suffering from an acute infection of the respiratory tract to engage in maternity work. It is also unwise for nursing homes and small hospitals to deal with maternity and surgical cases under the same roof unless adequate provision can be made for complete separation of the nursing staffs of the two departments. A wider employment of the laboratory services available throughout the country for the prompt detection of the puerperal case infected by the streptococcus, when it occurs, is to be desired. The results and lessons of this work, if rightly applied, should achieve a reduction in the incidence of haemolytic streptococcus infection following childbirth.

Anaesthetics

Twelve years ago the Council arranged with the Anaesthetics Section of the Royal Society of Medicine for the joint appointment of a special committee to promote research into the value, effects, and possible dangers of different methods of producing anaesthesia. The work of the committee has been maintained since then with the aid of grants made by the Council, and latterly also from a legacy administered by Mr. Gerald Heard under the will of the late Sir Horace Plunkett. The progress made during the period has recently been reviewed in a paper by the secretary of the committee, Dr. C. F. Hadfield, which provides the occasion for brief mention here.

One of the first tasks undertaken by the committee was to investigate the purity of supplies of nitrous oxide placed on the market for anaesthetic use. Although the gas supplied by different manufacturers was usually found to be of excellent quality, despite the absence of any official standard of purity, the investigation revealed causes of contamination of the gas with very small amounts of deleterious substances: as a result, methods for removing these impurities were found. Attention was similarly directed to the quality of anaesthetic ether from different sources. Here a high degree of uniformity in chemical purity and anaesthetic potency was found, and complaints of differences in these respects proved to have little foundation. More recently the committee have given much advice to the Pharmacopoeia Commission regarding the standards of purity which should be laid down in the British Pharmacopoeia in respect of various anaesthetic gases.

Another phase of the work has consisted of the experimental or clinical trial of some of the less known gases which have anaesthetic properties, and of new preparations which are introduced from

time to time as the result of chemical research in different countries. Substances which produce good anaesthesia are often found to be unsuitable in practical use owing to their possession of drawbacks of one kind or another, such as an unpleasant smell or the danger of explosion. Other new anaesthetics have proved to have advantages for particular purposes, and avertin and evipan—both German products—may be named as examples of new anaesthetics which have come into general use in this country after preliminary trials organized by the committee.

Physiological research work has also been promoted on occasion for the elucidation of particular problems that have arisen. This has included investigations into the effects of anaesthesia on metabolism, on respiration, and on kidney function. Other research has been concerned with the danger of explosions in operating theatres, and an important investigation was made by one of the members of the committee, the late Professor H. B. Dixon of Manchester, into the ignition points of different anaesthetic gases. The committee are at present taking part in the examination of evidence relating to one or two recent explosions in operating theatres which have brought that question again to official notice.

These various activities of the Anaesthetics Committee well illustrate one aspect of the work of the Council. The organization set up is an example of a standing committee which keeps continuously in view the questions requiring investigation in a particular field, and takes action regarding these when necessary.

Artificial Cultivation of Living Tissues

The Council have for many years been providing a substantial part of the financial support of the Strangeways Research Laboratory, at Cambridge, where a group of workers are engaged in investigations which may sometimes appear to be of a purely academic kind, but which have in reality a highly important bearing upon various practical problems of physiology and pathology. These workers are occupied in the study of fragments of living tissues in artificial culture: by methods of great refinement, these tissues are not only maintained alive for long periods, but undergo growth and development as separate entities. At first sight this work impresses, perhaps, mainly by the sheer delicacy of its technique, and by the beauty of the demonstration whereby a few cells may be seen under the microscope actually giving rise to a portion of, say, retina or tooth, with the natural characteristics of the particular tissue form. Further inspection, however, reveals the great practical convenience of the method for many purposes of research: a special kind of experimental subject is provided, which can be submitted at will to closely controlled conditions of

one sort or another, and kept continuously under intimate and exact observation.

The laboratory was originally endowed, under a private benefaction, as a small Research Hospital, and was for a number of years the scene of work by the late Dr. T. S. P. Strangeways on the subject of osteoarthritis, one of the crippling diseases of mankind not only at the present time but throughout the ages. After assiduous labours in clinical and pathological studies of this condition, Dr. Strangeways concluded that no real advance could be made until more was known of basic principles, and especially of the factors determining the growth and other reactions of bone. He therefore turned his attention to the study of living tissues grown in culture, but his death in 1926 threatened to end an institution of which the origin and development had depended so largely on his personal activity. It was to prevent this that the Council offered the additional financial support which they have ever since maintained, and the work was continued with Dr. J. Alford Andrews as Honorary Director. Two years later Dr. Honor Fell was appointed Director, and partly by her own distinguished investigations, and partly by her wisdom in collecting a body of able workers, she has brought the Strangeways Research Laboratory to a high pitch of success. This has been marked by the extension of tissue culture methods to many specific biological problems, with the collaboration of experts in the different fields.

One particularly fruitful line of investigation developed when it was found possible to grow bone by this method, in fulfilment of a prediction made by Dr. Strangeways. This allowed a study of the process of ossification in isolated living tissue under easily controlled conditions. Much work has now been done on the nature and function of osteoblasts, on the calcifying mechanism of skeletal tissues, on the influence upon ossification of vitamin D and of phosphorus and calcium salts, on the effect of starvation on bone-formation, and on the action of mechanical stresses and strains on intimate bone structure. Similar studies on dental tissue have recently been made possible by the successful cultivation of dentine.

For several years experimental work on the developmental mechanics of the early embryonic limb-skeleton has been in progress. Such problems as the factors concerned in joint-formation, and the nature of the skeletal abnormalities in a certain form of dwarfism, have been studied by tissue culture, in collaboration with workers elsewhere. A series of very fruitful investigations on the development of blood-vessels has also been in progress during the last three years. Other studies, again, have dealt with the action of the embryonic heart, and with the production of the visual purple in the eye.

Of particular interest are the experiments on the 'organizer' in early embryonic development. Spemann had shown that when certain structures found in the embryonic tissues of amphibians were introduced into abnormal situations in another egg, they induced the surrounding tissues to form a second, or part of a second, embryo. That this was true also of the warm-blooded vertebrates was first proved in the Strangeways Research Laboratory in cultures of the germinal area of the fowl. This work has recently been developed in collaboration with the University Departments of Biochemistry and Zoology, with special reference to the chemical nature of the organizer substance. This substance is probably related to the oestrogenic compounds, and these will, in fact, sometimes act as inducing agents when introduced into the early embryo.

One of the most important sections of the work is that dealing with experimental radiology, which has a direct bearing upon problems arising in the treatment of malignant disease. Originally begun by Dr. Strangeways, with colleagues in Cambridge and London, these investigations are now in the hands of Dr. F. G. Spear, in collaboration with several of the University laboratories and with St. Bartholomew's Hospital, the Westminster Hospital, and the Radium Beam Therapy Research Board in London. It has been shown that the earliest biological change to be observed in a tissue culture after irradiation, with the gamma rays of radium or with X-rays, is an alteration in the rate of cell division in the exposed tissue. As the dose is increased the biological response has been found to become more complex: cell migration is hindered and normal metabolic processes are disturbed, but only with relatively enormous doses can an immediate lethal effect be obtained. It has been demonstrated with beautiful precision that there are optimum values for the time and intensity factors if the maximum effect is to be produced in the particular cells irradiated. Using fowl embryos *in ovo* as experimental material, it has been possible to repeat much of the work which had been done on embryonic cells in culture, and thus to compare the effects of irradiation on the same tissues both in the presence and in the absence of a circulation. The results have shown that so long as the circulation remains intact, its presence favours the recovery of those more sensitive biological processes, such as cell division, which are first affected. If, however, the dose is raised sufficiently to destroy the circulation, then the degenerative effects of irradiation are enhanced by the generalized destruction which normally follows any interference with the blood-supply.

It may be added that many of the late Dr. R .G. Canti's well-known cinematograph films of living cells, including all the earlier ones, were photographed from cultures prepared here; and that

these beautiful films have been of the greatest assistance in the work of the Laboratory.

These examples of studies made at the Strangeways Research Laboratory during recent years will give some idea of its intense and successful activity. The results obtained fully justify, both in their scientific interest and in their practical value, the support given continuously by the Council for the maintenance of the Laboratory as an independent unit of research. Although the Laboratory has attracted further substantial assistance from other sources, it has clearly earned establishment on a more satisfactory financial basis than it at present possesses.

Standards for Sex Hormones

Frequent mention has been made in these reports of the endeavours made by the Council to meet the growing need for standardizing biological products used in medical practice. To be able to express the potency of such substances in quantitative terms is not only necessary to the progress of medical science, but gives to the practising doctor an essential weapon in the treatment of disease, allowing him to know both that his therapeutic remedy is active, and that it is active in a definite degree. Thus it has come about that quantitative control has now been established over such substances as several of the vitamins, many antitoxins, including those against diphtheria and tetanus, and various drugs such as digitalis, strophanthin, and arseno-benzene, and hormones such as insulin and pituitary extract.

In the course of the past year a conference, convened by the Permanent Standards Committee of the Health Section of the League of Nations, met in London under the Chairmanship of Sir Henry Dale to consider the possibility of extending the principle of standardization to sex hormones. No conference was more needed. The market is flooded with different preparations of the various sex hormones, and each manufacturing firm has given a proprietary name to its own particular product.. While some of these proprietary preparations are good, both their composition and activity being controlled, others are of a semi-bogus nature. The situation lent itself both to quackery and to ignorant treatment of disease, a condition of affairs unfortunate alike to the manufacturing firms of high repute and to the general public.

The decisions that the conference was able to make are, therefore, of first-rate importance, and they begin to bring order into a subject which threatened to become chaotic, so far as practical medicine was concerned. A uniform scientific nomenclature and standard units have been adopted for three important natural substances of which therapeutic preparations are now available. These are, firstly, 'oestrone', 'oestriol', and 'oestradiol', the

oestrus-producing hormones (the alternative names applying to hydroxy-ketonic, trihydroxy and dihydroxy preparations, respectively); secondly, 'progesterone', the hormone of the *corpus luteum* which produces in the female the changes associated with pregnancy and pseudo-pregnancy; and thirdly, 'androsterone', a chemical substance closely related to that responsible for the development of the secondary sex characteristics in the male.

It will be realized that, although international agreement as to nomenclature and quantitative methods of estimation is of great value, the effectiveness of the proposals must ultimately depend on the attitude of those who use the substances. It is therefore necessary that medical men using these substances in their work should insist on knowing the exact nature and strength of the preparations supplied. It may also be useful to point out here that clinical knowledge of the actions of these sex hormones is still at a very elementary stage, and that little is yet accurately known as to the circumstances in which they are capable of giving real benefit to the patient. On the other hand, it is certain that these substances are physiologically very potent, often in unexpected directions. If, therefore, the result of standardization is to provide the doctor with therapeutic agents of known constitution and activity, it will still be incumbent on him to judge accurately the occasions on which each of these substances should be administered, bearing in mind the present limitations of knowledge as to their clinical effects.

Iodine and Thyroid Disease

It is well known that the element iodine plays a very important part in the metabolism of the body, and particularly in relation to the functions of the thyroid gland. The quantities involved are nevertheless exceedingly minute, and study of the subject is hampered by the difficulty of estimating them with accuracy in complex biological substances. The results of defective methods of estimating these minute quantities of iodine have indeed formed a lamentable chapter in medical science. So long ago as 1850, Chatin began investigations into the distribution of iodine in foodstuffs and was led to formulate the hypothesis that simple goitre was related to deficiency of iodine—one of the earliest instances of a deficiency disease, a type of aetiology now recognized as being so common. A Commission appointed by the French Academy of Science was unable to repeat his chemical findings and repudiated his hypothesis, with the result that the latter remained discredited until Baumann in 1895 discovered iodine in the thyroid gland. Chatin's hypothesis has since been completely vindicated by the work of McClendon in the United States and of von Fellenberg in Switzerland: moreover, the

investigations of Marine and his colleagues in America have clearly shown the determining effect of the supply of iodine upon the structure of the thyroid gland.

Even in recent years, however, difficulties and discrepancies have arisen in the course of investigations undertaken in different parts of the world to determine the relation of the iodine content of foodstuffs and water supply to the incidence of goitre in particular regions. An explanation of these discrepancies was given in the report of an investigation which was made by Sir J. B. Orr and his assistants at the Rowett Research Institute, Aberdeen, and of which the results were published by the Council in 1931: this had been preceded in 1929 by another report by the same author and Dr. I. Leitch, reviewing all the existing information with regard to iodine in nutrition. This inquiry into the iodine content of soil and foods, in relation to the geographical distribution of simple goitre in Great Britain, yielded some suggestive indications, but the main conclusion was that further work on this and other aspects of the iodine problem could not profitably be undertaken until a more reliable method of chemical analysis for the purpose had been devised.

In these circumstances, the Council decided to promote work on the estimation of iodine in biological substances, with the direct aim of finding a reliable method for use in further studies of the main problem. In the first instance, to advise and assist them in the matter, they appointed a special committee of chemists, who have now completed their task. The Council were also fortunate in securing the co-operation of the Government Chemist, Sir Robert Robertson, F.R.S., with whom it was arranged that Mr. C. O. Harvey, of his staff, should undertake the actual investigation. The cost of the scheme, moreover, was provided from a donation generously placed at the disposal of the Council by the Nitrate Corporation of Chile, Limited.

As is shown in the report on the subject which the Council have published during the past year, Mr. Harvey was successful in devising an improved and standardized method—based on Dr. W. H. Hurtley's modification of Professor Th. von Fellenberg's procedure—for determining small quantities of iodine in biological substances, such as blood, milk, and vegetable foods. Practical trial of it by Miss M. G. Crabtree, working for the Council at the Lister Institute laboratories at Elstree, and by Miss G. Mason, at the Rowett Research Institute, has shown that the method is capable of giving consistent results when parts of the same specimen are tested by independent analysts.

Promotion of further work on iodine in relation to the nutrition and health of man and animals, in which Mr. Harvey's method is likely to prove useful, has been entrusted to a new

committee on iodine deficiency and thyroid disease, appointed jointly by the Medical Research Council and the Agricultural Research Council. An allied field of medical inquiry in which the new method of iodine estimation should prove of great value is that of hyperthyroidism. It is now known not only that iodine plays an important role both physiologically and therapeutically in hyperthyroidism, but that the blood-content of iodine in hyperthyroidism is very high as compared with the normal. A reliable method of estimating the iodine content of the blood may well permit a new kind of attack to be made by investigators of this condition.

Industrial Pulmonary Disease

In 1930 the Council appointed a committee, the constitution of which is shown on a later page, to advise and assist them in promoting research into industrial pulmonary disease. This step was taken in response to a request by the Home Office for further research into morbid conditions due to the inhalation of dust associated with occupation. The practical importance of the subject may be gauged by the fact that one of these conditions, silicosis, has been certified as the cause of over 300 deaths annually in England and Wales during the last three years, and has cost in compensation alone more than £100,000 in a single year. Silicosis is a disease arising directly from exposure to the inhalation of the siliceous dust which occurs in various important industries and occupations: these include mining, quarrying, and pottery manufacture, and the exposure is thus widespread. Preventive measures are hampered by lack of exact knowledge. Silicosis is insidious in its onset, but it is not known how much of the dangerous dust must be inhaled, and over what period, to produce disabling effects. Much also remains to be discovered as to the influence—as regards degree of danger—of the size-distribution and concentration of the dust particles at the time of inhalation, although the chemical and mineralogical characteristics of the dusts that are harmful, and the nature of their specific effects upon the body, have already been determined to some extent. Research into the physical nature of the dust clouds capable of producing disease was accordingly one of the first undertakings of the committee.

Fundamental to this purpose was a satisfactory instrument with which to collect atmospheric dust and to measure the concentration and size-frequency of the particles. A suitable apparatus was described in a report, published by the Council during the past year, by Mr. H. L. Green and Mr. H. H. Watson, investigators who were lent from the staff of the Chemical Defence Experimental Station at Porton, under an arrangement between the Council and the War Office by which

the former provided the cost. The new instrument is a form of thermal precipitator, developed from an apparatus originally devised by Professor R. Whytlaw-Gray and Dr. R. Lomax for the Department of Scientific and Industrial Research. The work covered by the report included preliminary use of the improved instrument in the practical investigation of dust clouds under actual industrial conditions, and with special reference to the occupation of stone-mason. Further application of the method to the study of the general problem of occupational dusts in relation to disease will form the subject of future work.

More recently the committee have been considering the need for further chemical investigation of dusts arising from industrial processes, complementary to the physical investigations just mentioned. As a result of careful examination of the question in consultation with chemical experts, they have come to the conclusion that the accurate knowledge at present available as to the chemical and physiological properties of the various dusts met with in industry is inadequate for the proper understanding of silicosis and allied diseases. Chemical properties of dusts about which it is necessary to have information include the composition of the particles and their solubility under different conditions. On the advice of the committee, the Council have accordingly provided grants for investigations to be made in close co-operation with those on the physical and pathological sides. It has been arranged that this work will be done at the Imperial College of Science and Technology under the direction of Professor H. V. A. Briscoe.

Meanwhile, various biological investigations on the subject which were begun at an earlier date are being continued. These include, on the one hand, pathological investigations of material from human cases of industrial pulmonary disease. On the other hand, experiments are being made on the effects which dusty atmospheres of various kinds have on the lungs of animals: strongly marked differences are found as between one kind of dust and another. Work on these lines has been done for the Council at St. Bartholomew's Hospital by Mr. F. Haynes, under the general direction of Dr. J. S. Haldane of Oxford, and by Professor E. H. Kettle, now at the British Post-Graduate Medical School at Hammersmith.

One aspect of Professor Kettle's work is of special interest. It has long been known that silicosis in man is often associated with a low-grade form of lung tuberculosis. Indeed, it may be difficult, in examining the lungs of people who have died of silicosis, to determine how much of the fibrosis is due to the dust and how much to the healing reaction of the tissues to tuberculous infection. It would appear that the combination of some silicon

compounds with tubercle bacilli is particularly effective in producing the fibrotic lung changes of silicosis. Professor Kettle, for instance, has found that the introduction of kaolin (aluminium silicate) alone into the lungs of guinea pigs does not cause any actual fibrosis, in spite of the fact that a large quantity of dust may remain in the lungs for long periods. If, however, a mixture of kaolin and dead tubercle bacilli is introduced into the lungs of these animals, a series of reactions takes place which leads ultimately to the formation of laminated fibrous tissue resembling very closely the isolated nodules met with in human infective tuberculosis or tuberculo-silicosis: in other areas of the lung a coarse reticular fibrosis may develop. It is clear that these results reopen the problem of the pathological changes of the lungs associated with silica, and emphasize the part that may be played by associated tubercle bacilli—even when dead—in producing the characteristic morbid change.

Direct studies of disease in the living subject are also being made as opportunity offers, but the possibilities of making progress in this direction are slight. This is partly because there has already been an abundance of purely clinical observation, and partly because most of the symptoms produced are not peculiar to disease owing its origin to dust. The question, indeed, inevitably becomes a statistical one, involving a comparison between the incidence of pulmonary disease among persons exposed to dust inhalation in their occupations and the incidence in the general population: the task of obtaining records for strictly comparable groups of people, differing only in the one respect of exposure to dust, is beset with serious practical difficulties which are apt to prove insurmountable.

The work in this field, as a whole, is by no means confined to silicosis, although that properly bulks very largely in the investigations. Mention may be made, for example, of the recently published paper by Professor M. J. Stewart of Leeds and Dr. J. S. Faulds of Carlisle, on the effects of haematite dust on the lungs of persons engaged in mining that ore. Then there are organic dusts, such as those found in card-rooms in the cotton industry. On this subject Professor Carl Prausnitz, partly supported by the Rockefeller Foundation, has recently completed an investigation for the Council in Professor H. B. Maitland's department at Manchester. The aim here was to determine the parts played respectively by allergy, mechanical irritation, and bacterial infection in the asthma and chronic bronchitis of card-room operatives. A report is now in the press.

In general, it is as yet too early to expect important new results capable of immediate application in the safe-guarding of health. It will be seen, however, that the committee appointed by the Council have now in progress a carefully planned and co-ordinated

programme of research which is attacking the problem from all possible aspects, physical and chemical, experimental and pathological, clinical and statistical.

Bed-bug Infestation

The infestation of human dwellings by the bed-bug presents a serious problem to the authorities concerned with housing and public health. Infestation is not confined to old and dilapidated houses, although these provide especially good harbourage. It is, indeed, easily transmitted to new dwellings, either by the spontaneous migration of the bugs themselves or by conveyance in furniture or other materials. The infestation is, in fact, not restricted to slum areas, but it is these that suffer most severely, some districts having practically every house affected. Once the bugs have gained a footing they are extremely difficult to dislodge.

Whether the bed-bug has a definite effect on human health is, perhaps, doubtful. It lives, of course, on human blood which it sucks from its sleeping victim, but the amount of blood lost is trifling in itself and the small quantity of saliva injected is not known to be poisonous to any serious extent: nor is there any evidence that the bed-bug ordinarily transmits the infective organisms of disease. It is, nevertheless, alleged that children from infested houses can be distinguished at school by their unhealthy appearance, but the connexion is naturally difficult to prove. If there is an effect, it is possibly due to irritation and subsequent loss of sleep. At the least, however, the bed-bug is a source of discomfort, unpleasantness, and mental distress.

The whole practical problem has recently been reviewed by a special committee appointed by the Ministry of Health, and a report was issued by the Ministry in 1934. This dealt with the different remedial measures, and made recommendations with regard to the use of those which, in the present stage of knowledge, are considered to be the most effective. The disinfestation of an affected house involves very thorough fumigation with highly poisonous substances, calling for skill and caution. The spread of infestation to other houses may be prevented by careful control, including treatment of furniture during removal. In the construction of new dwellings, too, much can be done in the way of diminishing the harbourage for possible infestation. Educational measures for the instruction of sanitary inspectors and health visitors, and to secure the ready co-operation of tenants, are also desirable.

In their report, the committee stated that they had been struck by the lack of accurate information on which recommendations could be based. As so often proves to be the case in practical

problems of this kind, the important deficiency was in fundamental knowledge of the natural history of the creature against which measures had to be taken. The matter thus becomes a question of further research in the field of medical entomology, and the Council were accordingly approached by the Ministry of Health with a request that they would undertake the promotion of new investigations in this direction. The Council accepted this suggestion, and to assist and advise them in the matter they have appointed the special committee of which the composition is shown on a later page.

The kind of information required relates, in the first place, to the effect of climatic conditions such as heat, cold, and moisture, and also of food supply and starvation, on the bed-bug at different seasons and at all stages of its development. The effect of such conditions on the rate of reproduction is also important; and another point to be determined relates to the period for which the bugs and their eggs can survive in various circumstances, including the extent to which the bugs can subsist on the blood of birds or mice, for instance, when deprived of access to human victims. It is also necessary to know the position and types of harbourage which are most favoured by the bugs under different conditions, the distances which they will travel, and the factors which particularly attract them. More complete knowledge on such points should make it possible to plan methods of control to the best advantage.

In addition, further experimentation is necessary to determine what chemical substances, including both contact insecticides and toxic gases, are most effective, and how these may best be applied in different circumstances. There is also the possibility that deterrents might be found—substances which, although not actively toxic to the bugs, might discourage them from making use of harbourages.

The new committee appointed by the Council met for the first time during the past year. With the clear indications given by their predecessors under the Ministry of Health, they were immediately able to recommend a programme of research to be undertaken with the aid of grants from the Council. Effect has been given to these recommendations, and work has been for some time in active progress. The programme includes, on the one hand, studies of the natural history of the bed-bug with reference to the conditions of its viability: these are being made under the direction of Professor P. A. Buxton, at the London School of Hygiene and Tropical Medicine. On the other hand, experiments with chemical methods for the destruction of the bed-bug and its eggs are being made under the direction of Professor J. W. Munro, at the Imperial College of Science and Technology.

Toxicity of Industrial Solvents

During the past year the Council have acceded to a request of the Home Office by undertaking to promote investigation into the possibility of various volatile substances having injurious effects upon the health of workers using them under industrial conditions. To advise and assist them in this matter the Council have appointed a special committee of persons having scientific knowledge or technical experience relevant to the problem. The whole question is now being explored by this body, the constitution of which is shown on a later page.

The need for action of this kind arises from the increasing use which is being made of volatile organic compounds, chiefly as solvents, in various industrial processes. The number of substances so used is already great, and is constantly receiving additions; and in many cases the possible physiological effects of the substance —even if it is not a new compound—are unknown. The risks involved in using a volatile substance on a large scale or in an enclosed space, if it should happen to possess toxic properties, are of course obvious: the difficulty has lain in lack of knowledge as to what compounds might be suspected to have deleterious action on human beings, a matter which it is by no means easy to determine.

The occurrence of fatalities in a few cases has drawn attention to unknown dangers, but the problem is not confined to the possibility of sudden accidents. It may well be supposed that if the inhalation of organic compounds can quickly result in acute illness or death, it may also be capable, in lower concentrations over longer periods, of causing serious damage to the tissues, possibly leading to permanent or fatal disease. This might possibly occur, although perhaps not to any great extent, without the disease being attributed to the industrial process; and it is, indeed, known that certain gases are insidious in their action on the kidneys or other organs.

There is thus a clear need for research into the possible effects of substances that seem open to suspicion either through having a chemical constitution closely allied to that of compounds already proved to be dangerous, or through complaints of ill health amongst those who constantly use them. The symptoms leading to these complaints may not be clear cut, or definitely referable to disorder in the action of any one system of the body, such as the respiratory or the excretory system.

The history of the 'dope' used in treating the fabric of aeroplane wings may be quoted as an example, as it was some time before the insidious and deadly effects of tetrachlorethane were recognized. This was doubtless due to the conditions of war-time

production, and it is unlikely that such a striking instance could occur under conditions of modern chemical industry. Nowadays, however, the by-products of industrial chemistry are so numerous, and their uses are being so exhaustively explored on the grounds both of economy and of improvement in manufacturing practice, that the extent of the problem has become much wider.

Travelling Fellowships

Frequent reference has been made in these reports to the arrangement under which the Rockefeller Foundation of New York generously entrusted to the Medical Research Council the award of travelling fellowships in medicine to candidates in this country. This is a responsibility which the Council have been glad to fulfil since 1923: the arrangement was then made for three years in the first instance, and it has been periodically renewed. The Council particularly welcomed the scheme because it supplemented in an important direction the provision which they administer from their own resources for the assistance of research work. They were also well placed for the purpose, through the close contacts which their ordinary work gives them with the universities and medical schools from which candidates are drawn.

The object of these fellowships has been to assist and encourage graduates who have had some training in research work in the primary sciences of medicine, or in clinical medicine or surgery, and are likely to profit by a period of work at a university or other chosen centre abroad before taking up positions for higher teaching or research in the United Kingdom. Under this arrangement the Council have been able to award an average of five or six whole-time fellowships each year. In the earlier years the fellowships were tenable only in the United States or Canada, but the scheme was afterwards widened to permit of the fellowships being held at approved centres in European countries where this was considered desirable. The value of the fellowships has usually been between £350 and £450, varying slightly according to the status of the holder and to the currency exchange situation in the country selected for study. In addition, travelling, tuition, research, and other special expenses have been provided up to about £100 to £150 in each case, the larger figure including the cost of trans-atlantic journeys. The general conditions governing the fellowships were contained in regulations which were similar to those made by the Foundation for general use, but which the Council were left free to modify as they thought fit in the particular circumstances.

The scheme is regarded both by the Foundation and by the Council as having been highly successful. In recent years several more fellowships could have been awarded on each occasion, had

the available funds permitted, without sensibly lowering the high standard which keen competition ensured. Evidence of this success can also be found in the subsequent careers of those who have held fellowships under the scheme. An analysis which was made a year ago of the positions occupied by the seventy men and women who had completed their tenure of Rockefeller Fellowships awarded by the Council, showed that twelve were professors in universities, that thirty-six others occupied whole-time positions for higher teaching and research, and that a further sixteen held part-time appointments of the same kind.

In these circumstances it is with great regret that the Council have to record that the arrangement will not be renewed after the end of the present academic year, and that the fellows who are now abroad are the last to be appointed. From what has already been said it will be realized that this decision is not due to any doubts as to the value of the scheme, or to any dissatisfaction with the results which have been achieved. Nor, happily, does it indicate any cessation of the active co-operation between the Foundation and the Council, in various directions, which is facilitated by the cordial personal relations between the officers of the two bodies. It is, in fact, entirely a consequence of a fundamental change in policy of the Foundation which involves abandonment of its whole present system of international fellowships in favour of concentration upon a more restricted programme for the promotion of research. A small number of fellowships will, however, still be awarded directly by the Foundation, but only to candidates in those fields of work to which special attention is now to be given.

The Council are anxiously concerned with the question of filling the gap in the national system of higher medical education which will be caused next year by the withdrawal of the provision for travelling fellowships which has hitherto been made through them by the Rockefeller Foundation. There are, as it happens, very few other fellowships of the kind generally available in this field: such as exist are distributed among different awarding bodies and are tenable under varying conditions. It seems obviously desirable, therefore, not only to obtain provision for a number of new fellowships, but also to arrange for their award as part of a co-ordinated scheme, even if the sources of revenue are different. An arrangement of that kind would certainly make for efficiency and for simplicity in operation. As the Council already possess the necessary administrative machinery and the appropriate contacts with centres of recruitment, as well as all the experience of the past twelve years, they have felt it incumbent upon themselves to attempt the organization of a new scheme. It may be added that they are also the trustees for the award of similar travelling fellowships, restricted to the particular field of tuberculosis,

permanently endowed under a benefaction named in memory of the late Dorothy Temple Cross.

It is with gratification that the Council are able to report that a first step in this direction has already been taken through the generous action of the trustees of the late Viscount Leverhulme, who have entrusted them with a fund of £500 per annum, for five years in the first instance, for the award of one travelling fellowship annually. The Council hope that other fellowships may be similarly provided from different sources; and while it is their intention that all fellowships so provided should be awarded as far as possible on identical terms, and on the basis of a single series of applications, each would be distinguished by the name of the body or person making the financial provision. The amount required for the permanent endowment of a fellowship is approximately £16,000: alternatively, as in the case just mentioned, an income at the rate of £500 per annum will meet the cost of a fellowship during whatever period it is maintained. It is the Council's unhesitating view that potential benefactors have here a great opportunity of performing an important national service.

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(With Farm Laboratories at Mill Hill)

Academic Year 1934–5

PHYSIOLOGY, PHARMACOLOGY, and BIOCHEMISTRY

Staff—

Sir Henry H. Dale, C.B.E., M.D., F.R.S. (*Director of the Institute*).
G. L. Brown, M.B., B.Sc.
J. Argyll Campbell, M.D., D.Sc.
H. W. Dudley, O.B.E., M.Sc., Ph.D., F.R.S.
H. King, D.Sc., F.R.S.
H. P. Marks, B.Sc.
Miss W. I. Strangeways, M.A.
T. A. Webster, F.I.C.

Attached Workers—

R. K. Callow, D.Phil.
W. J. C. Dyke, M.Sc., Ph.D., A.I.C.
G. A. C. Gough, B.Sc., Ph.D., A.I.C.
O. Rosenheim, D.Sc., F.R.S.

Visiting Workers—

Dr. W. Feldberg, Berlin.
Dr. A. Guimarais, Porto.
Dr. E. Lehnartz, Frankfurt a/Main.
Dr. A. M. Pappenheimer, Boston, Mass.
Dr. Marthe Vogt, Berlin.

Physiology of Sex Hormones

A. S. Parkes, Sc.D., F.R.S.

Attached Workers—

Miss R. Deanesly, D.Sc. (Mrs. Parkes).
I. W. Rowlands, M.Sc.

Visiting Workers—

Dr. M. K. McPhail, Montreal.
Dr. J. M. Wolfe, Nashville, Tenn.
Dr. F. G. Young, London.

EXPERIMENTAL PATHOLOGY and BACTERIOLOGY

Staff—

Captain S. R. Douglas, F.R.C.P., F.R.S., late I.M.S. (*Deputy Director of the Institute*).
C. H. Andrewes, M.D.
Clifford Dobell, M.A., F.R.S. (*Protistology*).
G. W. Dunkin, M.R.C.V.S., D.V.H. (*Farm Superintendent*).
W. E. Gye, M.D.
Sir Patrick P. Laidlaw, B.Ch., F.R.C.P., F.R.S.
J. R. Perdrau, M.B.
W. J. Purdy, M.B.
Wilson Smith, M.D.
P. Bruce White, B.Sc.

Attached Workers—

I. N. Asheshov, M.B.
S. E. B. Balfour-Jones, M.R.C.V.S., D.V.S.M.
I. A. Galloway, B.Sc., M.R.C.V.S.
Mrs. A. Pirie.
Charles Todd, O.B.E., M.D., F.R.S.
C. H. Stuart-Harris, M.B.

Visiting Workers—

Dr. U. Friedemann, Berlin.
Dr. W. Levinthal, Berlin.
Dr. J. Nakamura, Fusan, Korea.

MICROSCOPY and PHYSICAL METHODS

J. E. Barnard, F.R.S. (*Hon. Director*).

Staff—

W. J. Elford, B.Sc., Ph.D.
John Smiles, A.R.C.S.

BIOLOGICAL STANDARDS

Staff—

Percival Hartley, C.B.E., M.C., D.Sc. (*Director of Biological Standards*).
G. L. Brown, M.B., B.Sc.
H. P. Marks, B.Sc.
Wilson Smith, M.D.
Miss W. I. Strangeways, M.A.
P. Bruce White, B.Sc.

Attached Worker—

Miss M. Lewellyn Smith, M.Sc.

Visiting Workers—

Dr. L. Cotoni, Paris.
Dr. C. Pak, Shanghai.
Dr. P. Vassiliadis, Alexandria.

II. THE NATIONAL INSTITUTE FOR MEDICAL RESEARCH

The Council record their gratification that Sir Patrick Laidlaw has received the honour of knighthood during the year, in recognition of his distinguished services to medical science.

They also offer their congratulations to Dr. W. E. Gye, on his appointment to succeed Dr. J. A. Murray as Director of the Research Laboratories of the Imperial Cancer Research Fund. Dr. Gye joined the staff at the National Institute just after the war. Although he had previously served under Dr. Murray, he had not in view a renewal of investigations on cancer: his return to that field of activity, shortly afterwards, was incidental to a scheme of research on infections due to viruses which was taken up by the Institute at the Council's request. Thus Dr. Gye began what was planned as a preliminary study of the chicken sarcoma described by Rous, on account of the many analogies between the filterable infective agents, transmitting this and similar tumours, and the acknowledged viruses. This led to a series of researches on malignant tumours, to which Dr. Gye has not ceased to give the whole of his attention, with the direct co-operation in later years of Dr. Purdy. Dr. Andrewes has independently, but in constant touch with Dr. Gye and Dr. Purdy, made studies of transmissible tumours in relation to more general investigations on viruses. It may be said, therefore, that the investigations on malignant tumours with which Dr. Gye and other members of the staff have been concerned over a long period have never lost touch with their origin in a wider scheme of research on viruses; and that, in so doing, they have played a substantial part in a general revival of interest in that body of evidence which suggests an infective basis for the development of malignant tumours in general. It is an open question whether this conception will eventually prevail over those arising from other and apparently unrelated groups of experimental and observational data, or whether some reconciling conception will eventually embrace them all; but it is, in any case, desirable that each important line of investigation should receive its share of skilful and devoted work, and that the significance of the evidence that it yields should be given adequate emphasis. The Council, with his colleagues at the Institute, heartily wish Dr. Gye a continued and increasing success in the sphere of wider responsibility to which he has now been called. They are glad to think that the scheme for transferring the experimental investigations under the Imperial Cancer Research Fund to new laboratories at Mill Hill will centre Dr. Gye's research activities in close relation to the

Council's own Farm Laboratories, where he has worked for many years with such devotion.

With the deepest regret the Council have to record the untimely death of Dr. Harold Ward Dudley, F.R.S., on 3rd October 1935, before the completion of his forty-eighth year. Dr. Dudley joined the research staff of the National Institute in 1919, in advance of its permanent installation in the building at Hampstead, where he was largely responsible for the post-war equipment of the present chemical laboratories. Dr. Dudley had achieved a wide reputation in biochemistry, by a series of important researches showing a consistently high standard of accuracy and finish. His contribution to science, however, and his influence on his contemporaries, extended far beyond the researches which stand on record in his own name. His ready devotion of his knowledge and his time to the interests of other workers won for him the affectionate esteem of his colleagues, not only in the Institute but in a much wider circle of those concerned with biochemistry in all its aspects. Reference has already been made elsewhere to the important research of which he had just brought one stage to completion at the time of his death. It is proper here to recall the part played by his devoted labour in making insulin so early available for general application in this country. Dr. Dudley's death sadly terminates his career at the height of his powers and his influence.

The Council also greatly regret the death of Dr. G. A. C. Gough, a young biochemist of much promise who had been an attached worker at the Institute for several years, engaged particularly in chemical studies of the tubercle bacillus. He died on 8th November 1935, after a long illness.

During the year the Council have bought, from the Governors of Mill Hill School, eight acres of land adjoining the Farm Laboratories. When this property came on the market the Council decided to secure control of it—in an area now threatened by extensive speculative building—both to protect the amenities of the site already held and to keep open the possibility of some expansion if required at a future date. A long lease of the chief portion of this additional ground has since been granted to the Imperial Cancer Research Fund as a site for new laboratories, an arrangement which will bring the main scientific activity of the Fund into the closest proximity with the work done for the Council at their own Farm Laboratories. A small part of the original property was already in the occupation of the Fund: this will now revert to the Council, giving space for the erection of the Walter Fletcher Memorial Laboratory.

Viruses

Viruses and virus-like infective agents have continued to occupy a prominent position in the Institute's programme of research.

Influenza. Substantial progress has been made in the investigation of this virus, especially with regard to its transmission to ferrets and from ferrets to mice. The latter result was briefly mentioned in last year's report, when it was hoped that direct transmission of the virus from human cases to mice might prove to be possible: this hope has not yet been realized. On the other hand, the possibility of obtaining from human cases of epidemic influenza a virus infecting a ferret, and transmissible then to other ferrets and to mice, has been abundantly confirmed—first by Dr. Francis in the Rockefeller Institute, with material obtained from an epidemic of influenza at Porto Rico, and from Philadelphia and Alaska, where local outbreaks have occurred. It appears now to be generally accepted that the virus so obtained is the primary infective agent in true human influenza.

Sir Patrick Laidlaw, Dr. Andrewes, and Dr. Wilson Smith have also had opportunity to confirm their original observations on cases occurring in this country. In a local outbreak of epidemic influenza at Shorncliffe camp, the virus was obtained from six out of eight cases tested. A number of sporadic cases in various London hospitals were also investigated, and from two of these the virus was obtained. On the other hand, no virus was obtained from an epidemic at Woolwich, originally thought to be influenza, but less typical than that at Shorncliffe, although a number of cases were tested. The eight new strains of virus from the Shorncliffe outbreak and elsewhere, and two American strains kindly supplied by Dr. Francis, have all been compared with the original strain, which is still being maintained by animal passage. By cross-immunity tests, and by determining the neutralizing effects of an immune serum, it has not yet been possible to detect any difference between these ten strains of virus, some of British and some of American origin but all obtained from cases diagnosed as typical influenza. Although no success has yet resulted from attempts to inoculate mice directly with the human material, every strain of the virus which has passed by primary inoculation through the ferret has been found to be then infective to mice. This fact has been of great value in the titration of immune sera.

A certain method of producing complete immunity to the experimental infection has not yet been found, either for ferrets or for mice. A significant enhancement of resistance, however, can be obtained in either species by subcutaneous injection either of the living virus, which is not infective when thus applied, or of a formalinized vaccine prepared from it. Such treatment of the ferret appears to give protection against involvement of the lung in a subsequent infection, and causes the appearance of antibodies in the blood; it also reinforces a waning immunity in ferrets which

have been previously infected. In the mouse the active immunity following the injections appears to be more effective, preventing the symptoms which accompany a successful infection, and giving complete protection against the infection itself in a significant proportion of cases.

The last report mentioned that a serum neutralizing the infective activity of the virus had been prepared by immunizing a horse. This has been concentrated by the familiar procedure for separating the effective fraction of an immune serum, and injections of the stronger preparation into infected mice have given results, already published, which suggest that such a serum might have some value in the treatment of influenzal pneumonia.

Data are being collected as to the extent to which immune bodies for the virus are present in the sera of persons of different ages in a normal population. These data may possibly have significance as regards the epidemiology of influenza.

Further attempts to cultivate the virus on the chorio-allantoic membrane of the developing chicken have given evidence of its multiplication under these conditions, as demonstrated by increase of infective action on ferrets and mice. Even more successful has been the use of the method of cultivation in a saline medium containing fragments of surviving tissue from a chicken embryo. Dr. Wilson Smith's evidence of the cultivation of the virus by these two methods is in course of publication. Meanwhile, Dr. Francis and his colleagues in New York have published experiments, made independently, which provide similar convincing evidence of the multiplication of the virus in the medium containing embryonic chicken tissue.

Dr. Stuart-Harris, attached to the British Post-graduate Medical School at Hammersmith, with a Royce Fellowship for research on the common cold and influenza, has recently become associated with the group working on influenza at the Institute, to acquire experience of the experimental methods. It is hoped that when the opportunity occurs, Dr. Stuart-Harris will be able to give regular and effective clinical co-operation in the further development of these investigations.

Psittacosis. Dr. Levinthal, continuing his study of this infection, has proved the possibility of successfully immunizing mice against it by repeated injections of rich emulsions of the virus, inactivated either by treatment with weak formaldehyde solution or by exposure to light in the presence of methylene blue. After four or five injections of such material, the mice resisted the infective action of as much as ten million normally fatal doses of the living virus.

Vesicular stomatitis. Mention was made last year of this virus infection and its differentiation from foot-and-mouth disease, with

which it was at one time confused. Further joint work by Dr. Elford and Mr. Galloway has confirmed the possibility of differentiating the two viruses by the size of their infective units, those of vesicular stomatitis having about eight times the diameter of those of foot-and-mouth disease; they can also be distinguished by the readiness with which the former virus can be cultivated on the membranes of the developing chicken embryo. By a combination of these methods it has now been found possible to separate either virus from any mixture of the two, in any proportions. Confirmation has also been obtained of the results of other workers concerning the differential sensitiveness of the two viruses to varying hydrogen-ion concentrations. The possibility of separating agents which, but a few years ago, seemed so inaccessible to recognition and description by any property except their power of conveying infection, well illustrates the progress which is being made, by the work of many laboratories, in creating the new methods required for the study of viruses. Reference is made elsewhere to the prospect of differentiating the same two viruses by ultramicroscopical examination.

Louping Ill. Dr. Perdrau has continued, with Mr. Galloway, his studies of the sheep disease, louping ill, as it appears in the artificially infected monkey: the results are in course of publication. One curious point, observed both in monkeys and in sheep, is that with intracerebral inoculation the virus early appears in the circulating blood, as it does with natural transfer to the sheep by the bite of the tick. When it is administered to the monkey by instillation into the nasal passages, the virus seems from the first to be localized strictly to the central nervous system, and never to appear in the blood at all.

In relation to this work Dr. Perdrau had the opportunity, through the kindness of Prof. J. B. Cleland, of examining material from monkeys to which the so-called 'X disease' had been transmitted in serial infection. This was an infective disease of the central nervous system of man, which occurred in several outbreaks between 1917 and 1926 among the sheep-farming community of Australia. Dr. Perdrau finds that the disease, as transmitted to the monkey, was due to a meningo-myelo-encephalitis, with a widespread destruction of the Purkinje cells of the cerebellar cortex. The pathological picture closely resembles that produced in the monkey by louping ill, and the two diseases are certainly closely related. The lesions found in the brains of fatal human cases of 'X disease' were rather different; on the other hand, no material from a fatal case of known louping ill in man is available for comparison. It is clear in any event, that the study of louping ill has an important bearing on human as well as on veterinary medicine. The problem of its relation to the Australian

'X disease' is also being investigated in Melbourne by Dr. F. M. Burnet, who earlier worked as a visitor in the Institute.

Artificial cultivation of viruses. Mention is made elsewhere of the success now attained in attempts to cultivate the influenza virus on the embryonic membrane of the chick, and in the medium containing chopped chick-embryo. This latter method appears to have a wide application. Dr. Levinthal, who had previously used it with success for the virus of psittacosis, has now employed it—following a previous demonstration by Downie and McGaughey—for the cultivation of the virus of the mouse disease, discovered some years ago at the Institute, and known as ectromelia. In this case also it has been possible, by special staining methods, to follow the multiplication of the minute virus bodies in the protoplasm of the surviving embryo cells. As in the tissues of the living mouse, they show two different kinds of development in the chicken-embryo cells; in some, as in the epidermal cells of the mouse, the multiplying particles become embedded in a faintly staining, uniform matrix, to form typical cytoplasmic inclusions; while in others, as in the liver cells of the mouse, the multiplying particles form colonies free in the protoplasm, without any specialized matrix. In similar experiments the multiplication of the virus of vaccinia has been studied, in a long series of subcultures, both by microscopical demonstration of the increase of the elementary bodies, as free intra-cellular colonies, and by measurement of the parallel multiplication of infectivity. In the case of the virus of louping ill, the infective units are too small for recognition by microscopical methods yet available; but, on the lines of earlier experiments by Rivers of the Rockefeller Institute, Dr. Levinthal has now carried this virus, as recognized and measured by its infectivity for mice, through a hundred and forty consecutive subcultures in the medium containing fragments of chicken embryo, without appreciable loss of its infective potency. One of the intermediate subcultures was tested on sheep by Dr. W. S. Gordon of Edinburgh, and found to be still fully virulent for this original host species.

Photodynamic inactivation. Reference has been made in earlier reports to the experiments of Dr. Perdrau and Dr. Todd upon the inactivation of different viruses and bacteriophages by the action of light, in the presence of dyes such as methylene blue and acriflavine. Experiments on the immunizing properties of preparations of different neurotropic viruses, thus inactivated, have been continued by these investigators and by Mr. Galloway. In last year's report it was stated that rabbits could be given a substantial degree of immunity against the 'fixed' virus of rabies by previous inoculation with the photodynamically inactivated virus. It has now been found that such inoculation protects them also against the 'street' virus, obtained directly from a rabid dog. On the other

hand, no perceptible protection against the virus of pseudorabies (Aujeszky's disease) is conferred on rabbits, by injection of this virus inactivated by photodynamic treatment. In that regard, however, it is proper to state that no method at all of protective inoculation against infection by this virus has yet proved effective. With the so-called B virus of Sabin, the results of attempts to obtain protection by this method are more promising; and it is of interest that immunization against the virus of herpes has been found to give a substantial measure of protection against the B virus.

A study of the photodynamic inactivation of a number of bacteriophages for the cholera vibrio showed a range of susceptibility to the treatment similar to that observed among bacteriophages in general. Thus, the more resistant of the cholera bacteriophages required an exposure thirty times as long for inactivation as that which sufficed for the most susceptible. A similar range of sensitiveness to the photodynamic treatment was found among different bacteria. For example, the cholera vibrio was killed in fifteen minutes, by a treatment which had to be continued for four to five hours to kill *B. pyocyaneus*. The most surprising discovery, however, was that of the relative ease with which certain bacterial spores are killed by the photodynamic action. Even anthrax spores, so highly resistant to heat and to various chemical disinfectants, and so notoriously tenacious of their viability under natural conditions, were killed by exposure for one hour to light from a 300 C.P. Osram lamp, at a distance of 13 cm., in the presence of a one in fifty thousand solution of methylene blue.

Measurement of dimensions of virus units. In several earlier reports reference has been made to the special technique of ultrafiltration through graded membranes, developed by Dr. Elford, and to its application to the measurement of the sizes of the infective units of different viruses, bacteriophages, and tumour filtrates. The size of the particles in any particular case was calculated from the average diameter of the pores of a filter which just retained them, using a formula based partly on empirical data obtained with particles of known dimensions and partly on theoretical considerations. It was important to have further experimental verification of this procedure, and careful determinations have now been made on two large-moleculed proteins, obtainable in a state of relatively high purity—haemocyanin and edestin. The results obtained by filtration for haemocyanin gave for its molecules a calculated diameter of 18 to 28 millimicrons, with a mean of 23, a millimicron being a millionth of a millimetre; for edestin the results indicated a diameter of 6 to 9 millimicrons, with a mean of 7·5. The results already recorded by Svedberg, with his method of ultracentrifugation, were, for haemocyanin 24 and for edestin

8 millimicrons. The good correspondence of these determinations by entirely different methods gives an added confidence in the measurement, by filtration, of the size of virus units of a similar order of magnitude. It seemed desirable, however, to have an alternative, centrifugal method which, unlike the method of Svedberg, could be directly applied to the measurement of virus units. Dr. Elford has accordingly devised, for use with an ordinary centrifuge capable of 15,000 revolutions a minute, a new type of inverted fluid container which enables the rate at which a fluid is freed from infective particles to be determined, without danger of re-suspension during deceleration of the rotor. Determinations of the particle sizes of vaccinia and Rous sarcoma filtrate have thus been made with Dr. Andrewes, as well as of several bacteriophages and, as a control, of haemocyanin. The results again show a good correspondence with those obtained by filtration. Determinations, by both methods, of the size of the units of the influenza virus are in progress.

Microscopy and Optical Methods

During the earlier part of the period since the report for 1932–3, the attention of Mr. Barnard and his immediate co-workers was largely directed to the further improvement of microscopical methods. These had already given results of great significance in their hands, but it was necessary to explore the possibilities of increasing the ease and rapidity of working by mechanical improvements, and of reaching a yet higher power of resolution by means of a lens system working at a shorter ultra-violet wave-length than that which had hitherto been available. On the mechanical side, an important advance was made by the design and construction of a new form of microscope stand, with a complete interchangeability of parts, enabling any material located by observation with visible light to be transferred at once to an exactly corresponding position on the ultraviolet microscope for photography. It became, for the first time, possible for one observer to be searching material by visual microscopy for appropriate fields, while another was photographing with the ultra-microscope those which had already been selected as suitable. This more than doubled the efficiency of working. On the optical side, a great advance was made possible by the delivery of a new quartz objective, constructed by Zeiss of Jena to Mr. Barnard's specification, for use with a wave-length of 257 millimicrons. The use of this shorter wave-length enables the photography of dark-ground images, hitherto obtained with a wave-length of 275 millimicrons, to be extended with success to yet smaller particles. It has the further great advantage that virus bodies which were too transparent to waves of 275 millimicrons to be photographed at

that wave-length, except by dark ground illumination, are sufficiently opaque to the shorter waves of 257 millimicrons to give real, critical images with the transmitted rays.

These advances in optical technique have accelerated progress in the study of viruses which have hitherto been beyond the reach of accurate microscopical study. Work on the virus of fowl plague, on which Mr. Barnard has been working for some years with Dr. Todd, now gives promise of definite results. This virus presents difficulties on account of its wide distribution through all the tissues, and it has been necessary to gain experience which enables a few virus particles to be recognized, by their characteristic size and refractility, in the protoplasm of a cell such as a leucocyte. Clear photographs of them have now been obtained, however, and measurement indicates a diameter of not more than 75 millimicrons. This figure, when allowance is made for the fact that the size measured by a graded filter is that of the smallest units, shows good correspondence with that of 65 millimicrons previously obtained by the filtration method.

Investigations are also in progress as to the possibility of recognizing and photographing the infective units of vesicular stomatitis and of foot-and-mouth disease. As already mentioned, these two viruses show great similarity of infective action, the cells infected being those of the epidermis of the foot or the mucous membrane of the mouth in both cases, and the lesions produced being closely similar. It is thus possible to compare not only the similar vesicular fluids produced by infection with the two viruses, but also the closely similar changes produced in the epidermal cells. Since these two viruses, so closely similar in their pathogenic action, were known from filtration data to differ widely with regard to the size of their infective units, there was ground for hope that a comparison of similar cells, infected by each virus, would enable the infective units to be recognized and photographed in the protoplasm. There is reason to believe that this has been done; and, when measurements have been worked out, comparison with the filtration measurements of extracellular virus particles should be of great interest. The study of corneal cells infected with the virus of herpes, which Mr. Barnard has had in hand for some years, also seems likely to lead to a definite conclusion, now that the optical system working at a shorter wave-length is available.

An additional ultraviolet microscope has been fitted up for the particular purpose of an investigation, in which Mr. Smiles has co-operated with Mr. Wrighton of Woolwich Arsenal, on the surface structure of metals and other opaque substances, as revealed by an incident beam of ultra-violet rays. This investigation has

not only yielded interesting results concerning the structure of metals, but it has led to an application of the same method in a study of the structure of the enamel of the teeth. On behalf of a Committee of the Royal Microscopical Society, Mr. Smiles has examined and reported on the absorption spectra of some of the stains widely used in microscopy, with a view to their standardization. He has further investigated the grading of gamboge emulsions in terms of the size of their particles, with a view to their use as testing standards in microscopical work.

Transmissible Tumours

Dr. Gye and Dr. Purdy have continued their work on the production in fowls of sarcomata in the neighbourhood of injections into the tissues of solutions of tar or of dibenzanthracene. Like other investigators, they have found that tumours appeared in a large proportion of the birds so treated. These, however, have proved in nearly all cases to be very difficult to propagate further in other fowls, even by cell-grafting; and it has not yet been possible in any case, not even in that of one tumour which grew readily when grafted, to transmit these tumours by a cell-free filtrate. On this point, therefore, Dr. Gye and Dr. Purdy have not yet been able to confirm the experience of some other workers. In the course of these studies three fowls have come under observation having multiple epitheliomatous nodules in the integument; but it has not been possible to propagate any of these by artificial transfer.

Dr. Gye also took part with Professor J. C. G. Ledingham of the Lister Institute in an investigation which resulted in the demonstration of the deposition of the active agent of the Rous chicken sarcoma by high-speed centrifugation of filtrates. The agent when so deposited was in the form of elementary bodies of considerably smaller size than those of vaccinia, and pure suspensions of them were agglutinated in a number of instances by the sera of tumour-bearing fowls.

The infective papilloma discovered by Dr. Shope of the Rockefeller Institute at Princeton, in a wild cotton-tail rabbit, has been further studied by Dr. Gye and Dr. Purdy, and also by Dr. Andrewes. This can be transmitted in the species of its origin by cell-free filtrates; and Dr. Shope has found one strain that can be propagated by serial transmission in the domesticated hutch-rabbit. Samples of this virus, received from Dr. Shope, have readily caused primary papillomata in domestic rabbits at the National Institute; but from these the tumour has not yet been further propagated, on any of the varieties hitherto tried, with a sufficient regularity for experimental study of the conditions of its propagation and the nature of the virus-like transmitter. In

some of the domestic rabbits, however, to which the papilloma has been successfully transferred, it has subsequently acquired the characters of a fully malignant epithelioma, in confirmation of the experience of Rous and Beard.

The work of Dr. Andrewes on the transmissible fibroma also discovered in American rabbits by Dr. Shope is being published in collaboration with the latter.

Bacteria and Bacterial Chemistry

Cholera Vibrios and related organisms. Mr. Bruce White, with various other workers, has made further studies of the vibrios of cholera, and the related vibrios, which present an important practical problem of differential diagnosis. In consultation with Dr. A. D. Gardner, of the Standards Laboratory at Oxford, he has confirmed conclusions regarding the general lines of sub-division in this group, and with Dr. Gardner has confirmed the findings of Japanese authors as to the existence of serological sub-types of the true *V. cholerae* itself. This agreement gives hope of a much needed basis of discrimination between the pathogenic and non-pathogenic vibrios. By the use of special methods, Mr. Bruce White has been able to isolate 'rough' (R) variants of many strains of the cholera vibrio, and of other groups of vibrios defined by Dr. Gardner and himself. He found that the R forms from all strains of the true *V. cholerae* were identical, whatever serological differences they had shown in the 'smooth' (S) condition. A wider grouping in the difficult series of the vibrios thus became possible, and will probably have a diagnostic importance. In several cases Mr. Bruce White has also obtained strains of the even more unnatural and generalized type which, in his study of the Salmonellas, he termed the 'ρ form'; and, in the case of the vibrios again, these degraded strains have lost even the wider specificity in agglutinating reactions of the R types, so that an agglutinating serum prepared from the ρ form of any vibrio reacts with the ρ forms from all others.

Apart from such degraded variants, showing loss of an original specific character, no evidence has been obtained of change of any vibrio into one of a different serological type, whether as the result of animal passage, of treatment with bacteriophages or immune sera, or of any of the various procedures to which a large number of vibrios of different types have been exposed in studies now extending over two years.

The vibrios from El Tor, commonly known by the name of this place of their discovery and generally supposed to be non-pathogenic, present a well-known problem in the diagnosis of cholera infection. They are serologically indistinguishable from the true *V. cholerae*, from which they can be differentiated only by their power

to cause haemolysis of the red corpuscles of sheep's blood. A visit to the Institute by Dr. Vassiliadis, of the Egyptian Quarantine Service, enabled him to demonstrate with Mr. Bruce White the correctness of a statement of Doorenbos, that when a culture of true *V. cholerae* has been exposed to the action of a potent bacteriophage, the survivors are found, on further cultivation, to have acquired some degree of this haemolytic action. Mr. Bruce White finds that this effect is especially well demonstrated with a particular bacteriophage, to which a natural 'El Tor' strain is highly resistant.

Study has been continued of the preparation and serological properties of a specific carbohydrate antigen, and of an alcohol-soluble protein, from cholera vibrios. A further practical outcome of these various studies has been the preparation, with Dr. Gardner, of stocks of stable antigens; with these it should be possible for any laboratory to prepare more satisfactorily specific agglutinating sera for *V. cholerae* than those which have hitherto been available. It was found that for accurate diagnostic tests the best agglutinating serum was produced by the use of a heated culture of the vibrio. Quantities of such heated antigen have now been prepared from two sub-types of the cholera vibrio, and transmitted by arrangement to the Research Laboratory of the Indian Government at Kasauli, where, under the supervision of Colonel J. Taylor, agglutinating sera will be prepared and their diagnostic value given a wide trial under practical conditions in India. The Office International d'Hygiène Publique and the Health Committee of the League of Nations are being kept in touch with an investigation which has a special interest in connexion with international problems of sanitary administration.

Accessory factor for bacterial growth. Mention was made last year of an investigation by Dr. A. M. Pappenheimer, working with the advice of the late Dr. Dudley and the direct co-operation of Dr. Fildes and Mr. Knight (p. 142), on the nature of a substance which must be added in traces to an otherwise efficient 'synthetic' medium to enable it to maintain the growth of certain bacteria, of which *B. sporogenes* is a type. Dr. Pappenheimer had separated the substance in sufficient quantity to show that it was a non-nitrogenous organic acid, and had prepared from it a methyl ester which distilled at a constant temperature and appeared to be homogeneous. It was hoped that larger supplies of material would enable the isolation and identification of the substance to be completed. Through the generous co-operation of Dr. A. Girard, of Paris, a large quantity of material rich in the specific factor was obtained. Sufficient of the methyl ester was thus obtained for further purification by distillation. Analysis, determination of the molecular weight, and titration results with the free acid, all gave

consistent results for the composition of the acid; but efforts to prepare crystalline derivatives have failed, and the evidence that a single chemical substance is responsible for the growth-promoting action must be regarded as still incomplete.

Johne's Bacillus. In several recent reports mention has been made of the preparation, by Mr. Dunkin, of a 'johnin' from Johne's bacillus, corresponding to tuberculin from the tubercle bacillus, and intended for a similar diagnostic use. This reagent has been steadily improved, by studies extending over a period of years, so that it has become at once more potent and more specific as the organism has been trained to grow with increasing luxuriance on artificial media, and as media consisting largely of pure materials have come into use. During the past year, the practical application of this reagent for the diagnosis of Johne's disease has acquired great importance, through the decision of the Government of the Commonwealth of Australia to prohibit, after July 1935, the importation of cattle which have not been tested with johnin and thereby proved to be free from the disease. In these circumstances, Mr. Dunkin has co-operated with the veterinary officers of the Ministry of Agriculture and Fisheries by providing the johnin required for testing cattle in this country, before their shipment to Australia, and by advising as to the instructions to be given to the veterinary surgeons chosen by the Ministry to apply the test. Johne's disease has been recorded in animals other than bovines, and a condition in sheep showing certain characteristics resembling this disease has been investigated by Mr. Dunkin and Mr. Balfour-Jones. An acid-fast organism has been isolated from the intestinal mucosa, and after a remarkably long incubation period—seven months—artificial cultivation has now been effected and growth has been observed on sub-cultures.

Protistology

Mr. Dobell has continued his investigations of the protozoa found in the intestines of man and of monkeys. The study of the life-history of *Entamoeba coli*, its development in artificial culture, and its transmissibility between various monkeys and man, is now approaching completion. Improved methods of cultivation have shown that cysts of this *Entamoeba* have a much longer survival outside the body, at low temperatures, than had hitherto been supposed; and, under similar conditions, the same has been found to be true for the cysts of the pathogenic *E. histolytica*. The discovery that the cysts of the latter may remain viable for at least a hundred days, at 1° to 2° C., has important bearings on the distribution and spread of amoebic dysentery.

Mr. Dobell has also completed for publication a report on his studies, extending over ten years, of the life-histories of the

flagellates *Enteromonas* and *Embadomonas* found in the intestines of man and of three species of monkey of the genus *Macacus*. The report includes an account of experiments on transmission between these different host species.

Individual specificity

In earlier reports reference has been made to Dr. Todd's investigations of the individual specificity exhibited by the red corpuscles of the common fowl, by the formation of 'isoagglutinins' when the blood of one fowl was injected into another. It was shown that the corpuscles of some members of the offspring of one pair of birds might be so closely similar as to be difficult to distinguish by this test. By brother-sister mating, starting with two birds selected as having such community of antigenic properties in their corpuscles, a strain of birds has now been obtained of which every member, as far as the third generation, shows this close similarity in the reaction of its corpuscles to isoagglutinating sera. It has been shown that sex difference, in such a strain, entails no difference of antigenic make-up in the corpuscles. The strain is at present being maintained in view of its potential value in genetic investigations.

Chemistry of Sterols and Related Substances

In previous years mention has been made of the rapid development in the chemical knowledge of the group of related compounds which includes the sterols, bile acids, and sex hormones, following the introduction by Dr. Rosenheim and Dr. King of a new conception of the fundamental plan of the sterol molecule. Instances of the remarkable and growing rate of progress in this field can be found in other sections of this report. Knowledge, however, is still completely lacking as to the stages by which the animal body brings about such changes as that from the cholesterol of the tissues and bile to the coprosterol characteristic of the faeces; or as to the process of transformation from cholesterol to bile acids, on the one hand, or to the sex hormones, on the other.

Dr. Rosenheim, with Mr. Webster, is now investigating the stages between cholesterol and coprosterol. It was first established that mild oxidation of cholesterol yielded a well-characterized substance, of which the structure was established as a cholestene glycol. This, by loss of water, is easily converted into cholestenone, which on reduction gives coprosterol. 'Definite evidence has already been obtained that cholestene glycol and cholestenone, administered to rats, undergoes reduction and is excreted as coprosterol. Work is in progress to ascertain whether this reduction can be effected *in vitro* by anaerobic bacteria. The possibility that this conversion of cholesterol to cholestenone may

lead under certain conditions to bile acids or to androsterone is also being investigated.

Pharmacology of Ergot, &c.

A historical account of work in this field has already been given in the Introduction, but the recent investigations at the Institute may be more particularly mentioned. Reference was made in the last report to the collaboration between the late Dr. H. W. Dudley and Dr. J. Chassar Moir, and the prospect that it might soon lead to the isolation of a then unknown active principle responsible for the prompt activity of the human puerperal uterus induced by oral administration of ergot extracts. This object had, in fact, already been attained by the time the report was in the press, and a preliminary description of the new alkaloid, ergometrine, was published by Dr. Dudley and Dr. Moir on 16th March 1935. The success had a sad sequel in the early death of Dr. Dudley in October, on the day on which his first complete description of the chemical and physical properties of ergometrine was published.

This new development in the pharmacology of ergot, which already had such a long and varied history, has excited a widespread interest. From no less than three other laboratories, two in the United States, and one in Switzerland, descriptions appeared within the next few months of independent success in isolating the new alkaloid. In two cases the search had been stimulated by Dr. Moir's description of his graphic method of recording uterine contractions, and of the unknown principle in ergot which it had revealed; in the third, the alkaloid had apparently been found by purely chemical investigation, interest in its properties being stimulated by the demonstration of its practical significance by Dr. Dudley and Dr. Moir. Each of these other investigators has given a different name to an alkaloid which, in every case, is almost certainly identical with ergometrine. When once this identity has been certainly established, it is obviously important that confusion in the literature should be avoided by agreement on one common name for scientific use.

From the different centres which had thus become interested in this alkaloid, preliminary accounts of the main features of its pharmacological action were soon published. Dr. Brown and Sir Henry Dale have now published a fuller account of the pharmacology of ergometrine, simultaneously with Dr. Dudley's complete account of its chemistry. There is general agreement among those who have examined it that ergometrine has practically none of the characteristic 'sympathicolytic' action of the previously known ergot alkaloids. On the uterus of most of the species examined, in the non-pregnant condition, its action differs little from that of

the earlier known alkaloids of the ergotoxine group; but from that of the rabbit, with a predominantly motor sympathetic innervation, it elicits a characteristically prompt and vigorous motor response. The puerperal uterus of any species, normally quiescent except for occasional small contractions, is immediately thrown by ergometrine into a powerful and persistent rhythmic activity. In the familiar cock's comb test for the action of ergot, ergometrine produces the characteristic pallor and cyanosis of the comb as definitely as, and more rapidly than, the earlier known alkaloids; and, unlike these, it produces the effect almost as rapidly with oral as with intramuscular administration. This effect of ergometrine, unlike that of the other alkaloids, is nevertheless evanescent; it has disappeared by the following day, and even with repeated administration of large doses it does not terminate in the gangrene which the other alkaloids so characteristically produce.

In general, it may be said that the most characteristic effect of ergometrine is its stimulation of the activity of the uterus, especially in the puerperal condition; that this activity is much more rapid in onset and more rhythmic in character than that produced by the earlier known alkaloids; and that the characteristic toxic effects of these other alkaloids, in paralysing sympathetic actions and causing gangrene, are not produced by ergometrine. Thus, ergometrine appears to give in uncomplicated form the action of ergot required for its most familiar applications in obstetrics and gynaecology. On the other hand, it is unlikely to have any value for those therapeutic applications, in which ergot alkaloids are used for their 'sympathicolytic' action. It seems safe to predict that, with the discovery of ergometrine, the way is open for the therapeutic use of ergot to emerge from the stage of empiricism, and to find a rational basis in exact pharmacology.

Curare alkaloids. Dr. King's work on tubocurarine, the preparation of which in crystalline form was mentioned last year, has now progressed to a stage at which it is possible to assign a probable structure to the molecule of this alkaloid, and to indicate its relationship to that of *d*-berberine, an alkaloid of *Chondrodendron tomentosum.*

Arsphenamine derivatives. Dr. King and Dr. Dyke have now completed their investigation of the structure of sulpharsphenamine, showing that it has three substituent methylene-sulphurous acid groups, all attached to the amino-nitrogens of the parent arsphenamine molecule. With Miss Strangeways, experiments are now in progress to test the effects of varying the proportion of the substituent methylene-sulphoxylic and methylene-sulphurous acid groupings on the toxicity and the therapeutic potency of the derivatives thus obtained.

Chemical transmission of nervous effects

A detailed account was given last year of the rapid increase of evidence as to the chemical transmission of the effects of nerve impulses: this had long been available for the peripheral endings of autonomic nerves, but was extending to the synapses in autonomic ganglia, and even to the endings of motor nerve-fibres in voluntary muscle. This new evidence regarding the function of acetylcholine, as the transmitter of nervous effects across ganglionic synapses and from motor nerve to voluntary muscle, continues to accumulate. With Dr. Marthe Vogt, the evidence obtained by Sir Henry Dale and Dr. Feldberg for transmission of excitation to voluntary muscle by such a mechanism has been brought to the stage at which detailed publication can be made. A number of experiments were required to eliminate various possible sources of the acetylcholine which appears in a fluid perfusing a voluntary muscle when the motor nerve is stimulated. Fibres of other kinds than voluntary motor fibres had to be excluded, and it had to be shown that the effect was not due to mechanical stimulation of autonomic nerve endings in other tissues of the muscle, or to the squeezing of interstitial fluids into the circulation by the mechanical effects of the muscular contractions. It could in fact be shown that, on the one hand, no acetylcholine is liberated when a denervated muscle responds to direct stimulation of its fibres, and that, on the other hand, stimulation of the motor nerve-fibres to a muscle paralysed by curare causes an output of acetylcholine quite similar to that observed when the unpoisoned muscle contracts in response to motor nerve impulses.

Dr. Brown and Dr. Feldberg have completed a long investigation, now in course of publication, on the effects of potassium ions injected into the fluid with which a ganglion is being artificially perfused. In small doses the potassium ions reinforce the effects of submaximal preganglionic stimuli, or submaximal doses of acetylcholine applied to the ganglion through the circulation. Larger doses of potassium ions act as a direct stimulus to the ganglion cells, and at the same time cause a liberation of acetylcholine into the perfusion fluid. If, according to an already familiar conception, the impulse travelling along a nerve-fibre involves a mobilization of potassium ions, the suggestion arises that this process, on reaching the preganglionic ending, causes liberation of acetylcholine, by which the excitation is transmitted across the synapse to the ganglion cell. That potassium ions are not alone concerned in transmission across the synaptic gap seems to be clearly indicated by a recent experiment, in which Dr. Brown and Dr. Feldberg found the effects of preganglionic impulses and of acetylcholine on the ganglion cells to be simultaneously annulled

by a concentration of curarine, which left them fully responsive to potassium ions. The function of potassium in connexion with the transmission of nervous effects has been further explored in experiments of different types. Dr. Vogt has estimated the loss of potassium from a ganglion subjected to prolonged preganglionic stimulation; and Dr. Lehnartz, of Frankfurt, is repeating the early observations of Howell and Duke on the liberation of potassium in the heart by stimulation of the vagus nerve, in order to obtain further light on the relation of this phenomenon to the transmission of the inhibitor effect of vagus impulses to the heart muscle.

Salivary secretion. The fact, observed some years ago by Demoor and Guimarais, that injection of saliva into the arteries of a salivary gland causes secretion of saliva by the gland cells, had led to the suggestion that acetylcholine passes into the saliva. Dr. Feldberg and Professor Guimarais, who has worked as a guest in the Institute during the year, have made a careful examination of the nature of the depressor and secretagogue substances found in saliva secreted in response to various stimuli, and have proved that they are not acetylcholine, nor substances having any apparent relation to it. On the other hand, Professor Guimarais has extended the original observation to the pancreas, and to the parotid as well as the submaxillary gland. The pancreatic juice, injected into the pancreatic arteries, causes renewed pancreatic secretion; but neither will the pancreatic juice cause secretion by the submaxillary gland, nor will saliva cause secretion by the pancreas. Parotid and submaxillary salivas excite secretion by either salivary gland. In no case, however, has the secretagogue substance, found in the secretion, any relation to the transmission of the effects of secretory nerves.

Sex Hormones

Male hormone. The substance known as androsterone, a form of the male hormone, can be produced artificially from cholesterol by a process due to Ruzicka. Dr. Callow has repeated this preparation with certain modifications, and comparisons have been made between the physiological activities of androsterone and of extracts containing the male hormone from various natural sources, certain differences being detected. Dr. R. Deanesly, Dr. Parkes, and Dr. Greenwood (of Edinburgh) have been concerned with various aspects of the general investigation. Other artificial compounds made by Professor Ruzicka were tested by Dr. Deanesly, but none was equal in activity to the 'testosterone' obtained from the testis by Laqueur. As elsewhere mentioned, testosterone has now also been made artificially.

Occurrence of male and female hormones. The studies by Dr. Parkes and his co-workers seem likely to provide the explanation

of certain effects of the gonads, in producing secondary sexual characters in birds, which seemed to cut across the broad distinction between male and female. Although the male hormone and the secondary characters produced by its action are in the main characteristic of the male, as those produced by oestrone are characteristic of the female, this distinction does not strictly hold in either case. Thus, certain plumage effects in the cock, known to be dependent on the presence of the testis, are not produced in capons by androsterone, but are produced by oestrone. Their natural occurrence can thus be attributed only to the production by the testis of an oestrogenic as well as a purely male hormone; and this supposition is in keeping with the known production and excretion of oestrone by the stallion. Similarly growth of the comb in the hen, dependent on the ovary, is not produced by oestrone, but is produced by androsterone. It is therefore reasonable to suppose that the hypertrophy of the comb seen in the laying hen is due to the increased production by the ovary of a male hormone, just as there is evidence of the occurrence of some male hormone in the urine of women. From various directions evidence is thus accumulating to indicate that the sex distinction is due rather to a preponderance than to an exclusive production of male or female hormones, as the case may be.

Effects of sex hormones on male monkeys. The view that the testis produces both male and oestrogenic hormones, of which the former may lose its preponderance as maturity gives way to senescence, seems likely to have an important bearing on the late degenerative enlargement of the prostate in man. A number of observers have described the enlargement of the prostate in the rat caused by injections of oestrone. In order to study the action of both male and female hormones in a species having a prostate more definitely homologous with that of man, Dr. Parkes and Dr. Zuckerman (working in the Department of Anatomy at Oxford) have made a series of studies on young male monkeys. Administration of oestrone to such animals causes a pronounced fibromuscular hypertrophy of the prostate and seminal vesicles, but the only part of the organ showing epithelial changes is the *uterus masculinus*. If this, as in the rhesus and most other monkeys, is of the vaginal type, with a stratified epithelium, the effect of oestrone is to produce cornification. In certain monkeys, as in man, it is of the glandular, 'uterine' type, and in the one of these species hitherto available for test oestrone causes glandular hypertrophy. On the view that enlargement of the prostate in man is at least partly due to the glandular hypertrophy of the *uterus masculinus* embedded in the middle lobe, it is reasonable to associate the condition with a growing predominance of an oestrogenic hormone from the senescent testes. It has also been shown

that the effect of oestrone on the *uterus masculinus* of the male rhesus monkey can be opposed by simultaneous administration of a male hormone. Progesterone causes no resolution, in this case, of the hypertrophy due to oestrone; it remains to be seen whether either progesterone or male hormone will do so in a species in which the *uterus masculinus* is, as in man, of glandular type.

Assay of hormones from the anterior pituitary lobe

Such evidence as has been produced concerning the chemical nature of the numerous hormones produced by the pituitary gland, gives no hope of the early isolation of any of them in pure form, and no definite steps have yet been taken towards the adoption of standard preparations or units for any of the specified types of activity. In the case of most of these hormones of the anterior pituitary lobe, the effect is largely indirect, the primary action being on another endocrine organ which is stimulated to growth or activity by the pituitary hormone. Dr. Parkes and his co-workers have further investigated the possibility of finding a quantitative basis for estimating the gonadotropic, lactogenic, and thyreotropic properties of anterior pituitary preparations.

Dr. Deanesly has prepared standardization curves for gonadotropic activity, using the increase in weight of the ovary of the immature rat as the index of activity. She has thus been able to give quantitative expression to the difference, already recognized, between the strictly limited response of the ovary to preparations from urine of pregnancy, and its far wider range of reaction to the hormone obtained from the pituitary body itself. On similar lines an examination is being made of the gonadotropic action of extracts from the suprarenal cortex. The association of virilism with adrenal hyperplasia, and its possible connexion with the now recognized production of male hormone by the ovary, is one of the points which suggests itself for investigation.

Mr. Rowlands has constructed a standardization curve for the strength of anterior pituitary preparations in 'prolactin', using the reaction of the crop-gland of young pigeons as a specific index of this activity. Mention was made in an earlier report of the use of the increase in weight of the thyroid gland of the immature guinea-pig, as an index of the thyreotropic activity of anterior pituitary preparations. The method has now been used in determining the relative activities of the pituitary bodies from different species, as regards this thyreotropic action. The method has also enabled Dr. Parkes and his co-workers to confirm the observation of Collip and Anderson that the serum of an animal treated with repeated injections of a preparation rich in the thyreotropic hormone acquires an activity antagonistic to the action of this hormone. Serum from a rabbit so treated was found to prevent the

usual effect of thyreotropic pituitary extract on the thyroid gland of an immature guinea-pig. On the other hand, if this serum is injected into a Leghorn fowl, no changes are produced in the plumage such as follow removal of either the thyroid or the pituitary gland: the same is true if the fowl itself is treated with a course of injections of the thyreotropic extract to induce an antagonistic activity.

Prolonged inhalation of tar dust, &c.

In continuation of his experiments on the effect of dust from tarred roads in causing cancer of the skin in mice exposed to it, and a greatly increased incidence of primary adenoma of the lung, Dr. Campbell is now making a control experiment in which the same dust has been used after tar and oily matter have been removed from it by thorough extraction with benzene. The experiment, which to make it comparable will involve daily exposure of the mice to the dust for many months, has as yet run about half its course; but it is already possible to say that the extraction has at least greatly reduced the harmfulness of the dust, as compared with its effects at the same stage without extraction.

Earlier reports have mentioned similar long-range experiments by Dr. Campbell, in which mice were being daily exposed, for the natural term of a mouse's life, to cigarette smoke and to exhaust gases from a motor-car engine, the latter in a concentration similar to that likely to be encountered in a traffic block. These experiments have now reached their conclusion. No effect of any kind on the health or longevity of the mice has resulted from either of these treatments. In particular, there has been no change from the normal low incidence of lung adenomata.

Oxygen requirements

Dr. Campbell has continued his experiments on mice, and has confirmed the former conclusion that animals cannot be acclimatized for healthy life in an atmosphere containing less than 10 per cent. of oxygen, such as exists at an altitude of 20,000 feet. With Mr. H. J. Taylor, he has made further modifications in Krogh's micro-method of gas analysis, and these have been adopted by Professor Krogh. Dr. I. Singh, working with Dr. Campbell at the Institute and in the laboratories of Messrs. Siebe Gorman & Co., has shown that a large part of the oxygen requirements of an animal can be provided by the slow intravenous injection of oxygen gas, provided that the animal is kept under an increased atmospheric pressure. Dr. Campbell has also collaborated with Dr. E. P. Poulton in a book on *Oxygen and Carbon Dioxide Therapy*, in which the whole subject is reviewed from the points of view of

laboratory and clinical experiment and of practical therapeutic experience.

Library

During the year 516 bound volumes have been added to the Library, and 5 volumes withdrawn. The total number of books belonging to the Library is approximately 13,480. Of the 218 periodicals taken, 97 are purchased, 66 received on an exchange basis, and 55 presented. The additions to the Library during the year include *Records of the Malaria Survey of India*, complete from volume 1, 1929–30; *Rivista di Malariologia*, new series, complete from volume 1, 1926; and various volumes of the *Public Health Reports*, Washington, received from the Surgeon-General, and completing the Library series except for volumes 1 and 11.

Approved persons interested in medical research are allowed to consult books in the Library by arrangement with the Librarian.

The Council are glad to record again their gratitude to Lady Murphy for her continued voluntary work in the cataloguing of reprints, and express thanks to all those who have given books, periodicals, or reprints, among whom are: Dr. C. H. Andrewes; Mr. J. E. Barnard; Dr. J. Argyll Campbell; Dr. and Mrs. H. D. Dakin; Sir Henry Dale; Director-General of Health, Commonwealth of Australia; Mr. Clifford Dobell; Captain S. R. Douglas; the late Dr. H. W. Dudley; Professor H. v. Euler; Dr. E. Fourneau; Dr. M. H. Gordon; Sir Patrick Laidlaw; The Medical Officers of Health for Aberdeen, Birmingham, Glasgow, Jersey, Newcastle-on-Tyne, Paddington, and Preston; Merck & Co.; Mond Nickel Co.; the National Research Council of Japan; the Neurological Institute of New York; Professor M. Nicloux; Dr. A. S. Parkes; Dr. P. Pauli; the Pharmaceutical Society of Great Britain; Public Health Department of the London County Council; The Registrars-General of Northern Ireland and of Scotland; Dr. O. Rosenheim; Dr. Wilson Smith; the Surgeon-General, United States Public Health Service.

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III. THE DETERMINATION OF BIOLOGICAL STANDARDS AND THE METHODS OF BIOLOGICAL ASSAY AND MEASUREMENT.

Work upon Biological Standards at the National Institute for Medical Research

(*For Staff see p.* 35)

The regular distribution of specimens of the standard preparations held by the Institute under the Therapeutic Substances Act, or on behalf of the Health Organization of the League of Nations, or for the purposes of the British Pharmacopoeia, has been maintained. Since the last report the standards for the gas gangrene antitoxins (vibrion septique and *B. oedematiens*), staphylococcus antitoxin, and antipneumococcus serum (Types I and II), have been brought into official use by the promulgation of Regulations under the Therapeutic Substances Act; samples of these standards have been supplied to licensees and others, and the usual arrangements for their issue at regular intervals have been completed.

The original British standard for diphtheria antitoxin is now almost exhausted. A new dry stable standard has accordingly been prepared by Miss Llewellyn Smith, and its potency has been exactly determined in terms of the original standard, which it now replaces, and of the international standard maintained in Denmark. The unit value obtained by Miss Llewellyn Smith has been confirmed by independent tests at Copenhagen. The diphtheria antitoxin standard was the first of the national serum standards to be prepared and issued from the Institute, and the quantity prepared has proved sufficient for a period of only ten years. The relatively short currency enjoyed by this standard is due, in part, to the unexpectedly large demands which have been made upon it. It is of interest to record that, since it was first made available in 1925, the standard has been supplied to thirty-five different workers in eighteen countries, and that over 700 separate issues have been made. Much larger quantities of the newer serum standards have been prepared, and should serve for much longer periods. It is estimated that the quantity prepared of the new diphtheria antitoxin standard, now in regular use, will suffice for over fifty years.

A dry stable standard for gas gangrene antitoxin (*B. histolyticus*) has been prepared at the State Serum Institute, at Copenhagen, and submitted for international investigation. Mr. Bruce White has made tests with this preparation and reported upon it. At the meeting of the Permanent Standards Commission held at

Geneva last September, this standard, and a unit defined in terms of it, were adopted for international use. A suitable quantity of the standard will be supplied to the National Institute, for British use, and will be available as soon as its application is officially required.

A large quantity of antityphoid serum, prepared in the Elstree laboratories of the Lister Institute, on the basis of the recent work of Dr. A. Felix, has been supplied to the National Institute and reduced to the dry condition. The dry stable preparation is intended to serve as a provisional standard in investigations relating to the biological assay of the antibodies present in this new antityphoid serum. Workers at the Institute are co-operating with Dr. Felix and Dr. Petrie in this work.

Miss Llewellyn Smith has continued her work on the immunizing properties of staphylococcus antigens, mainly with a view to evolving a satisfactory method of biological assay for these products. To this end she has studied the development of immunity in different species of animals, the effect of administering the antigen by different routes and at different intervals, the response produced in normal and immunized animals, and other factors which affect the rate and extent of antibody production. As in the case of similar studies with other antigens, it has been found that the individual variation in the response of different animals of the same species to injections of staphylococcus antigen is very large. The experiments have been made on such a scale, however, as to permit of an estimate being made of the precision with which the relative potencies of two antigens can be estimated, in relation to the number of animals used in the tests. A clearer conception of what is possible, and what is practicable, in the way of a biological assay of antigenic potency has thus been obtained. In the course of this work, Miss Llewellyn Smith has examined the preparations of staphylococcus toxoid which were used in the clinical investigations for the Therapeutic Trials Committee, and has made an extensive examination of the preparations of toxoid at present being used in this country and in Canada, in the latter case through the courtesy and co-operation of workers at the Connaught Laboratories, Toronto. With a view to preparing a staphylococcus antigen causing less local and general reaction than toxoid, Miss Llewellyn Smith has made a number of toxin-antitoxin floccule, and toxoid-antitoxin floccule preparations, and has studied their immunizing properties. Some of these have been of such a potency as to satisfy the requirements of the present Regulations under the Therapeutic Substances Act.

In some joint investigations on diphtheria antigens, in which Dr. Hartley has collaborated with Dr. Madsen of Copenhagen and the late Geh. Dr. Kolle of Frankfurt, it has been repeatedly

demonstrated that the guinea-pigs maintained for use at Hampstead develop a higher degree of immunity than those used at Copenhagen and Frankfurt. Dr. Hartley has accordingly continued his investigations on the factors affecting the production of antitoxin in animals. He has found that, in guinea-pigs, antitoxin production is markedly affected by the diet administered before and during the period of active immunization; and he has also shown that, other conditions being constant, antitoxin production is related to the volume in which the dose of injected antigen is contained.

Vitamin Standards. In accordance with the recommendations of the Second International Conference on Vitamin Standards, held in London in 1934, the new international standards for vitamin A (pure β-carotene), and vitamin C (pure *l*-ascorbic acid), with further quantities of the international standards for vitamins B_1 and D, have been supplied to the national distributing centres, nominated by the Health Organization of the League of Nations, in twenty-one different countries. The conference recommended that the new standard for vitamin A should be supplied in the form of a standard solution of pure β-carotene in coconut oil. Mr. Webster investigated the properties and solubilities of the pure β-carotene preparation supplied by Professor Karrer, of Zurich, for use as the international standard, and devised a method for bringing it into the prescribed form of solution without exposure to air or other deleterious treatment. The quantity of β-carotene initially available proved to be quite inadequate to meet the international demands for this standard. Through the League of Nations Health Organization arrangements were made with Professor Karrer, by whose valuable co-operation an adequate supply of the standard to meet all needs is now assured. Arrangements were meanwhile completed between the Health Organization and the Committee of Revision of the United States Pharmacopoeia, whereby the 'reference' cod liver oils of the United States Pharmacopoeia, recommended by the conference for adoption as subsidiary standard for vitamin A, may be obtained. A quantity of approximately 500 grammes of pure *l*-ascorbic acid, to serve as the international standard for vitamin C, was received at the Institute from Professor Szent-Györgyi, of Szeged, Hungary, in January 1935. It was distributed into approximately 0·5 gramme quantities in sealed tubes, and adequate supplies have been forwarded to the national distributing centres.

Insulin. The first international standard for insulin, adopted in 1925, was prepared in the dry, stable condition by the late Dr. H. W. Dudley, using material provided from five different sources and representing a total activity of about 500,000 units. This does not seem a large quantity from the point of view of present-day

production, ten years later. It has, however, served for the whole decade as the international standard of reference, and its introduction rapidly produced a world-wide uniformity in the value of the unit of insulin, in place of the threatened confusion of competing units, unstably based on the reactions of animals of different species. This first insulin standard was nearing exhaustion; it had, further, become less suitable as a standard of reference for the comparative testing of the relatively pure insulins now produced by efficient manufacture. At the time of its preparation in 1924, and of the definition in 1925 of the unit as 'the specific activity contained in one-eighth part of a milligramme' of this first standard, it represented a good average of the purity of the best preparations of insulin then obtainable. Insulin as now manufactured often contains upwards of twenty units per milligramme; indeed, some manufacturers convert their whole output into the pure, crystalline form. When such pure insulins were assayed in comparison with the original standard preparation, a significant difference was found in the result, according as to whether the test was made by one or the other of the two generally used methods. The original standard accordingly had to be replaced by one more strictly comparable to modern, pure insulins. It was decided that it should be made entirely of the purest insulin obtainable, by crystallization and recrystallization. The preparation of the material was, on this occasion, undertaken by Dr. D. A. Scott of the Connaught Laboratories, Toronto, and his work was greatly facilitated by his discovery, during its progress, of the remarkable fact that the crystalline insulin consists of a zinc salt of the true hormone. Eventually, rather more than fifty grammes of the pure recrystallized insulin was thus prepared, and presented by the Connaught Laboratories to form the new international standard. It was transferred to the National Institute at Hampstead, where it has been distributed in suitable small quantities into some thousands of glass tubes, which, after final complete desiccation of their contents, were filled with pure dry nitrogen and hermetically sealed. Part of this new international standard will be distributed by the Insulin Committee of Toronto to the North American continent; the remaining portion will be kept at the National Institute for distribution to the rest of the world.

A question of first importance was the determination of the unit value of the new standard in terms of the old; in other words, the redefinition of the unit in terms of the new standard without significant change in its value. Comparative tests were organized from the three centres which had participated in the original fixation of the unit in terms of the first standard. As was to be expected, the results from the centres employing the mouse test for the comparison were regularly higher, mostly from twenty-five to

twenty-seven units per milligramme, than those from the centres employing the rabbit test, which varied between twenty-one and twenty-two units. An international committee, consisting of Professor Best (Toronto), Professor Krogh (Copenhagen), and Sir Henry Dale, had some difficulty in reaching a uniform decision as to the appropriate value from these results. Ultimately, after considering the ruling value of the unit of the insulins in current practical use in the different countries, the majority decided that the proper value to be assigned to the new standard was twenty-two units per milligramme. In making this decision, they acted on the principle that, while even a fractional change in the value of the unit was undesirable, no risk should in any case be taken of a fractional *decrease* in the value of the unit, in thus redefining it. This majority recommendation was, in due course, accepted by the Permanent Commission on Biological Standards, and the unit is thus defined, for all the world, in terms of the new standard. Since the quantity of the new standard available represents more than twice the number of units in that of 1925, it should, with the increased economy in its use which modern conditions permit, last for many years. Moreover, since all evidence indicates a uniform activity for the pure, crystalline insulin, whenever prepared, it should be possible at any time to replace the present standard with a closely equivalent new one, without any recurrence of difficulty in defining the unit: the value of the latter is, in effect, firmly established for all time by the recent decision.

Pituitary Posterior Lobe. The International Conference of 1925, which adopted the first standard for insulin, dealt also with the standardization of the potent extract of the posterior lobe of the pituitary body. A unit of activity of this preparation was defined as the specific activity contained in 0·5 milligramme of a stable dry preparation, consisting of the gland substance extracted with acetone and ether. Professor Voegtlin, of Washington, undertook the preparation of a first, small sample of this standard, as a basis of verification for similar standards prepared in other countries. It was thought that no large quantity of this standard would be required for general and repeated distribution, but this expectation has not been fulfilled: for lack of a centrally adopted international standard, samples of the British standard have therefore been widely distributed in the intervening years in response to requests from other countries. The Permanent Commission, at its meeting in September 1935, decided formally to adopt the British standard for international use, and to ask the National Institute to be responsible for its custody and maintenance in the international interest.

Arsphenamine and its derivatives. The International Conference of 1925 also dealt with the question of international standards

for arsphenamine (salvarsan) and its derivatives. The preparation and custody of the standards for the original '606' and its formaldehyde-sulphoxylate derivative (neosalvarsan, neoarsphenamine) were committed to the Georg-Speyer Haus at Frankfurt, where these substances and their therapeutic properties had been discovered under the direction of Paul Ehrlich. Professor Voegtlin, of Washington, undertook the preparation of a standard for the formaldehyde-bisulphite derivative (sulpharsphenamine), and transferred it for custody and distribution to the National Institute at Hampstead. A new arrangement being made necessary by the secession of Germany from the League of Nations, the Permanent Commission decided, at its meeting in September 1935, to transfer the responsibility for the preparation and distribution of all these international standards to the National Institute at Hampstead.

Sex Hormones. The Council's report for 1931–32 mentioned the meeting in London, in 1932, of a small international conference which adopted a standard preparation for the ovarian, oestrogenic hormone. Of the forms of this hormone then known, the keto-hydroxy form was the most active, and, in accordance with the decision of the conference, a supply of this was obtained and is held at the National Institute for distribution to other countries.

In the intervening three years, however, other forms of this hormone had come to light, including one (oestradiol) which appears to represent the hormone in its most active form, as produced by the ovarian follicles, whereas the forms found in the urine are of lower activity. Artificial esters of these different oestrogenic substances, in particular their benzoates, had further been introduced into therapeutic practice, their greater solubility in oil making them much more convenient for administration. Experience had shown that the standard already adopted was not suitable for the comparative testing of these esters, which, according to the form of the animal test chosen, showed widely different activities in relation to it. Knowledge, moreover, of the progestational hormone of the corpus luteum, and of a male hormone obtainable from urine, had so far advanced that the question of international standards for these hormones had also become ripe for practical discussion. Accordingly a second and more widely representative conference met in London in July 1935, Sir Henry Dale again acting as chairman and Dr. A. S. Parkes as secretary.

The conference agreed to adopt an additional standard for the oestrogenic hormone, consisting of a preparation of pure oestradiol benzoate. They recommended that all benzoylated preparations of the oestrogenic hormone should be standardized in relation to this benzoate standard, the unit of activity for such preparations being defined as the specific oestrogenic activity in 0·1γ of this

standard. They further decided to adopt androsterone, a form of hormone found in male urine, as the international standard for the male hormone. For preparations of the progestational hormone, they decided to adopt as a standard a preparation of the pure crystalline hormone, henceforth to be known in science as 'progesterone'. The conference recommended that these standards should be kept and maintained at the National Institute at Hampstead, and this recommendation was adopted by the Permanent Commission, when it met at Geneva in September.

An incidental, but scientifically important outcome of this international conference was the adoption for general use, in the scientific literature of different countries, of agreed names, free from all trade associations, for these hormones of the gonads in their various forms. Names had previously been given in bewildering variety by those working with the support of different commercial organizations, with a resulting widespread confusion. A uniform and freely available nomenclature for these hormones was therefore second only in importance to an agreed notation for indicating their activities. The following names were thus adopted for such common scientific application, in accordance with definitions given in the full report of the conference: oestrone, oestriol, oestradiol, and, in each case, the corresponding benzoate; progesterone, androsterone, androsteranediol, &c.

As illustrating the rapidity of development in this field, it may be recorded that at the conference in July, Professor Laqueur, of Amsterdam, described the isolation from fresh testicular substance of what was apparently the most active form of the hormone, which appears in the urine as androsterone. He had named this new substance 'testosterone'; but as there seemed then no prospect of obtaining it in quantity sufficient for use as an international standard, the more readily available androsterone was adopted for the purpose. By the beginning of September, however, the synthesis of a substance identical with 'testosterone' had been announced by Ruzicka and Wettstein in Switzerland and by Butenandt at Danzig. The possibility of adopting this substance as a standard, in place of, or in addition to the urinary 'androsterone', thus seems likely to come under discussion at a much earlier date than could have been foreseen at the meeting in July.

The rapid progress which is now being made in the chemistry of these hormones led the conference to recommend that, when they are offered as solutions or preparations of pure chemical substances, dosage shall be indicated gravimetrically as well as in the agreed units of activity. This recommendation embodies in a rather more definite form a recognition, already implied in the report of an earlier conference on the vitamins, of the fact that biological standardization is in many cases a temporary expedient,

and an aid to such chemical progress as will eventually replace the cumbrous and approximate biological measurements by the convenience and accuracy of the chemical balance.

The material for the new standards thus adopted by the conference will be obtained from various sources, with the proffered co-operation of several members of the conference. Through Dr. Miescher, five grammes of androsterone has already been presented by the Ciba Company of Basel, as a first instalment of the material for that standard.

In the case of 'progesterone', the National Institute has taken a more direct responsibility for preparing and collecting the material. Dr. Callow has produced about 0·4 grammes of progesterone from pregnandiol, and, with the co-operation of Dr. Beall of Toronto, work is in hand for the production of a further quantity, by a longer series of chemical changes, from stigmasterol —the sterol of the soya bean. Meanwhile, an abundant and unexpected source of crude progesterone has been found in the corpora lutea of whales. Attention was drawn to these by Mr. A. H. Laurie of the Discovery Expedition, and a large supply has already become available. By the kind permission of Dr. Kemp, Director of the expedition, arrangements are being made for the collection of a further supply during this winter. These bodies vary in weight from one to nearly seven kilogrammes; and, in spite of preservation for some months in a formaldehyde solution, their substance has been found to be nearly as active, weight for weight, as that of fresh corpora lutea from the pig.

The National Collection of Type Cultures

Staff—
R. St. John-Brooks, M.D. (*Curator*).
Miss M. Rhodes (*Assistant Curator*).

The National Collection of Type Cultures of micro-organisms continues to be accommodated at the Lister Institute of Preventive Medicine, London, by the courtesy of the Governing Body. The staff is in the whole-time service of the Council.

The number of cultures of bacteria and fungi distributed during the year under review, to workers at home and abroad, again exceeded 5,000, and some 250 new types were deposited for maintenance.

Among the types added to the collection were the following:

Strains of *Salmonella typhi* containing the 'Vi' antigen from Dr. A. Felix, Lister Institute; new serological types of *Salmonella* spp. from Dr. Fritz Kauffmann, Statens Seruminstitut, Copenhagen, Dr. E. O. Jordan, University of Chicago, Dr. J. Smith, City Hospital, Aberdeen, and the Instituto Bacteriologico, Buenos Aires.

Human pathogenic fungi from Prof. G. Pollacci, Pavia University, and from Sir Aldo Castellani, London. Phytopathogenic fungi from

Centraalbureau voor Schimmel-cultures, Baarn, Holland, and the Imperial Mycological Institute, Kew.

Lignicolous fungi from Prof. S. R. Bose, Carmichael Medical College, Calcutta, and a collection of *Mucor* spp. and other types from Dr. Ivimey Cook, University College, Cardiff.

Actinomyces spp. from the American Type Culture Collection, Chicago, Dr. J. T. Duncan, London School of Hygiene and Tropical Medicine, Dr. A. G. Gibson, Radcliffe Infirmary, Oxford, and Professor E. Pribram, Vienna. Anaerobic actinomyces from Dr. L. P. Garrod, St. Bartholomew's Hospital, London.

Serological types of *Streptococcus pyogenes* from Dr. F. Griffith, Ministry of Health Pathological Laboratory, London, and serological groups of *Streptococci* (*S. agalactiae*, &c.) of bovine origin from Dr. A. W. Stableforth, Royal Veterinary College, London. Anaerobic streptococci and other streptococci from puerperal sepsis from Dr. L. Colebrook, Queen Charlotte's Hospital, London.

Species of mycobacteria from Dr. H. C. de Souza Araujo, Centro International de Leprologia, Rio de Janeiro: strains of *Mycobacterium pseudotuberculosis* (Johne) from Mr. G. W. Dunkin, National Institute for Medical Research; and *M. tuberculosis*, Schroder-Mietsch-Baumgarten strain, from Prof. K. W. Jötten, Münster, Germany, through Dr. H. Schütze.

Strains of *Corynebacterium pyogenes*, *C. ovis*, and the virus of Pleuropneumonia contagiosa boum, from Dr. H. R. Carne, Sydney University, N.S.W.

Serological groups of *Vibrio* spp. from Mr. P. Bruce White, National Institute for Medical Research, and from Dr. A. D. Gardner, Standards Laboratory, Oxford.

Bacillus alcalophilus from Dr. A. Vedder, University of Amsterdam; *B. putrificus* from Dr. N. E. Goldsworthy, Sydney University, N.S.W.; and a collection of facultative spore-forming organisms from water supplies sent by Dr. R. Porter, Iowa State College, U.S.A.

Haemophilus influenzae, Pitman types from Dr. A. E. Platt, London School of Hygiene and Tropical Medicine, and *H. influenzae-suis* types from Dr. C. H. Andrewes, National Institute for Medical Research.

Bacterium salmonicida strains from Dr. D. C. B. Duff, University of British Columbia; *Bacterium sp.* from locust disease in the Belgian Congo from M. G. Bouvier through the Imperial Institute of Entomology; lacticolous bacteria from Mr. J. G. Davis, National Institute of Dairy Research, Reading; and phytopathogenic bacteria from Dr. W. J. Dowson, Botany School, Cambridge University.

A collection of bacteria ('*Escherichia*' spp.) isolated from ice cream by Dr. M. Grimes and Dr. A. J. Hennerty, University College, Cork, I.F.S., and *Chromobacterium* spp. from Mr. G. Creuss-Callaghan, Department of Agriculture, I.F.S.

Bacterium dispar (Andrewes) from Dr. H. A. Yenikomshian, American University of Beirut, Syria; *B. proteus* types from Dr. A. Felix; and *B. alkalescens* (Andrewes) from Dr. F. A. Pickworth, Birmingham.

Entomophagous fungi from Dr. T. Petch.

For all these donations the Council desire to express their gratitude.

The revised list of fungi and bacteria of economic importance maintained in the collection, referred to in the last report, was published during the year in the *Transactions of the British Mycological Society*: a few reprints are available to correspondents, free of charge. A new edition of the catalogue of the Collection has been prepared for publication. Following the recommendations

of the Nomenclature Committee of the International Society of Microbiology, of which the Curator is one of the permanent secretaries, the use of the specific name *'Bacillus'* has been restricted in this catalogue to spore-bearing organisms. A statement on this subject by the Nomenclature Committee has been published in the *Zentralblatt für Bakteriologie.*

The taxonomic study of the *Actinomyces* group by Miss Dagny Erikson, working in the laboratory of the Collection with a personal grant, has now been published by the Council.

R. S. Breed and R. St. John-Brooks—
'Report on Proposals submitted by R. E. Buchanan and H. J. Conn Relative to the Conservation of *Bacillus* as a Bacterial Generic Name, Fixing of the Type, Species, and of the Type or Standard Culture.' Nomenclature Committee of the International Society for Microbiology. *Zbl. Bakt.*, Abt. 2, 1935, **92**, 481.

D. Erikson—
'The Pathogenic Aerobic Organisms of the Actinomyces Group.' *Spec. Rep. Ser. Med. Res. Coun.*, Lond., No. 203, 1935.

R. St. John-Brooks and M. Rhodes—
'A List of Fungi, &c., maintained in the National Collection of Type Cultures, 1935.' *Trans. Brit. mycol. Soc.*, 1935, **19**, 315.

The Standards Laboratory, Oxford

Staff—
A. D. Gardner, D.M., F.R.C.S.
Miss E. F. Stubington, B.Sc.

The work of producing and standardizing bacterial suspensions and agglutinating sera for the diagnosis of bacterial infections has been maintained at the Standards Laboratory, in the School of Pathology at Oxford, by the staff in the whole-time service of the Council. Between 350 and 400 laboratories at home and abroad have made use of the standardized products, the output of which has increased by about sixteen per cent. in the last twelve months. In addition to routine supplies, for which a charge is made, considerable quantities have been sent out free for purposes of research; and from time to time the laboratory has undertaken the making of extra suspensions and sera for special investigations.

The nature of the work constantly calls for the reinvestigation of the antigenic structure and relationships of bacteria. Dr. Gardner's work on the cholera group of vibrios, with Dr. K. V. Venkatraman (Rockefeller Fellow), has been concluded; it has led to the substitution of a highly specific cholera 'O' serum for the type hitherto produced, which had been shown to be capable of error. In this work, which was originally instigated by the Health Organization of the League of Nations, a constant interchange of ideas and materials has been maintained with Mr. P. Bruce White at the National Institute. As a result of this collaboration Mr. Bruce White has prepared a dry 'standard' cholera antigen,

to be used for the production of 'O' agglutinating serum, and this is being distributed to approved laboratories in India by the Standards Laboratory and through the Central Research Institute at Kasauli. Dr. Gardner has undertaken to receive records of investigations done with the resulting standard 'O' serum, and to report them in due course to a meeting of representative bacteriologists and health officers.

A reinvestigation of methods of preparing and standardizing suspensions of the *Proteus* group for the Weil-Felix reaction has been made necessary by the discovery that the serum of immunized rabbits is an unreliable indicator of the sensitiveness of the suspensions to human typhus serum. This work is being done with the co-operation of Colonel R. F. Bridges, R.A.M.C., of the Enteric Laboratory, Kasauli, who drew attention to the phenomenon, and also with the voluntary assistance of Miss M. Campbell Renton at Oxford.

The Laboratory has arranged to supply standardized suspensions to be used, in comparison with the various local materials, in a European test of methods for the Widal reaction arranged by the Health Organization of the League of Nations. A 'standard' technique for the use of the suspensions, based on that already followed by the clients of the Laboratory, was agreed upon by an *ad hoc* committee of bacteriologists which met in London last July. Specimens of serum from patients with typhoid fever are to be divided into fractions and distributed to a selection of leading laboratories in different European countries. Each serum is to be titrated by both the local method and the standard method. In this way it is hoped to achieve a much greater accuracy and uniformity of results than is at present attained. Dr. Gardner has undertaken to participate in the experiment, and also to receive and correlate the results of the different laboratories before reporting to the Typhoid Committee under the League of Nations.

A. D. Gardner and K. V. Venkatraman—
'The Antigens of the Cholera Group of Vibrios.' *J. Hyg.*, Camb., 1935, 35, 262.

IV. CLINICAL RESEARCH UNITS

THE DEPARTMENT OF CLINICAL RESEARCH, UNIVERSITY COLLEGE HOSPITAL, LONDON

Staff—	*Visiting Workers*—
Sir Thomas Lewis, C.B.E., M.D., F.R.C.P., F.R.S. (*Director*).	Dr. B. B. Gelfand (New York).
G. W. Pickering, M.B., M.R.C.P.	Dr. Milton Kissin (New York).
	Dr. P. Rothschild (Frankfurt a/Main).

The post of Director has been permanently endowed by the Rockefeller Foundation, but this department is otherwise staffed and supported by the Council.

Early in the year Sir Thomas Lewis published from this department a book entitled *Clinical Science*, containing a plea for recognition of the importance of studying disease directly in mankind, an outline of methods of approach which the author has himself found to be of value, and an account of personal researches illustrating their use. The book was published with the intention of encouraging young workers to contemplate clinical science as a field of fruitful and interesting life work.

With Dr. Pickering, Sir Thomas has published a full account of various maladies in which the blood-supply to digits ceases intermittently or permanently, and dealing also with bilateral gangrene of digits. Upon the basis of observations and inquiries into the pathology of the different diseases, a new classification has been arranged to facilitate their further study. The inquiries emphasize the conclusion that many distinct conditions have been described under the common name 'Raynaud's disease'; they point to the existence of a local fault as the cause both of Raynaud's phenomenon and of bi-lateral gangrene. It is suggested that gangrene is never the result of uncomplicated spasm of arteries, but depends always upon structural occlusion of vessels; to determine this, it is necessary to examine more than the main arteries, as the obstructive disease may occur, as is shown, in a number of small arteries simultaneously.

After working in this department in successive collaboration with Dr. Camp, Dr. Graybiel, and Dr. Rothschild, Dr. Grant —now at Guy's Hospital—has completed his further observations on the vessels and nerves of the rabbit's ear, and these have been published. They were undertaken to obtain better understanding of similar phenomena occurring in man as a result of operative procedures for the relief of diseased conditions of the peripheral vessels. Strong evidence has been produced to show that the return of vascular tone which follows denervation is due to an

increased responsiveness of the denervated vessels to various stimuli, including an adrenaline-like substance circulating in the blood-stream. The source of this substance remains unknown, but it appears to be neither the adrenal glands nor the pituitary body. Its concentration in the blood is increased by nervous or muscular activity, and is reduced by rest. The evidence suggests that this substance may play a part in maintaining normal vascular tone and body temperature, and that an increase in its concentration may be responsible for the pallor of ill health and for the rise of body temperature in fever.

Dr. Pickering has completed an investigation, lasting over a number of years, of the variations in cerebrospinal fluid pressure in arterial hypertension. Patients with cerebrospinal fluid pressures exceeding that of 250 millimetres of water were all found to be cases of nephritic or malignant hypertension with a rapidly fatal course; all presented signs of albuminuric retinitis. Patients with lower fluid pressures were chiefly cases of benign hypertension or inactive chronic nephritis with a relatively good prognosis; they presented either no retinal lesions or those of arteriosclerotic retinitis. The present work suggests that the difference between the two forms of retinal lesion, long recognized as occurring in arterial hypertension, consists in the presence in albuminuric retinitis, and the absence in arteriosclerotic retinitis, of an excessive accumulation of fluid in the nerve head and retina, and that this in turn is a simple consequence of the level of the intra-cranial pressure. The cerebrospinal fluid pressure is probably in part a direct consequence of the diastolic arterial pressure, which reaches particularly high levels in the terminal stage of chronic nephritis and in malignant hypertension.

Among patients suffering from severe anaemia, angina pectoris is not uncommon, and an anticipation that intermittent claudication might also occur has now been substantiated by Dr. Pickering and Dr. E. J. Wayne, who have fully investigated the relation of these two types of pain to the condition of the blood. They have shown that, in anaemic patients without recognizable peripheral vascular disease, suitable exercise of the limbs produces severe muscular pain identical with that of intermittent claudication; in the same patients, after cure of the anaemia, similar exercise produces very slight or no pain. The occurrence of intermittent claudication in anaemia is due to a deficient oxygen supply and not to a deficient blood-flow to the active muscles. Similarly, patients who in the anaemic state experience anginal pain on walking, experience no pain when their anaemia is cured, or pain only after more severe exercise. It is concluded that the factor which is chiefly responsible for the development of anginal pain, in anaemia, is a deficient oxygen supply to the working myocardium, although associated changes

in blood-pressure and pulse-rate undoubtedly contribute. This observation serves further to emphasize the close similarity existing between angina pectoris and intermittent claudication, previously insisted upon in work from this department. Earlier work here had suggested that the two pains are both due to an accumulation in the tissue spaces of a chemical substance or substances liberated from heart or skeletal muscle during work: the present investigation suggests that such substances are normally removed by oxidation.

Dr. Wayne, before leaving the service of the Council to become Professor of Pharmacology at Sheffield, had completed with Dr. Graybiel a series of observations on the angina of effort: these have now been published. By means of a standard exercise test, the influence of a number of factors on the amount of exercise required to produce pain in effort angina was investigated. After a heavy meal exercise tolerance was definitely reduced, but in the same cases it was unaffected by inflation of the stomach with air: this showed that the reduction of exercise tolerance after food was due to an increased energy expenditure of the heart, and not to gastric distension. Variations in external temperature did not affect exercise tolerance in six cases of pure effort angina. It was shown that two types of case existed; in both, exercise tolerance was constant if sufficient rest was allowed between the end of one attack and the recommencement of exercise. In one type, however, as this period of rest was reduced, exercise tolerance gradually diminished; in the other, there was a phase during which exercise tolerance was increased. A case was fully studied with symptoms resembling those previously described under the term *angina sine dolore*, but investigation showed that the attacks were due to paroxysmal ventricular action brought on only by exercise. With Dr. Kissin, Dr. Wayne began investigations here of the exercise tolerance in effort angina at different levels of blood-sugar, and he is now continuing this work at Sheffield.

T. Lewis—
Clinical Science. London (Shaw & Sons, Ltd.), 1934.
'The Huxley Lecture on Clinical Science within the University.' *Brit. med. J.*, 30th Mar. 1935.

T. Lewis and G. W. Pickering—
'Observations upon Maladies in which the Blood Supply to Digits Ceases Intermittently or Permanently, and upon Bilateral Gangrene of Digits; Observations relevant to so-called "Raynaud's disease".' *Clin. Sci.*, 1934, **1**, 327.

R. T. Grant—
'Further Observations on the Vessels and Nerves of the Rabbit's Ear, with special reference to the effects of Denervation.' *Clin. Sci.*, 1935, **2**, 1.

G. W. Pickering—
'The Cerebrospinal Fluid Pressure in Arterial Hypertension.' *Clin. Sci.*, 1934, **1**, 397.

G. W. Pickering and E. J. Wayne—
'Observations on Angina Pectoris and Intermittent Claudication in Anaemia.' *Clin. Sci.*, 1934, **1**, 305.

E. J. Wayne and A. Graybiel—
'Observations on the Effect of Food, Gastric Distension, External Temperature, and Repeated Exercise on Angina of Effort, with a note on *Angina sine Dolore*.' *Clin. Sci.*, 1934, **1**, 287.

The Clinical Research Unit, Guy's Hospital, London

Staff—
R. T. Grant, M.D., M.R.C.P., F.R.S. (*Director*).
Attached Worker—
R. S. Bruce Pearson, D.M., M.R.C.P.

In the introduction to the last Annual Report mention was made of the establishment at Guy's Hospital of a new Unit for research in clinical medicine. The Unit, which began work in October 1934, is directed by Dr. R. T. Grant, of the Council's staff, who has also been appointed Assistant Physician to the hospital. Since January 1935 he has had the whole-time assistance of Dr. R. S. Bruce Pearson provided by the Council. The hospital has given accommodation to the Unit in both the Medical School and the Medical Block, the Director having charge of six beds and of an out-patient clinic.

During the year under review Dr. Grant has completed his work on the recovery in the tone of blood-vessels after destruction of their nerve-supply. This inquiry was begun while he was working in the Department of Clinical Research at University College Hospital, and has been noticed in the report of that department. With Dr. Pearson he has investigated a series of cases of urticaria, in which the agent responsible appears to be released in the skin through activity of the peripheral nerves. Observations are also being made on the part played by the peripheral nerves in the production of fever. Dr. Grant has devised a portable thermo-electric couple for measuring skin-temperature; this instrument has already proved very serviceable in the bedside study of diseases of the circulation. Dr. Pearson has concluded a study, begun before he joined the Unit, of recurrent, non-infective, swellings of the parotid gland. He has since begun an inquiry into some of the factors involved in the production and relief of asthmatic attacks.

The Neurological Research Unit, National Hospital for Diseases of the Nervous System, Queen Square, London

Staff—	*Attached Worker*—
E. A. Carmichael, M.B., F.R.C.P. (*Director*).	Mrs. B. Bolton, M.R.C.S.
Halley Stewart Scholars—	*Visiting Workers*—
D. H. Brinton, B.M., M.R.C.P.	Dr. J. P. Evans, Montreal.
D. E. Denny Brown, M.B., M.R.C.P.	Dr. O. Maas, Berlin.
J. B. Gaylor, M.B.	Dr. G. Stürup, Copenhagen.
S. Nevin, M.D., M.R.C.P.	Dr. V. Uprus, Tartu, Esthonia.

The Director of this Unit is in the whole-time service of the Council. The Scholars who assist him are remunerated from a fund placed at the disposal of the Council by the Sir Halley Stewart Trust. Workers in other departments of the Hospital, both members of the staff and visitors, also participate in the activities of the Unit from time to time.

The main work of the Unit has been directed towards a study of the autonomic nervous system, although various subsidiary problems have also been investigated. To this end, a series of observations upon temperature regulation have been made by Dr. Carmichael with the help of Dr. Uprus, holding a fellowship from the Rockefeller Foundation, and of Dr. Gaylor. It has been determined that, with an adequate stimulus, there is no difference in the rate of dilatation or constriction of the blood-vessels of a hemiplegic limb, as compared with a normal limb. To ascertain whether the vaso-constriction reflexes were in any way abnormal in such cases, plethysmographic records of fingers were taken; in this work Dr. Stürup, holding a fellowship from the Rockefeller Foundation, and Dr. Bolton have collaborated. By this method reflex activity was also found to be normal in the hemiplegic limb. Further studies by both methods are now being undertaken in a large series of cases with isolated lesions of the nervous system.

During the course of this work a vaso-constrictor reflex associated with deep inspiration was encountered. This reflex was analysed fully, and the results are being prepared for publication. Methods for registering the pilomotor response have been evolved, and a careful study is being made of this manifestation of sympathetic activity. The presence in the wards of a patient with abnormal sweating in a localized area in association with eating gave an opportunity to investigate this condition; by a series of experimental procedures it was determined that the sweating was dependent upon an abnormal growth of fibres from the lingual nerve. This work has been published.

Dr. J. Cummings, Assistant Pathologist to the Hospital, has

continued to investigate, with Dr. Carmichael, the chemistry of the blood and cerebrospinal fluid. Special attention has been directed to the estimation of the absorption rate of the fluid.

Collection of the facts regarding the sensory disturbance found in subacute combined degeneration of the spinal cord has been continued by Dr. J. G. Greenfield, Pathologist to the Hospital, with Dr. Carmichael. By a careful analysis of the number and size of myelinated fibres in peripheral nerves obtained from cases of this condition, the poverty of myelinated fibres has been found to be due chiefly to an absence of any showing heavy myelination. The study is continuing, and sensory tests are now being made in an attempt to discover the type of sensation most affected. A related study of cases of peripheral neuritis has been undertaken, not only in respect of sensory disturbances, but also by careful dietetic treatment to determine the part which may be played by vitamin deficiency.

Dr. Stürup has continued his work, begun in Copenhagen, on oesophageal pain and its mechanism. He has determined the various areas of reference of pain from the oesophagus, and has made a special study of states modifying the referred pain. With Dr. Carmichael, it has been determined that no pathway for pain from the periphery of a limb exists along the periarterial plexus. This has been shown by exposing an artery and stimulating it during the blocking of a nerve with novocaine.

Dr. S. Obrador, a visitor from Madrid working in the Hospital with a research fellowship, has collaborated with Dr. Carmichael and Dr. Stürup in work dealing with sensation in the peripheral nerves.

Dr. Denny-Brown and Dr. Nevin have continued their electro-myographic studies in myotonia, myasthenia, and other muscular affections. Electro-myographic records of fibrillation from cases with various diseases of the nervous system have been obtained: they have been analysed and are being prepared for publication. Dr. J. Pennybacker, during his tenure of posts in the Hospital, has assisted in the electro-myographic work. With Dr. E. Graeme Robertson, who held a Grocers' Research Fellowship at the Hospital, Dr. Denny-Brown studied the mechanism of defaecation, with results that have been published: the functional activity has been found to resemble closely that of the bladder. With Dr. J. P. Evans, holding a fellowship from the Rockefeller Foundation, Dr. Denny-Brown has now begun an experimental investigation into the mechanism of motor cortical activity.

Dr. Nevin has continued his work on the study of various muscular affections. Myasthenia gravis has occupied his special attention, and he has made progress with his investigations, especially as regards the chemistry of the muscle. His studies have also

included the possible therapeutic effect of various glandular extracts, and the results, although in an early stage, promise well. With Dr. Bolton, he has made a series of observations on wasting of muscle in association with lesions of the cerebral hemispheres. He has paid special attention to a group of myopathies limited to the later decades of life, making histological and chemical investigations of these diseases. Dr. Nevin, with the help of Dr. S. Meadows, has investigated cases with defect of vision in an attempt to determine the anatomical basis of the 'réaction à défense', optic nystagmus, and visual inattention.

With Dr. S. Behrman, Registrar to the Hospital, Dr. Brinton has continued to study the bromide content of blood and cerebrospinal fluid. The difficulty of obtaining an accurate method of estimating bromide content has been overcome. An account of the methods and results is being prepared.

Facilities have been given to Dr. O. Maas (p. 109) to study the functional activity of the autonomic system in cases of dystrophia myotonica. The co-operation of Dr. A. S. Paterson has been obtained to determine the intellectual age and to make a detailed psychological study of the cases.

D. Denny-Brown, J. B. Gaylor, and V. Uprus—
'Note on the Nature of the Motor Discharge in Shivering.' *Brain*, 1935, **58**, 233.

D. Denny-Brown and E. G. Robertson—
'Observations on Records of Local Epileptic Convulsions.' *J. Neurol. Psychopath.*, 1934, **15**, 97.
'An Investigation of the Nervous Control of Defaecation.' *Brain*, 1935, **58**, 256.

G. K. Stürup and E. A. Carmichael—
'Pain: the Peripheral Pathway.' *Brain*, 1935, **58**, 216.

V. Uprus, J. B. Gaylor, and E. A. Carmichael—
'Localized Abnormal Flushing and Sweating on Eating.' *Brain*, 1934, **57**, 443.
'Shivering: a Clinical Study with Especial References to the Afferent and Efferent Pathways.' *Ibid.*, 1935, **58**, 220.

V. EXTERNAL RESEARCH SCHEMES

Clinical Medicine

At St. Bartholomew's Hospital, London, a grant for expenses has been made to Professor L. J. Witts, Director of the Medical Unit, who is investigating the causes of agranulocytosis and the effects of treatment with liver extract and pentnucleotide upon it. He is also comparing the therapeutic potencies of different salts of iron in anaemia, and is examining the influence of variations in the calcium content of the diet upon the iron treatment of blood diseases. In the same Unit, Dr. A. W. Spence has had part-time and expenses grants. With Dr. E. F. Scowen, he has continued his studies in the treatment of toxic goitre with various endocrin preparations. Attempts are being made, with Dr. Parkes and Mr. Rowlands of the National Institute (p. 55), to produce a serum for use in Graves's disease. Dr. Scowen and Dr. Spence have published a preliminary account of a trial of gonadotropic hormones, as an alternative to surgical operation, for the treatment of undescended testis: the results so far have been very encouraging, and the work is being extended.

Dr. E. P. Poulton, at Guy's Hospital, London, has again had a grant for expenses. With Mr. T. W. Adams, he has continued his work on the treatment of pneumonia and other diseases by means of an oxygen-tent. The design of the tent has been further improved, and it has been used with success at a number of London and provincial hospitals. Dr. Poulton and Mr. Adams have also extended their work on the calculation of heat production in man, and have used their methods to study the growth-metabolism of children from birth to puberty. The clinical possibilities of an apparatus suggested by Dr. J. Plesch for the treatment of pulmonary oedema have been examined by Dr. Poulton. The apparatus, which produces a positive pressure inside the lungs, has been found useful in cases of nocturnal breathlessness and cardiac asthma.

At St. Thomas's Hospital, London, Dr. W. J. Griffiths has had a personal grant for assistance to Professor O. L. V. de Wesselow. He has investigated the metabolism of patients with high blood-pressure, in an attempt to assess the parts played by endocrine disturbances in this condition. The effects of increased metabolism on the size of the heart have been studied experimentally. Dr. Griffiths has also done further work on gastric secretion in various types of anaemia. Dr. T. H. Hodgson had a part-time grant at this hospital to examine the amount of carbonic anhydrase enzyme in human blood in health and disease.

At King's College Hospital, London, Dr. R. D. Lawrence again

had a grant for assistance by Dr. Kate Madders. On behalf of the Therapeutic Trials Committee (p. 87), an inquiry was made, with Dr. R. S. Wale, into the claim that staphylococcal toxoid produced benefit in diabetes. It was found that this treatment had no value in diabetic patients without overt staphylococcal lesions. Dr. Madders has collected data on the health and longevity of 3,000 patients with diabetes treated with and without insulin: these data have been submitted to the Council's statistical staff for analysis. Dr. R. A. McCance (p. 98) and Dr. Lawrence have continued work on the secretion of urine in diabetic coma, and have observed the effects of chloride deficiency on kidney function in man.

In the Courtauld Institute of Biochemistry at the Middlesex Hospital, Dr. N. F. Maclagan received a personal grant for work under the general direction of Professor E. C. Dodds (pp. 130 and 136). With Dr. F. P. L. Lander and Dr. F. G. Nicholas, he examined the secretion, position, and motility of the stomach in a large series of normal subjects and in patients with peptic ulcer and with cancer of the stomach. Investigations in healthy students failed to confirm the commonly accepted view that there is a correlation between gastric secretion on the one hand and physique and stomach position on the other. It was found also that the acid-base balance of the blood had no direct relation to the degree of gastric acidity. Attempts have been made to determine the biochemical mechanism underlying the production of acid in the stomach, and the reactions of the gastric mucous membrane to different endocrine preparations have been studied experimentally.

With an expenses grant at the British Post-Graduate Medical School, London, Dr. C. H. Stuart-Harris has investigated the resistance to haemolytic streptococci of fibrin from the blood of patients with streptococcal and other diseases. Under normal conditions, the blood fibrin is usually rapidly dissolved by the 'fibrinolysin' of these streptococci. It was found, however, that in more than half the patients with haemolytic streptococcal diseases, the fibrin resisted solution by this means. Similar results were obtained in patients with rheumatic fever, the resistance being associated with the active rather than the convalescent stages of the disease. No such resistance appeared to be developed in the blood of patients with rheumatoid arthritis.

Dr. W. Evans, of the London Hospital, has completed the studies of the course of the oesophagus in health and in heart disease, for which he received a part-time grant. A report on his work is being issued by the Council.

Reference is made at p. 162 to the arrangements under which experimental and clinical research on ultra-short wave therapy is being promoted at the London Hospital, with the aid of a

benefaction provided by the Stock Exchange Dramatic and Operatic Society. The work is being done under the supervision of Professor D. T. Harris, Dr. E. May, and Sir Robert Stanton Woods. Grants for assistance in the inquiry have been made to Dr. J. B. Bateman and Dr. H. Rosenberg from the special fund.

An expenses grant has been made to Dr. G. L. F. Rowell for work under the direction of Dr. James Maxwell at the Royal Chest Hospital, London, on the blood sedimentation-rate in asthma and chronic bronchitis, and on the effects of oxytocic pituitary extract in the treatment of these diseases. The preliminary results indicate that cases of chronic bronchitis with asthma ordinarily have high sedimentation rates, and that the rates may be lowered by injections of the extract, with improvement in the patients' symptoms: cases of spasmodic asthma, on the other hand, usually have normal or low sedimentation rates, and are not influenced by this treatment.

At Manchester, Dr. J. C. Bramwell has again had grants for expenses and for assistance by Dr. Edith Longson They have continued, at the Royal Infirmary and St. Mary's Hospital, their clinical studies of the effects of pregnancy and labour upon women with heart disease. Over 300 cases have now been observed from this point of view. Analysis of the records of these patients has emphasized the importance of ante-natal care: a large majority of the patients who died of heart failure before or shortly after confinement had failed to attend for observation at an earlier stage of pregnancy. The results of the whole inquiry suggest that, if patients receive adequate ante-natal supervision and treatment, auricular fibrillation and congestive heart failure are the only common heart complications which are likely to be dangerous in pregnancy. The investigation is now being extended to include the after-histories of patients followed through pregnancy in earlier years: by this means it is hoped to determine the influence of childbearing upon the more remote prognosis in different types of heart disease. Dr. Bramwell has also made further observations on the clinical significance of 'gallop rhythm' of the heart and on the symptoms associated with it. The origin of the heart-sounds in this condition has been analysed by means of graphic records. The serious import of the rhythm is confirmed by the fact that, of 62 patients showing it, only 15 lived for more than eighteen months from the time when the rhythm was first noticed. It appears that 'gallop rhythm' only develops when the heart-muscle is so lacking in tone as to be unable to respond physiologically to the ordinary strains of life.

A part-time grant has been made to Dr. J. F. Wilkinson at the Department of Clinical Investigation, Manchester Royal Infirmary, and he has been provided with the whole-time assistance of

Dr. L. Klein and Dr. C. A. Ashford and the part-time assistance of Dr. G. S. Smith. The records of nearly 700 cases of pernicious anaemia treated during the past six years indicate that adequate dosage of hog's stomach or parenteral liver extracts enables normal health to be regained and maintained, and that involvement of the spinal cord does not develop in patients thoroughly treated by these means. With Dr. R. Ellis and Dr. J. Scully, further observations have been made on the treatment of subacute combined degeneration of the spinal cord. It seems clear that those patients with symptoms due solely to involvement of the peripheral nerves respond well to anti-anaemic treatment given in full dosage: in this respect desiccated hog's stomach has proved of special value. Dr. Klein, Dr. Ashford, and Dr. Wilkinson have continued to study the properties of the anti-anaemic principle in hog's stomach ('haemopoietin'), the anti-anaemic liver principle, the 'extrinsic factor' of Castle, and their interrelationships. It has been shown that haemopoietin, or a closely similar substance, is present not only in pig's stomach, but also in the normal human stomach, and there is evidence of its presence in the stomachs of patients with aplastic anaemias. On the other hand, in pernicious anaemia the stomach does not contain sufficient haemopoietin to be detected by current methods. Examinations of the distribution of the anti-anaemic principle in human liver suggest that it is absent only from the livers of untreated cases of pernicious anaemia in relapse: it has been found in normal quantity in treated cases of pernicious anaemia, and in aplastic and other anaemias. Studies of the properties of the 'extrinsic factor' have confirmed that it is not vitamin B_2. With Dr. M. C. G. Israëls, a Lady Tata Memorial Scholar, Dr. Wilkinson has been able to differentiate a special form of anaemia which had not hitherto been described. An account of this disease (termed 'achresthic anaemia') has been published. On behalf of the Therapeutic Trials Committee, Dr. Wilkinson and his colleagues have continued to investigate the aetiology and treatment of agranulocytosis, and the value of suprarenal cortical extracts in Addison's disease.

Dr. R. W. Brookfield, who had grants at Liverpool, has investigated the claim of Hirschfelder that uraemic coma is associated with a very high content of magnesium in the blood. He has been unable to confirm this view, and concludes that the comparatively slight increase in serum magnesium which may occur in the later stages of nephritis probably has no bearing on the symptoms of the disease.

At the General Hospital, Newcastle-upon-Tyne, Mr. S. F. Evans had personal and expenses grants for work on the artificial production of fever by high-frequency electric fields. By the methods now used, it is possible to raise a patient's temperature to 105°–

106° F., with confidence that the fever can be controlled. With Dr. S. Whately Davidson, fifteen cases of general paralysis of the insane have been treated by this means: five of the patients have been greatly benefited and two others have improved. A number of other diseases have been treated by this means, but it is too early yet to record results.

With a part-time grant at the Royal Victoria Infirmary, Newcastle-upon-Tyne, Dr. C. C. Ungley has continued his work on the nutritional aspects of anaemia. He has analysed the case-records of a series of patients with subacute combined degeneration of the spinal cord who were treated with liver extract intramuscularly during a period of two and a half years: the results in the main were very satisfactory. With Dr. F. J. Nattrass and Mr. S. F. Evans, pyrexia induced by high-frequency electric fields is being tried in cases which have ceased to improve under liver treatment. Dr. Ungley has also made further observations on the properties of the blood-regenerating material produced by the interaction of gastric juice or stomach tissue and yeast extracts.

Grants have again been made to Dr. C. P. Stewart and Dr. D. M. Dunlop for work in Professor D. Murray Lyon's department at Edinburgh. Dr. Stewart and Dr. W. O. Kermack have examined the effects of fructose upon the glucose content of the blood in man: the results indicate that fructose stimulates the production of insulin but is not itself directly affected by the hormone. With Dr. R. Gaddie and Mr. Dickson, Dr. Stewart has also done further work upon the method by which glycogen is broken down to lactic acid in voluntary muscle, and on the chemistry of the blood fats in health and in diabetes. Professor A. J. Clark, Dr. Gaddie, and Dr. Stewart have studied the metabolism of the isolated amphibian heart poisoned by iodoacetic acid. It has been found that, in the presence of oxygen, lactic and pyruvic acids are oxidized by the heart-muscle and cause rapid recovery from the poisoning; similar, but slower, recovery is brought about by fatty acids and by some amino-acids. Research by Dr. Stewart and Mr. W. C. Wilson, on the causes of death after severe burns, is mentioned at p. 88.

Professor Murray Lyon and Dr. Dunlop have investigated the value of mandelic acid in the treatment of infections of the kidney and bladder. Their results confirm the favourable claims of Rosenheim, the originator of this treatment. Work has also been done on the metabolism of sodium chloride in Addison's disease, and on the action of suprarenal cortical extracts in this condition. With Professor C. R. Harington of University College Hospital, London, Dr. Dunlop has continued to study the effects of the synthetic thyroid principle (di-iodothyronine) on cases of myxoedema

and of obesity. It appears that this compound is in every way a satisfactory therapeutic substitute for natural thyroid gland, and it seems to have less toxic effect on the heart.

Dr. J. D. S. Cameron, at Edinburgh, has had a grant for the expenses of a follow-up study of the cases of nephritis and high blood-pressure which have passed through Dr. Edwin Matthew's wards at the Royal Infirmary during the past ten years.

At St. Andrews University, Professor David Waterston has again had a grant for assistance by Miss M. H. Kidston in work on the mechanism of pain. They have continued their microscopic studies of the distribution of the nerves to human skin, in an attempt to explain the differences in pain-sensibility between the superficial and deeper layers.

A grant is made for the expenses of work by Professor L. S. P. Davidson and his colleagues at Aberdeen. The study of blood diseases, asthma, goitre, diabetes, and rheumatoid arthritis has been continued at the Royal Infirmary, in special clinics formed for the purpose. Further therapeutic tests have been made of preparations supplied by manufacturers for the treatment of pernicious anaemia, and an investigation of anaemia due to iron deficiency has been completed. Observations on 3,500 patients of the poorest classes have shown that this type of anaemia is uncommon in men, but very frequent in children between two and five years of age and especially in adult women. The cause is almost certainly a lack of iron in the diet, and the disease can readily be cured by giving iron. It is of interest, however, that examination of several hundred working girls in the city revealed no anaemia comparable to the 'chlorosis' of thirty years ago. This finding supports the view that chlorosis was not due solely to iron deficiency, though it may well be that iron deficiency, while still widespread, is less severe now than at the beginning of the century. An account has been published of a series of cases of Weil's disease which occurred mainly among workers in the fish-curing industry of Aberdeen. The factors determining the spread of this type of infectious jaundice have been investigated with Dr. H. J. Rae and Dr. J. Smith of the City Public Health Department. Improvements since adopted in the fish-curing factories have already led to a rapid fall in the local incidence of the disease. With Dr. C. E. van Rooyen (p. 139) of Edinburgh, observations are being made on the value of Gordon's test for the diagnosis of lymphadenoma from other conditions associated with enlargement of the lymphatic glands. Dr. W. Goldie, who has charge of the arthritis clinic, has begun an experimental inquiry into the parts played by infection and allergy in acute and chronic rheumatism: he is using methods devised by Professor Klinge of Münster, under whom he recently worked. Dr. I. G. W. Hill and Dr. Barton, of

Chicago, have examined the effects of X-ray treatment upon the human thyroid gland.

Professor Davidson at Aberdeen, Professor E. J. Wayne at Sheffield, and Dr. C. C. Ungley at Newcastle, have, at the request of the Council, made clinical tests of a substance recently isolated by Dakin and West in America from commercial liver extract, and which it is thought may represent the pure, or nearly pure, anti-anaemic liver principle: supplies of this substance were provided for the purpose by British Drug Houses, Ltd. A single dosage of 200 milligrammes intravenously has proved effective for blood-regeneration in cases of pernicious anaemia, and its value in subacute combined degeneration of the spinal cord is at present being examined.

T. W. Adams and E. P. Poulton—
'A New Study of Heat Production in Man. I. A Fundamental Error in Indirect Calorimetry.' *Guy's Hosp. Rep.*, 1934, **84**, 473. 'II. The Output of Carbon Dioxide as a Measure of Heat Production in Basal Metabolism.' *Ibid.*, 1935, **85**, 56.

C. A. Ashford—
'Glycolysis in Brain Tissue.' *Biochem. J.*, 1934, **28**, 2229.

J. C. Bramwell—
'Sounds and Murmurs Produced by Auricular Systole.' *Quart. J. Med.*, 1935, n.s. **4**, 139.
'Gallop Rhythm.' *Ibid.*, 1935, n.s. **4**, 149.
'Prognosis of Heart Disease in Pregnancy.' *Lancet*, 16th Mar. 1935.
'Treatment of Heart Disease in Pregnancy.' *Brit. med. J.*, 1st June 1935.

R. D. Clay and R. D. Lawrence—
'An Insulin-Resistant Diabetic.' *Brit. med. J.*, 6th Apr. 1935.

L. S. P. Davidson, R. M. Campbell, H. J. Rae, and J. Smith—
'Weil's Disease (Leptospirosis); Clinical and Bacteriological Study of 19 Cases Occurring Chiefly among Fish Workers.' *Brit. med. J.*, 22nd Dec. 1934.

L. S. P. Davidson, H. W. Fullerton, and R. M. Campbell—
'Nutritional Iron-deficiency Anaemia.' *Brit. med. J.*, 3rd Aug. 1935.

W. Deutsch and J. F. Wilkinson—
'The "Methaemoglobin-Production" Test for Assaying the Anti-Anaemic Potencies of Liver Extracts.' *Brit. J. exp. Path.*, 1935, **16**, 33.

D. M. Dunlop and H. Scarborough—
'The Specific Effect of Ascorbic Acid on the Anaemia of Scurvy.' *Edinb. med. J.*, 1935, **42**, 476.

R. Gaddie and C. P. Stewart—
'The Anaerobic Breakdown of Carbohydrate in the Isolated Ventricle of the Frog.' *J. Physiol.*, 1934, **80**, 457.
'The Role of Glutathione in Muscle Glycolysis.' *Biochem. J.*, 1935, **29**, 2101.

H. Jackson, L. Klein, and J. F. Wilkinson—
'The Iron and Copper Contents and the Haemopoietic Activities of Stomach and Liver Preparations.' *Biochem. J.*, 1935, **29**, 330.

F. P. L. Lander, N. F. Maclagan, and F. G. Nicholas—
'Gastric Acidity in Relation to the Position and Motility of the Stomach.' *J. Physiol.*, 1934, **83**, 17 P.

D. M. Lyon and D. M. Dunlop—
'Studies in the Nephrotic Syndrome.' *Edinb. med. J.*, 1935, n.s. **4**, 68.
'Mandelic Acid in the Treatment of Urinary Infections.' *Brit. med. J.*, 7th Dec. 1935.

R. A. McCance—
'Effect of Sudden Severe Anoxaemia on the Function of the Human Kidney.' *Lancet*, 17th Aug. 1935.

R. A. McCance and R. D. Lawrence—
'The Secretion of Urine in Diabetic Coma.' *Quart. J. Med.*, 1935, n.s. **4**, 53.

N. F. Maclagan—
'The Influence of the Acid Base Equilibrium on Gastric Secretion.' *J. Physiol.*, 1934, **83**, 16 P.
'Gastric Secretion and Physique.' *Ibid.*, 1935, **83**, 39 P.

E. P. Poulton—
'Dyspnoea.' *Guy's Hosp. Gaz.*, 14th Sept. 1935.

E. F. Scowen and A. W. Spence—
'A Concentrated Liver Extract for Parenteral Administration in Pernicious Anaemia.' *Brit. med. J.*, 9th Feb. 1935.

A. W. Spence—
'Researches on the Aetiology of Goitre.' *St. Bart.'s Hosp. med. Rep.*, 1934, **67**, 203.

A. W. Spence and E. F. Scowen—
'The Use of Gonadotropic Hormones in the Treatment of Undescended Testes: Preliminary Report.' *Proc. R. Soc. Med.*, 1935, **28**, 427.
'The Effect of Ascorbic Acid on Experimental Goitre.' *Biochem. J.*, 1935, **29**, 562.

C. P. Stewart, J. P. Dickson, and R. Gaddie—
'The Determination of Lactic Acid in Muscle.' *Biochem. J.*, 1934, **28**, 1945.

C. P. Stewart and E. B. Hendry—
'The Determination of Total Fatty Acids in Blood.' *Biochem. J.*, 1935, **29**, 1677.
'The Phospholipins of Blood.' *Ibid.*, 1935, **29**, 1683.

C. H. Stuart-Harris—
'Haemolytic Streptococcal Fibrinolysis.' *Brit. J. exp. Path.*, 1935, **16** 513.

D. Waterston—
'Pain and the Mechanism of its Production.' *Brit. med. J.*, 15th Dec. 1934.

J. F. Wilkinson—
'The Treatment of Pernicious Anaemia.' *Practitioner*, 1935, **134**, 272.
'A Note on Agranulocytic Angina.' *Ibid.*, 1935, **134**, 283.
'Early Diagnosis and Treatment of Pernicious Anaemia.' *Fasciculus Cestriensis in honour of Sir William Hodgson*, 1934, p. 103.

J. F. Wilkinson and W. Deutsch—
'Der "Methämoglobintest" für die Bestimmung der antianämischen Wirksamkeit von Leberextrakten.' *Klin. Wschr.*, 1935, **14**, 926.

J. F. Wilkinson and M. C. G. Israëls—
'Achresthic Anaemia. *Brit. med. J.*, 26th Jan. 1935.

Clinical Trials of New Remedies

The Therapeutic Trials Committee (p. 164) continue to receive applications from manufacturers for clinical trials of new remedies

which seem likely, on experimental grounds, to have value in the treatment of disease. During the year under review the Committee have arranged for tests of three new remedies and the trials of eight others previously accepted have been extended.

In July, 1935, a conference was held of the various clinicians and pathologists who had tested staphylococcal toxoid on the Committee's behalf. The conference considered the reports of some fifteen workers on more than 400 cases treated by this means. In addition, Dr. C. E. Dolman of the Connaught Laboratories, Toronto, attended the meeting to give the members the benefit of his experience of the treatment in Canada. From the results as a whole, the conference concluded that the staphylococcal toxoids at present available in Great Britain may be useful antigens for the treatment of boils and styes, but are of relatively little value in the treatment of sycosis. Individual members of the conference are publishing papers on their results.

The Council would here again express their strong sense of indebtedness to the experts in many different branches of medicine and surgery who so generously give help in testing new remedies on behalf of the Committee.

L. Forman—
'On the Treatment of Sycosis with Staphylococcal Toxoid.' *Delib. IX Congr. Internat. Dermatol.* (1935), Vol. II.

D. S. Murray—
'Staphylococcus Toxoid: A Clinical Trial.' *Lancet*, 9th Feb., 1935.

G. Stewart Smith—
'A Case of Agranulocytosis treated with Pentnucleotide.' *Lancet*, 16th Mar., 1935.

Surgery

In Sir David Wilkie's department at Edinburgh, Mr. W. C. Wilson has had a part-time grant to study the cause of death after extensive burns. With Dr. C. P. Stewart and others, it has been shown that, a few hours after a burn is sustained, the tissue fluid from the burned area contains poisons produced by breakdown of the damaged cells. The process of cell breakdown is accelerated by bacterial infection, but is not primarily dependent upon it. Injection of this toxic fluid produces effects similar to those which follow burns. Attempts are being made to determine the chemical nature of the poisons concerned: it seems likely that they are globulin derivatives. Mr. Wilson has also made observations on the nervous control of sweating in man, and on the effects of acetylcholine upon the hypothalamic centres of the human brain. In the same department, grants have been made to Dr. S. B. Stoker for work on blood-coagulation in relation to surgery. Dr. W. Ritchie Russell, working here, has completed the clinical and pathological studies of head-injuries for which he received a part-time grant.

Mr. G. L. Alexander, at Edinburgh, has had part-time and expenses grants for work under the direction of Mr. Norman Dott. He has studied various clinical problems of neuro-surgery and has investigated experimentally the neurological and endocrine factors in polyuria and diabetes insipidus. The inquiry is being extended to include observations on the central control of carbohydrate metabolism and body heat.

With an expenses grant at Glasgow, Dr. D. P. Cuthbertson has extended his studies of the effects of accidental injuries on human metabolism. It has been shown that diets rich in protein and of high caloric value will partially control the excessive breakdown of tissue protein which ordinarily occurs after fractures of the long bones. From a series of clinical and biochemical observations on patients hurt in accidents, it is concluded that the general treatment of severe injuries should include diets of this type.

At the Buckston Browne Surgical Research Farm, Downe, Kent, Mr. L. F. O'Shaughnessy has had a personal grant for experimental work in surgery. With Dr. D. Slome, he has investigated the causation and treatment of shock after injury. Their results indicate that the view that this type of shock is due to the liberation of poisons from the damaged tissues is incorrect: it appears that the two significant factors in traumatic shock are local fluid loss and the discharge of nerve impulses from the injured area, the latter probably being the more important. Attempts to treat shock by the elimination of nerve impulses by spinal anaesthesia have been encouraging. The work is being extended in co-operation with Sir Henry Dale, Dr. G. L. Brown, and Dr. W. Feldberg of the National Institute (p. 52). Mr. O'Shaughnessy has also continued his clinical and experimental studies of thoracic surgery, with special reference to the possibilities of surgical treatment for coronary thrombosis and other diseases of the heart.

The Council have again provided the expenses of research by Mr. J. W. Tudor Thomas in Professor T. Graham Brown's department at Cardiff. In relation to his clinical work on a surgical treatment of blindness due to opacities of the cornea, Mr. Thomas has made further observations on the factors influencing the union and clarity of corneal grafts and the return of sensitivity in the grafted cornea.

At St. Mark's Hospital, London, Mr. W. B. Gabriel has had a grant towards the expenses of the follow-up scheme for patients with cancer. The histories of patients after operation are traced by means of regular inquiries every six months, and a systematic record is now available of every case of cancer of the colon or rectum admitted to the hospital since 1910. During the year under review a special study has been made of the cases of rectal cancer treated here by colostomy: a paper has been published on the

immediate and late results of this operation in a large series of cases.

Mr. Harold Dodd, at the King George Hospital, Ilford, has received expenses for a clinical, biochemical, and radiological study of cases of peptic ulcer, chronic appendicular dyspepsia, and gall stones, before and after surgical treatment. The objects of the inquiry are to determine whether chronic appendicitis predisposes to peptic ulcer, and to elucidate some of the factors influencing the rate of post-operative recovery in gastro-intestinal disorders.

With a grant for expenses at the Royal Free Hospital, London, Miss D. J. K. Beck and Miss S. T. Widdows are investigating the blood-chemistry of patients with thyrotoxicosis, with special reference to the cause of the serious reactions which occasionally follow partial removal of the thyroid gland for this condition. So far, no characteristic difference has been observed between the blood-sugar curves of patients with simple and toxic goitre, recorded before and after operation.

At the British Red Cross Clinic for Rheumatism, London, Dr. F. C. Golding has had part-time and expenses grants to study the relationship between sacro-iliac disease and the type of arthritis of the spine known as 'spondylitis ankylopoetica'. Ninety-one cases of this spinal lesion have been examined clinically and radiologically, and in all of them the sacro-iliac joints were diseased. A further series of patients had arthritis of the sacro-iliac joint without spinal changes, although their symptoms resembled those of spondylitis. It is concluded that sacro-iliac arthritis may be the earliest manifestation of spondylitis, making it possible to diagnose and treat the condition months or years before the spine itself becomes involved.

A grant for expenses has been made to Mr. A. G. Timbrell Fisher at the St. John Clinic and Institute of Physical Medicine, London. He is examining, by means of the arthroscope, the early pathological changes in chronic infective arthritis and in other forms of rheumatism. The bacteriology of the affected joints is being studied by Dr. G. H. Eagles, of the Lister Institute, who also has an expenses grant.

Clinical and experimental research on the treatment of cancer with radium is noticed separately, at p. 120.

D. P. Cuthbertson and S. L. Tompsett—
'Note on the Effect of Injury on the Level of the Plasma Proteins. *Brit. J. exp. Path.*, 1935, **16**, 471.

W. B. Gabriel and O. V. Lloyd-Davies—
'Colostomy.' *Brit. J. Surg.*, 1935, **22**, 520.

L. O'Shaughnessy and D. Slome—
'Etiology of Traumatic Shock.' *Brit. J. Surg.*, 1935, **22**, 589.

H. M. Traquair, N. M. Dott, and W. R. Russell—
'Traumatic Lesions of the Optic Chiasma.' *Brain*, 1935, **58**, 398.

W. C. Wilson—
'Some Aspects of Sweat Secretion in Man: with Special Reference to the Action of Pilocarpine.' *Brain*, 1934, **57**, 422.

ANAESTHETICS

Research in this subject is directed by the Committee shown at p. 164, appointed jointly with the Section of Anaesthetics of the Royal Society of Medicine. An account of the Committee's work in the first eleven years of its existence has been published in the *Proceedings* of the Society.

During the year now under review, the Committee have made extensive trials of a special preparation of divinyl ether, known as 'vinethene'. Generous supplies of this substance were placed at their disposal by the American manufacturers, Messrs. Merck & Co., of New Jersey. The results of the tests were published by Sir Francis Shipway, whose report showed it to be an anaesthetic of undoubted value.

Another new general anaesthetic, cyclopropane, has also been examined by the Committee. Supplies of the gas, which has hitherto been obtainable only from the United States, were distributed to anaesthetists at various hospitals, and at the same time steps were taken to promote its manufacture in this country. A British firm of chemical manufacturers has now undertaken to place supplies of the gas on the market. Small amounts already made by this firm have been tested by the Committee and found, in purity and potency, to equal the American product.

The Council were recently consulted by the Ministry of Health and the Home Office as to the steps that might be taken to prevent the explosions of anaesthetic gases which occasionally happen in operating theatres. At a conference between representatives of the Committee and of the other bodies concerned, it was agreed that, especially with respect to the part played by static electrical discharges, further information, involving detailed research, was necessary. Through the Department of Scientific and Industrial Research, the National Physical Laboratory was invited to undertake the inquiry. Since then, members of the staff of the Laboratory have been in consultation with the Committee and an investigation is in progress.

The results of work by Dr. N. E. Pitt of Guy's Hospital on the influence of avertin upon renal function have now been published. The expenses of this study and of some of the work on cyclopropane have been defrayed from a special bequest for research on anaesthetics which was allocated by the executor, Mr. Gerald Heard, on the advice of the Committee.

Work on anaesthesia for obstetric cases is mentioned separately below (p. 94).

C. F. Hadfield—
'The Joint Anaesthetics Committee: A Retrospect of Eleven Years Work.' *Proc. R. Soc. Med.*, 1935, 28, 1133.

N. E. Pitt—
'Influence of Avertin upon the Renal Function.' *Lancet*, 30th Mar. 1935.

F. Shipway—
'Vinethene.' *Brit. med. J.*, 12th Jan. 1935. Also *Lancet*, 12th Jan. 1935.

Obstetrics and Gynaecology

Disorders of Pregnancy

At the Royal Maternity and Women's Hospital and the Royal Infirmary, Glasgow, Dr. D. F. Anderson (p. 160) had a part-time grant for work on the toxaemias of pregnancy. He has studied especially the metabolism of chlorides in the pre-eclamptic state. No striking variation has been found in the sodium chloride of the blood in this condition, but the percentage of the salt in oedema fluid has always considerably exceeded that in the blood. As improvement occurs and oedema diminishes, the percentage of sodium chloride in the fluid decreases. With Dr. S. L. Tompsett, Dr. Anderson has also investigated the copper content of the blood in pregnancy. It has been shown that in the majority of normal pregnancies this increases during the last three months. Blood-copper values in the anaemias of pregnancy were found to be closely similar to those in normal pregnancy.

With an expenses grant at the same hospitals, Dr. Dugald Baird has continued his work on infections of the urinary tract in pregnant women. A follow-up study is being made of the late results of pregnancy pyelitis, with special reference to the incidence of chronic urinary infections and of recurrence of acute pyelitis in subsequent pregnancies. Some of the patients have been under observation since 1928, and have been followed through as many as four pregnancies. An inquiry has been begun into the relationship between cervicitis and chronic infections of the urinary tract: the possibility is being examined of curing persistent urinary infection by treatment of the infected *cervix uteri*.

Dr. H. R. MacLennan of the Royal Samaritan Hospital, Glasgow, who had part-time and expenses grants to study the geographical distribution of contracted pelvis in Scotland, has completed his survey, and is preparing an account of the findings.

At the Royal Free Hospital, London, Mrs. E. C. Pillman-Williams has had a grant for laboratory assistance in studies of the effects of iron and vitamin B therapy on the health of pregnant women. She is investigating the incidence of anaemia and of toxaemia in women so treated and in untreated controls. The preliminary results indicate that the treatment will prevent the so-called 'physiological anaemia' of pregnancy.

Reference is made at p. 129 to work on the physiology of the uterus and to studies of the action of oestrone and other sex hormones.

D. Baird—
'The Upper Urinary Tract in Pregnancy and Puerperium, with Special Reference to Pyelitis of Pregnancy. I and II.' *J. Obstet. Gynaec.*, 1935, **42**, 577 and 733.

S. L. Tompsett and D. F. Anderson—
'The Copper Content of the Blood in Pregnancy.' *Brit. J. exp. Path.*, 1935, **16**, 67.

Puerperal Infections

At Queen Charlotte's Hospital, London, Dr. Leonard Colebrook, of the Council's staff, has continued to direct studies of puerperal fever under a scheme generously assisted by the Rockefeller Foundation. Dr. R. Hare and Dr. Dora Colebrook have again received personal grants here. As already mentioned, Dr. Dora Colebrook has extended her inquiry into the sources of infection in puerperal fever. An account of her work on this subject has been issued by the Council in their series; the report calls attention to the risks of haemolytic streptococci being conveyed to the parturient woman from her own nose or throat or from a member of her family, as well as from an attendant carrier or another septic case. Dr. Hare, working with Mrs. R. Lancefield of the Rockefeller Institute, New York, has been able to confirm, by means of a precipitation reaction, his previous observation that the great majority of haemolytic streptococci isolated from puerperal infections can be distinguished from strains obtained from the genital tract in the absence of puerperal fever. By application of the same test he has also thrown new light on the throat-carrier problem, showing that many of the haemolytic streptococci derived from healthy throats belong to groups which seldom, if ever, give rise to infections in man, although they may do so in the lower animals. It is expected that this finding will have practical value in determining whether it is safe for throat carriers of haemolytic streptococci engaged in midwifery, surgery, or the handling of milk supplies, to continue in these occupations. Work on similar lines by Dr. Hare and Dr. Leonard Colebrook has dealt with the possible danger to women after child-birth of haemolytic streptococci present in the lower bowel or on the skin. By studying the changes in the bactericidal power of the patient's blood, Dr. Hare has further investigated the mechanism of recovery from puerperal fever and the factors which tend to prevent it. The protective value of anti-streptococcal sera in experimental infections of animals, and in human puerperal fever, has been studied by Dr. Leonard Colebrook. His analysis of case-records suggests that the antitoxic sera at present available do not ordinarily increase the chances of

recovery from this disease. In the hope of avoiding the irritant effects produced in the eyes of new-born infants by the routine applications of silver nitrate, Dr. R. M. Fry, of this hospital, has investigated the uses of a number of other antiseptics for preventing infections of the eye.

With a grant for assistance to Professor M. H. Phillips at the Firth Auxiliary, Jessop Hospital for Women, Sheffield, Dr. C. G. Paine has extended his work on immunity to haemolytic streptococcal infections. It has been shown that an acid-soluble protein isolated from virulent streptococci will readily kill normal human leucocytes *in vitro*. This effect can be prevented by the previous addition to the protein of an antiserum prepared by repeated injections of heat-killed cocci. The toxic effects of other streptococcal extracts are being similarly studied.

D. C. Colebrook—
'The Source of Infection in Puerperal Fever due to Haemolytic Streptococci.' *Spec. Rep. Ser. Med. Res. Coun.*, Lond., No. 205, 1935.

L. Colebrook—
'Treatment of Puerperal Fever by Antistreptococcal Serum; some new evidence and a retrospect.' *Lancet*, 11th May 1935.

L. Colebrook, W. R. Maxted, and A. M. Johns—
'The Presence of Haemolytic and other Streptococci on Human Skin.' *J. Path. Bact.*, 1935, **41**, 521.

R. Hare—
'Alterations in the Bactericidal Power of the Blood which occur during Haemolytic Streptococcal Infections in the Puerperium.' *J. Path. Bact.*, 1935, **41**, 61.
'The Classification of Haemolytic Streptococci from the Nose and Throat of Normal Human Beings by Means of Precipitin and Biochemical Tests.' *Ibid.*, 1935, **41**, 499.

R. Hare and W. R. Maxted—
'The Classification of Haemolytic Streptococci from the Stools of Normal Pregnant Women and of Cases of Scarlet Fever by means of Precipitin and Biochemical Tests.' *J. Path. Bact.*, 1935, **41**, 513.

R. C. Lancefield and R. Hare—
'The Serological Differentiation of Pathogenic and Non-Pathogenic Strains of Haemolytic Streptococci from Parturient Women.' *J. exp. Med.*, 1935, **61**, 335.

C. G. Paine—
'The Aetiology of Puerperal Infection, with Special Reference to Droplet Infection.' *Brit. med. J.*, 9th Feb. 1935.
'Haemolytic Streptococcal Leucocidin.' *Ibid.*, 29th June 1935.

Anaesthetics in Child-birth

With part-time and expenses grants in the Obstetric Unit at University College Hospital, London, Dr. Freda C. Kelly has continued her work on anaesthetics for preventing the pains of childbirth. She has examined the value of sodium soneryl and syrup of chloral given together for the first stage of labour: in the great majority of the patients tested a suitable dosage of these drugs gave relief from pain without producing any ill effects on mother

or child. Paraldehyde given by the rectum was less satisfactory as an anaesthetic, and was found to cause drowsiness in the babies. Further tests have been made of different methods of administering chloroform in labour, and a limited trial has been made of divinyl ether as an anaesthetic for obstetric cases.

Paediatrics

Dr. Helen Mackay continues her work in this field as a part-time member of the Council's scientific staff. At the Queen's Hospital for Children, Hackney Road, London, she is examining the value of a soya bean preparation as a supplement to milk in the diet of infants. The iron content of the bean is comparatively high, and it is thought that it may possibly replace inorganic iron salts for the prevention and treatment of nutritional anaemia. With Miss L. Goodfellow, Dr. Mackay has extended her studies of the incidence of anaemia among mothers attending the out-patient department of this hospital. Observations made at the Mothers' Hospital, Clapton, suggest that the so-called 'early anaemia' of premature infants does not develop if the infant's general health has been satisfactory from birth. The average haemoglobin level of healthy premature infants two to three months old was only slightly lower than that of full term infants of the same age. Giving iron and injections of blood to premature babies did not diminish the 'physiological' fall in haemoglobin level which ordinarily occurs during the first few months of life. An inquiry at the North Eastern Hospital, Tottenham, into the effects of adding extra rations of vitamins A and D to the diets of children with measles has been completed. The results showed that this treatment was without effect on the course of this disease or on the incidence of the minor skin infections which commonly complicate it.

At Birmingham, Professor L. G. Parsons has again had grants for expenses and for assistance by Dr. E. M. Hickmans. They have continued their studies of the anaemias of childhood, special attention being given to those associated with infantile scurvy and with cretinism. From observations of the blood-picture at different stages of these diseases, it would appear that the respective curative agents, vitamin C and thyroxin, stimulate the blood-forming tissues throughout the whole process of red-cell maturation. Further work on nutritional anaemia in infants has included tests of the therapeutic action of predigested yeast given by mouth. This treatment, which has been shown to have special value in the idiopathic hypochromic anaemia of adults, was not more effective than untreated yeast in improving nutritional anaemia in infants. The role of bile pigment in blood-formation is at present being examined. Preliminary studies have shown that bile pigment will

raise the haemoglobin level in nutritional anaemia without causing a significant reticulocytosis. These results in iron deficiency anaemia of infants confirm those of Minot and Patek in adults, and suggest that bile pigments are by no means waste-products, but play a definite part in blood-formation. Other research by Professor Parsons and his colleagues has included studies of the glucose-tolerance curve in children at different ages and observations on the biochemistry of cystinuria. An inquiry into the seasonal variations in the anti-rachitic power of sunshine and sky-shine in Birmingham has been completed.

A grant has been made for the expenses of work jointly by Dr. J. C. Hawksley at University College Hospital, London, and Dr. R. C. Lightwood at Great Ormond Street Hospital. They have investigated the factors causing nutritional anaemia in children past the age of infancy, examining especially the parts played by gastro-intestinal diseases, and by achlorhydria, in hindering the normal absorption of iron from the bowel. Observations have been continued upon the mean diameter of the red-blood cells in acholuric family jaundice. The 'microcytosis' of this disease has been found to vary in degree from case to case and also in the same case from time to time. The effect of blood-transfusion is to raise the mean diameter of the cells for a short period: this, however, is due mainly to admixture of normal cells. Treatment by operative removal of the spleen causes a shift of the mean diameter towards the normal, but complete normality is seldom reached, and the microcytosis tends to recur.

At the David Lewis Northern Hospital, Liverpool, a grant has been made to Dr. A. L. Smallwood for the cost of apparatus needed for an investigation of the effects of different milk foods upon the composition and acidity of the gastric juice in infants.

The Council have again provided the expenses of work by Dr. G. B. Fleming and his colleagues, at the Royal Hospital for Sick Children, Glasgow. These workers have continued their clinical and biochemical studies of metabolic, renal, and blood diseases of childhood. Dr. Noah Morris, who has received a part-time grant here, has investigated the phosphatase content of the blood in conditions associated with disturbances of mineral metabolism. With Miss O. D. Peden, he has examined especially the changes in blood-phosphatase which occur during the healing of rickets and of fractures, and in children with dental caries. An inquiry into the effects of acute and chronic infections upon the chlorine content of the blood and tissues has been made by Dr. J. W. S. Blacklock (p. 115) and Dr. Morris. It has been shown that acute pneumococcal, streptococcal, and staphylococcal infections lead to an excessive retention of chlorine in the tissues without a corresponding increase in the water content. Chlorine retention does not occur

in chronic infections with these bacteria, and attempts are being made to determine whether it occurs in tuberculosis. Dr. Jessie W. Ogilvie has made further observations on gastric secretion in childhood, and has found that in coeliac disease there is frequently a reduction in the free hydrochloric acid of the stomach. She has also investigated the relationship between the acid content of the stomach and hypochromic anaemia in children.

Dr. W. R. F. Collis, who had part-time and expenses grants at the National Children's Hospital, Dublin, has continued the studies of erythema nodosum and of tuberculosis in children which he began at Great Ormond Street Hospital, London. An account of work on primary pulmonary tuberculosis in children is being prepared for publication.

R. T. Fletcher and O. D. Peden—
'A Note on the Blood Chemistry in Epilepsy.' *Lancet*, 15th June 1935.

S. Graham—
'Dehydration and Acidosis in Gastro-Enteritis.' *Practitioner*, 1935, **134**, 441.

J. C. Hawksley—
'A Note on the Occurrence of Auer's Bodies in Monocytic Leukaemia.' *J. Path. Bact.*, 1935, **40**, 365.

J. C. Hawksley and U. M. Bailey—
'The Mean Diameter of the Erythrocytes in Acholuric Family Jaundice and Effects of Splenectomy.' *Lancet*, 15th Dec. 1934.

J. C. Hawksley, R. Lightwood, and U. M. Bailey—
'Iron-Deficiency Anaemia in Children: its Association with Gastro-intestinal Disease, Achlorhydria and Haemorrhage.' *Arch. Dis. Childh.*, 1934, **9**, 359.

E. M. Hickmans and W. C. Smallwood—
'A Study of Cystinuria in Two Sisters.' *Biochem. J.*, 1935, **29**, 357.

R. Lightwood, J. C. Hawksley, and U. M. Bailey—
'Supravital Staining in the Diagnosis of the Leukaemias.' *Proc. R. Soc. Med.*, 1935, **28**, 405.

H. M. M. Mackay—
'Dietetic Deficiencies and Susceptibility to Infection, with Special Reference to Children.' *Lancet*, 29th Dec. 1934.
'The Haemoglobin Level among London Mothers of the Hospital Class.' *Lancet*, 22nd June 1935.
'The Early Anaemia of Premature Infants: the Haemoglobin Level of Immature Babies in the first Half-year of Life and the Effect during the First Three Months of Blood Injections and Iron Therapy.' *Arch. Dis. Childh.*, 1935, **10**, 195.
'Anaemia in Infancy and Childhood.' *Practitioner*, 1935, **135**, 200.

J. W. Ogilvie—
'Gastric Secretion in Coeliac Disease.' *Arch. Dis. Childh.*, 1935, **10**, 93.
'The Gastric Secretion in Anaemia.' *Ibid.*, 1935, **10**, 143.

L. G. Parsons and W. C. Smallwood—
'Studies in the Anaemia of Infancy and Early Childhood: Part X. The Anaemia of Infantile Scurvy.' *Arch. Dis. Childh.*, 1935, **10**, 327.
'The Anaemias of Infancy and Childhood.' *Practitioner*, 1935, **134**, 298.

J. B. Rennie—
'The Pathogenesis and Treatment of Renal Oedema.' *Glasg. med. J.*, 1935, **123**, *Trans. Roy. med.-chir. Soc. Glasg.*, **29**, 57 and 65.

Nutrition

Professor E. P. Cathcart, at Glasgow, has again had a grant for assistance by Mrs. A. M. T. Murray. They have completed the analysis of data on family diets collected from various towns in Great Britain over a period of years, and a report has been prepared for publication. The object of the work has been to obtain accurate knowledge of the nature and nutritive values of the foodstuffs used in different types of household. Particular attention has been given to the iron, calcium, and phosphorus contents of the diets. The possibility is being explored of making a quantitative survey of the diets of crofters and others in the remote Highland areas of Scotland, for purposes of comparison with the data from the towns.

At King's College Hospital, London, Dr. R. A. McCance has had grants for expenses and for assistance by Dr. L. R. B. Shackleton and Miss E. M. Widdowson. Observations have been continued on the chemical composition of fruits and vegetables and their losses in cooking. The amounts of inorganic iron and available phosphorus in different foods have been specially investigated. It appears that most of the iron of vegetables and bread, and little of the iron of meat, are utilized in human nutrition, and that about half the phosphorus of cereals, nuts, and pulses is in a form which cannot be absorbed. A quantitative study of the ordinary diets of 120 men and women has been completed by Miss Widdowson, and the results are being analysed. Other work by Dr. McCance is mentioned at pp. 81 and 132.

With an expenses grant at King's College of Household Science, London, Miss W. M. Clifford has continued to study the influence of halogen salts on enzyme action. She has published an account of the parts played by these salts in the coagulation of milk by trypsin, and is investigating their effects on the actions of pancreatic amylase and of invertase.

Expenses have again been provided for work by Professor S. J. Cowell at St. Thomas's Hospital, London. He has done further experiments on the factors controlling the excretion of calcium in the intestine. The relation between the rate of excretion and the total calcium of the blood has been examined under conditions which cause changes in the level of the blood-calcium. It appears that the rate of excretion depends on the degree of saturation of the tissues generally with calcium, but that it is not much affected by sudden variations in the calcium content of the blood.

In the whole-time service of the Council at the Lister Institute, London, Miss E. M. Hume (p. 100) has a grant for assistance by Miss H. Henderson Smith. With Dr. I. Smedley MacLean, further observations have been made on the effects of fat deficiency which

were noted by Burr and Burr in rats. Experiments are in progress to determine what substances in lard and linseed oil are responsible for curing the lesions produced and for restoring the rate of growth to normal. An inquiry is also being made into the influence of the fats in the diet on reproduction.

At the London School of Hygiene, Dr. Marion Watson has had personal and expenses grants to study the bearing of diet and other factors on resistance to bacterial infection and on fertility, in animals. The work is being done under the general direction of Professor W. W. C. Topley (p. 149) and Professor E. P. Cathcart, and with help from a special advisory committee. The preliminary results indicate that diet and various environmental factors have specific effects on the fertility, growth and survival-rates of young mice. Attempts are now being made to determine whether it is possible by dietetic means to increase the resistance to *Bact. aertrycke.*

W. M. Clifford—
'The Effect of Halogen Salts on the Clotting of Milk by Trypsin.' *Biochem. J.*, 1935, **29**, 1059.

E. I. Jones, R. A. McCance, and L. R. B. Shackleton—
'The Role of Iron and Silica in the Structure of the Radular Teeth of Certain Marine Molluscs.' *J. exp. Biol.*, 1935, **12**, 59.

R. A. McCance—
'The Availability of Food.' *Med. Pr.*, 1934, **189**, 463.

E. M. Widdowson and R. A. McCance—
'The Available Carbohydrate of Fruits. Determination of Glucose, Fructose, Sucrose and Starch.' *Biochem. J.*, 1935, **29**, 151.
'The Use of Purified Casein in Salt-free Diets.' *Lancet*, 22nd June 1935.

Iodine in Foodstuffs

Work on this subject is directed by the Committee (p. 165) appointed jointly with the Agricultural Research Council. In the last report mention was made of the help given by the Government Chemist, Sir Robert Robertson, and his staff in attempts to find a satisfactory method for the measurement of minute quantities of iodine in complex biological substances. It was stated that after prolonged study of the technical difficulties involved, Mr. C. O. Harvey of the Government Laboratory staff, had been able to devise a modification of an existing method, which gave consistent results in the hands of different analysts. A full account of Mr. Harvey's research has now been published by the Council, in order that the details of his method may be made available to all interested in the micro-determination of iodine, including medical workers on hyperthyroidism and other diseases.

Under the supervision of the Committee named above, Miss M. G. Crabtree has used Mr. Harvey's method to study the iodine content of samples of milk, pasture, and drinking-water from parts of England where simple goitre is common among school-children,

and where it is rare. The clinical aspect of the inquiry has been undertaken for the Committee by Dr. Matthew Young (p. 126) of the Council's staff. The results of the field-work already completed confirm the findings of previous observers as to the high incidence of this form of goitre in Somerset and its relatively low incidence in Suffolk. It is hoped that, with the improved analytical methods now available, it may be possible to decide definitely whether the incidence of goitre in these districts is actually related to the iodine-content of the local milk and water supplies. Miss Crabtree's findings so far indicate that the iodine-content of milk from the non-goitrous districts of Suffolk is higher than of that from the goitrous districts of Somerset. Thanks are due to the Director of the Lister Institute, who kindly permitted Miss Crabtree to work for a period at the Institute's laboratories at Elstree, where there was little likelihood of her results being affected by the presence of iodine in the atmosphere. The Council would also again make grateful acknowledgement of a generous donation from the Nitrate Corporation of Chile, Ltd., towards the cost of work on iodine in relation to human and animal health. This donation has been used partly for the studies mentioned above and partly for an inquiry at the Rowett Research Institute, Aberdeen, into the supposed relationship of iodine-deficiency to contagious abortion in cattle.

C. O. Harvey—
'The Determination of Iodine in Biological Substances.' *Spec. Rep. Ser. Med. Res. Coun.*, Lond., No. 201, 1935.

Vitamin Studies

Mention was made last year of the work done by the Accessory Food Factors Committee (p. 164) and by other experts in this country, in preparation for the second International Conference on Vitamin Standardization, held in London in 1934. The work of the Committee was organized through a series of four sub-committees appointed to deal with the vitamins A, B_1, C, and D respectively. At the conference a new international standard, pure β-carotene, was adopted for vitamin A, and a spectroscopic method was accepted as an alternative to the biological test for its measurement in liver oils and concentrates. It was felt that the details of the various researches which made these decisions possible would have value for workers in the field of nutrition: they have accordingly been collected and edited by Dr. H. Chick and Miss E. M. Hume, and issued by the Council as a special report.

With a grant for work under Dr. Chick's direction at the Lister Institute, London, Miss A. M. Copping has examined the physiological properties of the pigment flavin and the 'supplementary substance' which have been shown to be constituents of 'vitamin B_2'. The results of the inquiry, in which Miss C. E. Edgar has co-

operated, have been in general agreement with those of Dr. P. György and his co-workers at Cambridge. Deficiency of the 'supplementary substance', when flavin is given, is marked in rats by restriction of growth and the occurrence of symmetrical dermatitis: when flavin is also absent from the diet, the limitation of growth is more severe and the skin-affection is generalized. The supplementary substance, or 'vitamin B_6', is abundant in wheat, maize, and rice, and seems to be identical with the 'Y factor' described by Chick, Copping, and Roscoe. Neither wheat nor maize, however, appears to contain an appreciable quantity of flavin, though this is present in yeast. Work on the nutritive value of wheaten bread, with special reference to the B vitamins, has been begun by Dr. Chick, Miss Copping and Miss M. H. Roscoe, the latter receiving a personal grant.

Dr. S. S. Zilva, of the Council's staff, and his assistants have continued their researches at the Lister Institute into the mode of action of vitamin C in animal and plant organisms. The Department of Scientific and Industrial Research have again made a grant towards the cost of the part of this work which has interest for the Food Investigation Board. Some compounds related to ascorbic acid have recently been shown to possess antiscorbutic activity in varying degree, while others are inactive in very high dosage. Examining the reasons for the variations, Dr. Zilva has found that when the compounds are introduced into the blood in vitamin C deficiency, only those which are active are taken up by the tissues, there being some relationship between the degree of fixation by the tissues and the antiscorbutic power. On the other hand, the quantities of the injected acids excreted by the kidney vary inversely with their antiscorbutic power. The use of generalized ether anaesthesia for the injections seems to augment the urinary excretion of the compounds by amounts proportional to their antiscorbutic activity: this effect of the anaesthetic on excretion is not, however, due to deficient uptake of the injected substances by the tissues, and further work is being done to determine the mechanism involved. When pure vitamin C (*l*-ascorbic acid) is injected into guinea-pigs depleted of the vitamin the substance is taken up in high concentrations by the intestinal canal, especially the small intestine, which thus appears to resemble the anterior lobe of the pituitary, the adrenal, and other organs with a selective capacity for the vitamin. *l*-ascorbic acid, which is stable in solid condition, slowly loses its activity when dissolved in distilled water. This loss of activity has been shown by Dr. Zilva and Mr. A. E. Kellie to be due to the catalytic action of traces of metals present in the water. In the absence of these catalysts the vitamin is stable even when the water is saturated with oxygen. The oxidative action of metals is greatly diminished by the

presence of tissues such as liver and kidney, and this fact is probably responsible for the stabilization of the vitamin *in vivo*. Prompted by the conclusion of Wolbach from histological studies that vitamin C is necessary for the formation of intercellular supporting tissue, Dr. S. W. Johnson has investigated the same problem from a chemical point of view. In preliminary studies he found that *l*-ascorbic acid had little activating influence on the hydrolysis of gelatin by pure cathepsin.

With Dr. F. Kidd and Dr. C. West of the Low Temperature Research Station, Cambridge, Dr. Zilva and Miss E. O. V. Perry have examined a possible relationship between vitamin C and the respiratory processes of the apple. They found that there was little difference in vitamin content between apples stored at 0° C. and 15° C. in oxygen and in nitrogen. It had previously been shown that the skin of the apple is much richer than the rest of the fruit in vitamin C: further experiments have indicated that when the skin has a marked flush the concentration of the vitamin in it is about twice as high as in the green portion of the apple. This applies equally to apples which are almost entirely red or green. The antiscorbutic activity of the flesh of the fruit is not, however, affected by the colour of the skin.

The identical physiological activity of synthetic *l*-ascorbic acid with the natural product suggested an inquiry into the desirability of adding the synthetic vitamin to various foods in the process of canning. Some experiments on these lines have been made by Dr. Zilva and Miss Perry with Mr. T. N. Morris. In preliminary tests it was shown that most of the vitamin added to vegetables and fruits before canning was present in the final product. In some cases it was taken up entirely by the vegetable tissues, while in others it was distributed between them and the surrounding liquid.

A grant has again been made for the expenses of work by Professor J. C. Drummond and others at University College, London. The chemistry of vitamin E has been studied further, and various substances associated with the vitamin have been isolated in pure form from the vegetable oils containing it. The most concentrated preparations of vitamin E so far available appear to consist very largely of one compound or possibly a mixture of closely related compounds. It seems probable that the active substance is a polycyclic alcohol containing a ring-system not dissimilar from that of the sterols and bile-acids. Observations on the physiological function of vitamin E have been continued by Miss E. Singer under the joint direction of Professor Drummond and Dr. A. S. Parkes of the National Institute. Attempts are being made to devise a method for the assay of the vitamin, based on changes in endocrine function in vitamin E deficiency. Professor Drummond and his colleagues have extended their studies of the method by

which vitamin A is stored in the mammalian liver. It has been found that, under certain conditions, neutral fat and phosphatides may pass to and from the liver, without parallel changes occurring in the vitamin A content of the organ. Work is also being done here on the chemistry of the substances excreted in urine which are believed to represent the break-down products of this vitamin.

At the Dunn Nutritional Laboratory, Cambridge, Dr. L. J. Harris and Dr. T. Moore give whole-time service as members of the Council's staff. Personal grants have been made to Dr. T. W. Birch and Miss C. F. Fischmann, and Mr. A. J. P. Martin works here with a scholarship awarded by the Grocers' Company. Various other workers have had the hospitality of the laboratory for special investigations.

Dr. Harris and Dr. S. N. Ray have continued their work on the diagnosis of vitamin C deficiency by chemical tests of urine. It has been shown that infants suffering from scurvy, or those who have received inadequate amounts of fruit in their diets, excrete less vitamin C than do healthy, well-nourished babies. Moreover, when a standard dose of the vitamin is given to children with vitamin C deficiency and to normal children, the tissues of the former retain more of the vitamin than do those of the latter. These observations have been applied to children under the care of Professor L. G. Parsons (p. 95) of Birmingham, and Dr. E. Pritchard, of the Infants' Hospital, London, with results which suggest that a sub-optimal intake of vitamin C is a common occurrence in artificially-fed infants. While the inclusion of orange-juice in the diet is recommended by most authorities, it seems frequently to be omitted by the mothers. Breast-milk is three to four times richer than cow's milk in vitamin C, which may account for the relative infrequency of scurvy in breast-fed infants. Observations on adults by Dr. M. A. Abbasy and Dr. Harris have indicated that the consumption of one or two oranges a day by persons whose diets were previously deficient in the vitamin suffices very rapidly to bring the reserves to normal.

Professor P. György has continued his work on the vitamin B_2 complex. He finds that lactoflavin, a constituent of this complex, differs from the factor which prevents the so-called 'pellagra-like' dermatitis of rats: the factor responsible for this action has been named 'vitamin B_6'. Clinical studies by Dr. W. J. Dann, who now works in North Carolina, have proved that lactoflavin will not cure pellagra in man. It is known that this disease is induced by diets consisting largely of maize, which is rich in 'vitamin B_6'. It seems likely, therefore, that pellagra is not due to deficiency of any recognized component of the vitamin B_2 complex. With Professor György and Dr. Harris, Dr. Ray has shown that deficiency of some component of vitamin B_2 destroys the normal reducing activity of

the lens of the rat's eye; vitamin C may disappear from the lens, and a new substance of unknown nature make its appearance; this substance is able to oxidize vitamin C. Dr. Birch and Dr. Harris have done further work on the chemistry of vitamin B_1, and Mr. Martin has examined some of the physical and physiological properties of vitamin E concentrates. As part of an inquiry into the vitamin B_1 content of human diets, Mr. P. C. Leong has measured the amounts of this vitamin present in genuine wholemeal wheat and in ordinary brown bread. He found that the difference between them was surprisingly small. Help in this investigation was given by the Government Chemist, Sir Robert Robertson, and his staff.

Dr. Moore has further examined the vitamin A reserves of human subjects as determined by the assay of specimens of liver obtained at autopsy. Very low reserves have been found in cases of chronic nephritis. It has been shown in animals that when the vitamin A reserves in the liver are abnormally high they may sometimes undergo a remarkable fall within the course of a few weeks. The conditions which lead to disappearance of the vitamin are not yet clearly understood, and further studies are in progress. Observations on seasonal and other variations in the fats of butter have been made by Dr. Moore and Dr. Dann, in association with workers at the National Institute for Research in Dairying, Reading. Miss Fischmann, working partly at the Strangeways Research Laboratory (p. 117), has continued to study ossification in tissue cultures as influenced by vitamin D and mineral metabolism.

Dr. R. A. Morton, at Liverpool University, has had a grant for assistance by Dr. J. R. Edisbury in work mainly on chemistry and standardization of vitamin A. The methods used for the physicochemical assay of the vitamin have been further refined, and the data thus obtained have been compared with a series of biological measurements. A discrepancy between the biological assays and physical data for some cod-liver oils suggests the presence of a substance similar in action to vitamin A but physically distinct from it. Attempts are being made to determine what factor, or factors, may be responsible for the divergent measurements. Difficulties have been encountered in the estimation of the vitamin in artificial foods in which it is present in small amount, but a method has been devised which seems likely to overcome these. With Dr. J. A. Lovern, of the Torry Research Station, Aberdeen, an inquiry is being made into the possibility that vitamin A occurs naturally in ester form. The results of work on the unsaturated fatty-acids of fish-liver oils have been published. Dr. Morton and Dr. Edisbury have been unable to confirm the claim of Olcott and McCann that carotene can be converted into vitamin A *in vitro*. As a side

investigation, they are studying the absorption spectrum of the urine in pregnancy in the hope of obtaining a spectroscopic substitute for the Aschheim-Zondek diagnostic test, which would obviate the need to use animals for the purpose.

At Oxford, Professor R. A. Peters has again had grants for expenses and for assistance by Mr. H. W. Kinnersley and Mr. J. R. O'Brien. Further work has been done on the nature and functions of the vitamin B complex. It has been shown that vitamin B_1 can be converted by oxidation into a substance with an intense blue fluorescence in neutral and alkaline solutions, and with a yellow fluorescence in acid solution which resembles that of flavin, a constituent of vitamin B_2. The chemical and biological possibilities arising from the suggested relationship between vitamin B_1 and part of the vitamin B_2 complex are being examined. It is thought that the blue fluorescent oxidation products may have physiological significance, because similar substances, of unknown chemical composition, have long been recognized as occurring in a number of tissues, including the skin and the lens of the eye. Research on the physiological function of vitamin B_1 has been continued by various workers in this department. From observations on brain tissue *in vitro*, they conclude that the biochemical changes in mammalian brain in vitamin B_1 deficiency are similar to those occurring under like conditions in the brain of the pigeon. Mr. R. S. Thompson and Mr. R. E. Johnson have obtained proof of the significance of the abnormal formation of pyruvic acid in vitamin B_1 deficiency by showing that the symptoms of deficiency are associated, both in birds and rats, with an increased amount of pyruvate in the blood. If a similar increase in pyruvate is found in human subjects with beri-beri, it may provide a useful test for diagnosing the disease. By arrangement with physicians at several hospitals, trials are being made of the therapeutic effects of vitamin B concentrates in 'pink disease' in children; encouraging results have been obtained in a few cases, although caution is required in their interpretation. The work is still in progress.

At Edinburgh, Professor G. Barger received a grant for assistance by Dr. A. R. Todd in work on the chemistry of vitamin B_1. Most of the material used in this study was supplied by Professor B. C. P. Jansen, of Amsterdam, who recently suggested the name 'antineurin' for the vitamin. Dr. Todd has obtained two crystalline fluorescent substances from antineurin, one of which is identical with thiochrome, which was isolated in minute quantity from yeast by Kuhn. Dr. Todd is continuing the investigation during the tenure of a Beit Memorial Fellowship, and the expenses of further research have been provided by the Rockefeller Foundation.

E. M. Hume and H. Chick (Editors)—
'Reports on Biological Standards. IV. The Standardization and

Estimation of Vitamin A.' *Spec. Rep. Ser. Med. Res. Coun.*, Lond., No. 202, 1935.

T. W. Birch and W. J. Dann—
'Glutathione and Vitamin C in the Crystalline Lens.' *Nature*, Lond., 8th Sept., 1934.

T. W. Birch and P. György—
'Vitamin B_6 and Human Pellagra.' *Chem. Ind.*, 1935, **54**, 507.

T. W. Birch and L. J. Harris—
'Titration Curve of Vitamin B_1.' *Nature*, Lond., 27th Apr. 1935.

R. G. Booth, S. K. Kon, W. J. Dann, and T. Moore—
'A Study of Seasonal Variation in Butter Fat. II. A Seasonal Spectroscopic Variation in the Fatty Acid Fraction.' *Biochem. J.*, 1935, **29**, 133.

H. Chick, A. M. Copping, and C. E. Edgar—
'The Water-soluble B Vitamins. IV. The Components of Vitamin B_2.' *Biochem. J.*, 1935, **29**, 722.

W. J. Dann—
'The Transmission of Vitamin A from Parents to Young in Mammals. IV. Effect of the Liver Reserves of the Mother on the Transmission of Vitamin A to the Foetal and Suckling Rat.' *Biochem. J.*, 1934, **28**, 2141.

W. J. Dann, T. Moore, R. G. Booth, J. Golding, and S. K. Kon—
'A New Spectroscopic Phenomenon in Fatty Acid Metabolism. The Conversion of "Pro-absorptive" to "Absorptive" Acids in the Cow.' *Biochem. J.*, 1935, **29**, 138.

A. W. Davies and T. Moore—
'Vitamin A and Carotene. XII. The Elimination of Vitamin A from the Livers of Rats Previously given Massive Doses of Vitamin A Concentrate.' *Biochem. J.*, 1935, **29**, 147.

J. C. Drummond, M. E. Bell, and E. T. Palmer—
'Observations on the Absorption of Carotene and Vitamin A.' *Brit. med. J.*, 15th June 1935.

J. C. Drummond and R. J. Macwalter—
'The Fate of Carotene Injected into the Circulation of the Rat.' *J. Physiol.*, 1934, **83**, 236.

J. C. Drummond, E. Singer, and R. J. Macwalter—
'A Study of the Unsaponifiable Fraction of Wheat Germ Oil with Special Reference to Vitamin E.' *Biochem. J.*, 1935, **29**, 456.

J. R. Edisbury, R. S. Morgan, and R. A. Morton—
'Further Work on the Absorption Spectra of the Acids from Cod-Liver Oil.' *J. chem. Indust.*, 1934, **53**, 1083.

J. R. Edisbury, R. A. Morton, and J. A. Lovern—
'The Absorption Spectra of Acids from Fish-Liver Oils.' *Biochem. J.*, 1935, **29**, 899.

P. György—
'Investigations on the Vitamin B_2 Complex. I. The Differentiation of Lactoflavin and the "Rat Antipellagra" Factor.' 'II. The Distribution of Lactoflavin and of the "Pellagra-preventing Factor" (Vitamin B_6) in Natural Products of Animal Origin.' 'III. The Inactivation of Lactoflavin and Vitamin B_6 by Visible Light.' *Biochem. J.*, 1935, **29**, 741, 760, and 767.

L. J. Harris—
'Flavin and the Pellagra-Preventing Factor as Separate Constituents of a Complex Vitamin B_2.' *Biochem. J.*, 1935, **29**, 776.
'Vitamins.' *Ann. Rev. Biochem.*, 1935, **4**, 331.

L. J. Harris and S. N. Ray—
'Diagnosis of Vitamin-C Subnutrition of Urine Analysis, with Note on Anti-scorbutic Value of Human Milk.' *Lancet*, 12th Jan. 1935.

A. E. Kellie and S. S. Zilva—
'The Catalytic Oxidation of Ascorbic Acid.' *Biochem. J.*, 1935, **29**, 1028.

H. W. Kinnersley, J. R. O'Brien, and R. A. Peters—
'Crystalline Vitamin B_1.' *Biochem. J.*, 1935, **29**, 701.
'Improved Yields of Vitamin B_1.' *Ibid.*, 1935, **29**, 716.
'The Properties of Blue Fluorescent Substances Formed by Oxidation of Vitamin B_1 (quinochromes).' *Ibid.*, 1935, **29**, 2369.

E. Mellanby—
'Lesions of the Central and Peripheral Nervous Systems Produced in Young Rabbits by Vitamin A Deficiency and a High Cereal intake.' *Brain*, 1935, **58**, 141.

T. Moore—
'The Frequent Occurrence of Low Vitamin-A Reserves in Cases of Renal Disease.' *Chem. Ind.*, 1935, **53**, 875.

R. S. Morgan, J. R. Edisbury, and R. A. Morton—
'A Discrepancy between Biological Assays and other Methods of Determining Vitamin A. I.' *Biochem. J.*, 1935, **29**, 1645.

R. A. Peters, H. Rydin, and R. H. S. Thompson—
'Brain Respiration, a Chain of Reactions, as Revealed by Experiments upon the Catatorulin Effect.' *Biochem. J.*, 1935, **29**, 53.
'The Relation of Pyruvic Acid in Brain to Certain Tissue Poisons.' *Ibid.*, 1935, **29**, 63.

S. N. Ray, P. György, and L. J. Harris—
'Effect of Deficiency of Vitamin B Complex on the "Redox" System in the Eye-Lens.' *Biochem. J.*, 1935, **29**, 735.

R. H. S. Thompson and R. E. Johnson—
'Blood pyruvate in Vitamin B_1 Deficiency.' *Biochem. J.*, 1935, **29**, 694.

S. S. Zilva—
'The Ascorbic Acid Content of the Intestine of the Guinea-pig.' *Biochem. J.*, 1935, **29**, 100.
'The Behaviour of *l*-Ascorbic Acid and Chemically Related Compounds in the Animal Body. Antiscorbutic Activity in Relation to Retention by the Organism.' *Ibid.*, 1935, **29**, 1612.
'The Behaviour of *l*-Ascorbic Acid and Chemically Related Compounds in the Animal Body. The Influence of Generalized Ether Anaesthesia on their Urinary Excretion.' *Ibid.*, 1935, **29**, 2366.
'The Isolation and Identification of Vitamin C.' *Arch. Dis. Childh.*, 1935, **10**, 253.

Dental Disease

The Committee named at p. 165 continue to advise the Council in this subject. An important contribution towards the cost of the work is made by the Dental Board of the United Kingdom.

At the Royal Dental Hospital, London, grants for research expenses have been made to Dr. E. W. Fish, Dr. H. H. Stones, Dr. R. V. Bradlaw, and Mr. W. Stewart Ross: the assistance of Miss J. Peet has also been provided. Dr. Fish has continued his investigation of the calcific scar tissue which is developed after injury to the dental pulp. Dr. Stones, who has recently been appointed to a Chair in Dental Surgery at Liverpool University, has done further work on the permeability of the dental cement and on the relation of local injury and other factors to chronic infection at the gum-margin. Dr. Bradlaw is examining the relationship between different dental lesions and neuralgic pain; and Mr. Stewart Ross extended his inquiries into the pathology of the cementum and the

microscopic changes in and around dead teeth. A personal grant has been made to Dr. P. Pincus, at this hospital, for work on the bacteriology of dental caries.

By arrangement with the Department of Scientific and Industrial Research, X-ray and crystallographic studies of human teeth have been continued at the National Physical Laboratory, Teddington. The work has been done by Dr. G. Shearer and Mr. J. Thewlis of the Laboratory, the Council providing the expenses. X-ray diffraction photographs have been used to examine the surface and internal structure of deciduous teeth, with special reference to the calcification and crystallographic orientation of normal and pathological dental enamel.

At Bedford College for Women, London, Miss M. M. Murray has had grants for expenses and for assistance by Miss J. H. Bowes in analyses of the chemical composition of normal and hypoplastic human teeth. It has been shown that hypoplastic enamel, as diagnosed by Mrs. Mellanby, contains less apatite and more carbonate than normal, and that the dentine of hypoplastic teeth is abnormally rich in magnesium. Miss F. Lowater is co-operating with Miss Murray in spectrographic examinations of dental material.

Grants for laboratory assistance and expenses have again been made to Mrs. M. Mellanby. With Dr. J. D. King, who receives a personal grant at Sheffield, further work has been done on the effects of different diets upon the teeth, periodontal tissues, and dental nerves. The parts played by physical and mechanical factors in the origin and spread of dental caries and periodontal disease are being studied experimentally by Dr. King.

Mrs. E. M. Johnson and Miss E. M. Still have had personal and expenses grants to take periodic measurements of the faces and jaws of children with normal and post-normal occlusion of the dental arch. The object of the inquiry was to determine the site of the defective or excessive bony growth which might lead to post-normal occlusion. Data collected by these workers from 1,600 London school-children are being analysed by Dr. Matthew Young, who has also co-operated with Miss K. C. Smyth in the examination of other anthropometric data relating to the growth of the jaws.

J. H. Bowes and M. M. Murray—
'The Chemical Composition of Teeth. I. The Estimation of Fluorine and the Fluorine Content of Normal Teeth.' *Biochem. J.*, 1935, **29**, 102.

E. W. Fish—
'Parodontal Disease: The Pathology and Treatment of Chronic Gingivitis.' *Brit. dent. J.*, 1935, **58**, 531 and 602.
'The Effect of Vitamin D on the Calcium Content of the Dentine.' *J. Physiol.*, 1935, **84**, 272.

J. D. King—
'The Production of Dental Disease in Experimental Animals, with Special Reference to the Rat. Part I. Dental Caries.' *Brit. dent. J.*, 1935, **59**, 233 and 305.

M. Young and C. Smyth—
'Growth of the Jaws with Special Reference to the Deciduous Dentition.' *Congrès International des Sciences Anthropologiques et Ethnologiques. Compte-rendu de la première Session Londres*, 1934, p. 105.

Neurology

Reference has been made at p. 77 to the work of the clinical research unit directed by Dr. E. A. Carmichael at the National Hospital, Queen Square, London.

At the same hospital and at King's College Hospital, Dr. Macdonald Critchley has had an expenses grant to study the anatomy of the brain arteries and the results of their disease in man. With Dr. M. J. Wilmers, he has used injection methods to examine the ultimate distribution of the anterior inferior cerebellar and posterior cerebral arteries, with the object of elucidating the neurological effects of their obstruction. Dr. Otto Maas, who received an expenses grant at the National Hospital, has investigated a series of cases of the rare disease, dystrophia myotonica, giving particular attention to the part played by hereditary factors in its causation and to the possibility of its treatment by drugs.

A grant for expenses has again been made to Dr. Ranyard West, working with a Beit Memorial Fellowship in the University Department of Pharmacology, Oxford, and at the Seamen's Hospital, Greenwich. He has completed his studies in the neurological mechanism of tetany, and has published the results. Further observations have been made on the pharmacological and chemical actions of substances related to curare. Samples of curarine, tubo-curarine, and curine have been prepared by Dr. H. King (p. 51) of the National Institute, from plants kindly supplied by the Forestry Department, British Guiana. These have been tested by Dr. West in experimental parathyroid tetany, and the first two have also been tried in chronic nervous diseases causing rigidity of the muscles in man. The main object of the inquiry is to identify the chemical principles which enable some samples of curare to relieve the stiffness of paralysis agitans. Two new alkaloids have been isolated by Dr. King from samples of *Strychnos diaboli* received from British Guiana, and these have been examined in parathyroid tetany. It was found that extracts of *S. diaboli* had some power to lessen the muscular spasm in that condition. Clinical observations on the value of curare and artificial respiration in the treatment of tetanus have also been made by Dr. West.

Electro-physical studies of nerve function have been continued by Dr. W. A. H. Rushton, with part-time and expenses grants at University College, London. He has investigated the physical basis of the 'electrical reactions' which are used for the diagnosis of nerve-degeneration.

In Sir Charles Sherrington's department at Oxford, Dr. J. C. Eccles has had a part-time grant. He has extended his work on the physiology of the autonomic nervous system, studying especially the functions of ganglion cells and the mechanism of transmission of the nerve impulses. Analyses have been made of the action potentials evoked by impulses to the superior cervical ganglion, and the relationship of acetylcholine to the passage of impulses between the ganglionic neurones has been examined.

In the Bernhard Baron Institute of Pathology at the London Hospital, Dr. Dorothy S. Russell gives whole-time service to the Council. She has continued to co-operate with Mr. Hugh Cairns and Dr. J. O. W. Bland in studies of the pathology of intracranial tumours. With the late Dr. R. G. Canti of St. Bartholomew's Hospital, cinematograph films were made of the growth of brain tumours in artificial culture. This method of study shed new light on the development of the different types of gliomata and on the relationships between them. Dr. A. C. Crooke and Dr. Russell have examined the microscopic appearances of the pituitary gland in various diseases associated with abnormal blood-pressure. A study of the gland in cases of Addison's disease has been completed. It has been established by differential cell counts of the anterior lobe that there is a striking numerical reduction in the basophil cells in this disease. Dr. Crooke has found a peculiar hyaline change in the cytoplasm of the basophil cells of the pituitary gland in a series of cases showing the syndrome now commonly known as 'pituitary basophilism'. The change is present in conspicuous degree whether the syndrome is produced by a basophil adenoma of the pituitary, hyperplasia or neoplasm of the suprarenal cortex, or growth of the thymus. It appears to be the only histo-pathological feature in the endocrine glands which is common to all such cases. Research is being continued by Dr. Russell on the causation of internal hydrocephalus in young children. A mechanism responsible for hydrocephalus in association with spina bifida has been described with Mr. Charles Donald. In relation to the work of Professor J. B. Duguid (p. 137), Dr. Russell has also investigated the vascular, renal, and pituitary changes in experimental hyper-vitaminosis D.

At Sheffield, Dr. Elizabeth C. Eaves has had an expenses grant for work on the pathology of nervous diseases. She has examined the brains from a further series of cases of chronic epidemic encephalitis, in an attempt to correlate pathological findings and clinical symptoms. The results indicate that Parkinsonian rigidity and tremor do not occur in this disease unless the cells of the substantia nigra are destroyed, and that it is possible for the hypothalamic region of the brain to be severely damaged without the occurrence of diabetes insipidus.

III

A. C. Crooke and D. S. Russell—
'The Pituitary Gland in Addison's Disease.' *J. Path. Bact.*, 1935, **40**, 255.

J. C. Eccles—
'After-discharge from the Superior Cervical Ganglion.' *J. Physiol.*, 1935, **84**, 50 P.
'The Action Potential of the Superior Cervical Ganglion.' *Ibid.*, 1935, **85**, 179.
'Facilitation and Inhibition in the Superior Cervical Ganglion.' *Ibid.*, 1935, **85**, 207.

H. S. Le Marquand and D. S. Russell—
'A Case of Pubertas Praecox (Macrogenitosomia praecox) in a boy associated with a tumour in the floor of the third ventricle.' *Royal Berks Hosp. Rep.*, 1934–5, p. 31.

W. A. H. Rushton—
'A Theory of Excitation.' *J. Physiol.*, 1935, **84**, 42 P.

D. S. Russell—
'Some Aspects of Pituitary Function.' *Lancet*, 8th June 1935.

D. S. Russell and C. Donald—
'The Mechanism of Internal Hydrocephalus in Spina Bifida.' *Brain*, 1935, **58**, 203.

R. West—
'The Pharmacology and Therapeutics of Curare and its Constituents.' *Proc. R. Soc. Med.*, 1935, **28**, 565.
'Studies in the Neurological Mechanism of Parathyroid Tetany.' *Brain*, 1935, **58**, 1.

Psychology and Psychiatry

Research in these subjects is directed by the Committee named at p. 165.

At the Royal Eastern Counties Institution, Colchester, an extensive inquiry into the psychological, physical, and genetic aspects of mental deficiency has been continued by Dr. L. S. Penrose and others, with help on the neurological side from Dr. S. Nevin (p. 77). The expenses of the work are borne jointly by the Council, the Institution, and the Darwin Trust. Clinical data and family histories have been obtained from more than 1,000 cases, and the examinations have been extended wherever possible to the relatives of patients. A special study is being made of the inheritance of phenylketonuria, a type of amentia described recently by Fölling. Genetically this condition appears as a Mendelian recessive character, but the carriers seem to have a predisposition to mental break-down at the involutional period of life. The biochemistry of phenylketonuria is being investigated with Dr. J. H. Quastel, of Cardiff.

An investigation of the family histories of mental patients who are the offspring of consanguineous marriages is being made by Dr. T. A. Munro in consultation with Dr. Penrose. Dr. Munro is supported by a grant provided to the Council by the Rockefeller Foundation, his expenses and the assistance of Miss P. M. Perrott being provided from the Council's own funds.

At the Maudsley Hospital, London, Dr. Florence M. Grant and Mr. A. Tingey have had part-time grants for work under the general direction of Dr. F. L. Golla. The expenses of research by Dr. A. Meyer and Dr. E. Wittkower have also been provided here. With Mrs. M. A. B. Brazier, who has a Commonwealth Research Fellowship, Dr. Grant has investigated the effects of the thyrotropic pituitary hormone upon the clinical condition, electrical reactions, and basal metabolism of mental patients; Mr. Tingey has examined the sodium and calcium content of the blood-serum in different psychoses, and is studying the distribution of iron and copper in the nervous system in health and disease; Dr. Meyer has done further work on the pathology of demyelination, and Dr. Wittkower has continued an inquiry into the relationship between respiratory rhythm and the mental state, with special reference to schizophrenia.

With a grant for expenses at Colney Hatch Mental Hospital, London, Dr. J. Brander has investigated the microscopic changes in the pituitary body and surrounding tissues in 'pituitary infantilism' and other diseases.

At the Cardiff City Mental Hospital under the general direction of Dr. P. K. McCowan, Dr. J. H. Quastel has had grants for assistance by Mr. A. H. M. Wheatley, Dr. E. D. Yates, and Miss C. E. M. Pugh. Further work has been done on the influence of narcotic drugs and of basic amines on the normal oxidative processes of the central nervous system. It had previously been shown, by experiments *in vitro*, that many of these substances would inhibit the respiration of brain tissue, the effects in most cases being temporary and reversible. The site of the break-down of the amines in the body is at present being investigated: it has been found that, in addition to the liver and kidney, the grey matter of the brain has the power to detoxicate them, giving ammonia as an end-product. Dr. Quastel and Dr. Jowett have made further observations on the normal fat metabolism of liver tissue, with the object of shedding light on the chemical origin of ketosis. Dr. T. J. Hennelly, Dr. Quastel, and Dr. Yates have extended an inquiry into the significance of the blood bromine content in health and disease: they have found that the rate of removal of bromine from the blood, after a dose of bromide has been given, is independent of the mental state of the patient. Variations in blood bromine may be caused partly by secretion of bromide into the gastric juice. On the other hand, Dr. Ström-Olsen and Dr. Yates have confirmed that a low ratio of serum bromide to cerebrospinal fluid bromide, after standard bromide treatment, is a feature of the toxic psychoses which may prove of diagnostic value.

At the Royal Hospital for Mental Disorders, Edinburgh, Dr. H. Tod has investigated the effects of hypnotics on the glucose toler-

ance test in normal and insane subjects. He has also studied the factors causing variations in the choline esterase content of human blood serum, and has examined the relation between serum esterase activity and different mental states.

L. C. Cook and A. Meyer—
'Unusual Size of Intraventricular Spongioblastoma in a Case of Tuberous Sclerosis.' *J. Neurol. Psychopath.*, 1935, **15**, 320.

T. J. Hennelly and E. D. Yates—
'Blood Bromine in the Psychoses.' *J. ment. Sci.*, 1935, **81**, 173.

M. S. Jones and H. Tod—
'The Inhibitory Action of Eserine upon Choline-Esterase *in vivo*.' *Biochem. J.*, 1935, **29**, 2242.

M. Jowett and J. H. Quastel—
'Studies in Fat Metabolism. I. The Oxidation of Butyric, Crotonic and β-Hydroxybutyric Acids in Presence of Guinea-Pig Liver Slices. II. The Oxidation of Normal Saturated Fatty Acids in the Presence of Liver Slices. III. The Formation and Breakdown of Acetoacetic Acid in Animal Tissues.' *Biochem. J.*, 1935, **29**, 2143, 2159, and 2181.

L. S. Penrose—
'A Method of Separating the Relative Aetiological Effects of Birth Order and Maternal Age, with Special Reference to Mongolian Imbecility.' *Ann. Eugen.*, Camb., 1934, **6**, 108.
'Two Cases of Phenylpyruvic Amentia.' *Lancet*, 5th Jan. 1935.
'The Inheritance of Phenylpyruvic Amentia (Phenylketonuria).' *Ibid.*, 27th July 1935.

H. Tod—
'The Effect of Hypnotics on Glucose Tolerance.' *Biochem. J.*, 1935, **29**, 914.

E. Wittkower—
'Further Studies on the Respiration of Psychotic Patients.' *J. ment. Sci.*, 1934, **80**, 692.

Experimental Psychology

A personal grant was made to Mr. G. C. Grindley for work at Cambridge under the direction of Professor F. C. Bartlett. He has examined some of the conditions of negative adaptation in response to repetitive stimulation. With Mr. A. F. Rawdon Smith (p. 125), who receives a grant, work has also been done on the influence of the rate of stimulation upon sensory thresholds. A series of observations has been made upon the function of hearing, and it is proposed to extend the inquiry to other senses. At the same place, Mr. G. C. Drew, with a personal grant, has studied the influence of mixed incentives upon learnt performances in animals; he has shown that unexpected effects, which have not yet been satisfactorily explained, frequently occur when there is a conflict of incentives. As it is thought that the findings are likely to have a significant bearing on clinical problems of abnormal psychology, the work is being continued.

Work by Dr. J. S. Rosenthal and Mr. W. G. Walter, in the School of Physiology at Cambridge, is noticed at p. 127.

Tuberculosis

Research in tuberculosis is directed by the Committee named at p. 165, appointed jointly with the Agricultural Research Council. Dr. N. F. Smith, of the Ministry of Health, and Mr. G. W. Dunkin, of the Council's staff, have succeeded Dr. J. A. Glover and Professor J. B. Buxton as secretaries on the medical and veterinary sides, respectively.

In the whole-time service of the Council at Cambridge, Dr. A. Stanley Griffith has continued his inquiry into the frequency with which bovine tubercle bacilli cause phthisis and other forms of tuberculosis in man. With Dr. J. Menton, he has determined the types of tubercle bacilli present in 49 cases of non-pulmonary and 230 cases of pulmonary tuberculosis in Staffordshire. Of the 49 non-pulmonary cases, 21 yielded cultures of bovine tubercle bacilli; the remainder, including two cases of renal tuberculosis, were due to bacilli of the human type. The percentage incidence of bovine infections in the non-pulmonary forms of tuberculosis in Staffordshire was closely similar to that already found in parts of Scotland. On the other hand, the frequency of bovine infections in pulmonary tuberculosis in Staffordshire fell far short of the high percentage of the Scottish figures. In rural districts of north-east Scotland, Dr. Griffith and Dr. J. Smith found that the proportion of cases of phthisis due to bovine tubercle bacilli was as high as 17 per cent., whereas in Staffordshire it was less than 1 per cent.

With Professor J. B. Buxton and Mr. R. E. Glover, Dr. Griffith is making further observations on the practicability of immunizing calves to tuberculosis with 'B.C.G.' vaccine given intravenously. The purpose of these experiments is to test the duration of the immunity given by the vaccine, and to establish its value as a protective agent under farm conditions where segregation from tuberculous animals is either impossible or is inevitably followed later by exposure to tuberculous infection.

At the London School of Hygiene, Mrs. H. Schwabacher has again had part-time and expenses grants for assistance to Professor G. S. Wilson in experimental work on the mode of development of chronic pulmonary tuberculosis. They have studied the rate and method of removal of tubercle bacilli inoculated into various tissues, and are attempting to assess the effects of varying degrees of allergy on the response to 'superinfection' with tuberculosis.

Expenses have been provided for work by Dr. Agnes R. Macgregor at the Royal Hospital for Sick Children, Edinburgh. With Dr. C. A. Green and Dr. W. S. Craig, she has examined the type incidence of tubercle bacilli isolated from cases of meningitis. A special study is being made of cases in which tubercle bacilli are present in the cerebrospinal fluid without clinical or other patho-

logical signs of diffuse tuberculous meningitis. In addition, Dr. Macgregor and Dr. Craig are investigating the clinical and bacteriological aspects of respiratory infections in new-born infants.

With a grant for expenses at Glasgow, Dr. J. W. S. Blacklock (p. 96) has continued his pathological studies of tuberculous meningitis, with special reference to the site of the primary lesion and the method by which the meninges become involved. An account of the anatomical distribution of the primary sites of tuberculous infection in children has been published. In all cases in which the primary disease was in the lungs, the bacilli isolated have been typed in an attempt to determine the comparative incidence of 'human' and 'bovine' infections of the lungs in children. Of 154 strains of tubercle bacilli isolated in this way, 6 have been of the bovine type: it has not so far been possible to trace the source of the primary lung infection in these cases. Dr. Blacklock has also extended his observations on the reactions to tuberculin given by children with and without clinical or radiological signs of tuberculosis.

A grant for expenses was again made to Dr. W. M. Cumming at the Bradford City Sanatorium, Grassington, Yorkshire. He has continued his inquiry into the incidence and origin of human phthisis due to bovine tubercle bacilli. An account has been published of the comparative frequency with which human and bovine tubercle bacilli were isolated from nearly two thousand recent cases of pulmonary tuberculosis in Great Britain and the Irish Free State. Special attention has been given to the possibility of the direct infection of farm workers with bovine tubercle bacilli from diseased cattle.

At the Papworth Village Settlement, Dr. E. Brieger and Dr. L. B. Stott received an expenses grant for clinical research under the general direction of Sir Pendrill Varrier-Jones. They have examined the effects of selected types of work on patients with pulmonary tuberculosis, with special reference to physical and economic efficiency at different stages of the disease. The conditions determining shortness of breath on exercise have been analysed by tests of respiratory function and of cardiac output. The factors influencing the fatigue response to effort in tuberculous patients have also been investigated.

Professor S. L. Cummins of the Welsh National Memorial Association, Cardiff, has had grants for expenses and for assistance by Dr. Enid M. Williams and Dr. P. K. Sen. Professor Cummins and Dr. Williams have continued their studies of pneumonoconiosis and tuberculosis in coal-miners, and have done further experiments on the detoxicating effect of carbon in tuberculosis. They have also investigated the chemotherapeutic properties in tuberculosis of two metallic salts prepared by Professor G. T. Morgan,

of the Chemical Research Laboratory, Teddington. With Dr. P. K. McCowan, of the Cardiff City Mental Hospital, attempts have been made to cultivate tubercle bacilli from the blood and cerebrospinal fluid of patients with dementia praecox. Blood cultures made by Professor E. Löwenstein's method have so far been negative in all cases, and the efforts to cultivate the bacilli from the spinal fluid have been unsuccessful. In relation to an investigation promoted by the Royal College of Physicians under the terms of the Prophit Trust, clinical, radiological, and haematological observations are being made on groups of medical students at the Welsh National School of Medicine: the object of this inquiry is to determine the normal X-ray appearances of the lungs at different ages and to establish criteria for the early diagnosis of tuberculous infection. Dr. Sen has examined clinically and pathologically the incidence of tuberculosis among a series of coal-miners with symptoms of respiratory disease.

An expenses grant made to the Joint Tuberculosis Council in 1934 is being used for a follow-up investigation of the late results of the artificial pneumothorax treatment of pulmonary tuberculosis.

Reference to the Dorothy Temple Cross Research Fellowships in Tuberculosis is made at p. 160.

D. Band, J. M. Alston, A. S. Griffith, and W. T. Munro—
'Renal Tuberculosis.' *Edinb. med. J.*, 1935, **42**, 162.

J. W. S. Blacklock—
'A Study of Tuberculous Disease in Infancy and Childhood, with Particular Reference to the Primary Site of Infection.' *Brit. J. Tuberc.*, 1935, **29**, 69.

J. W. S. Blacklock and M. A. Griffin—
'Tuberculous Meningitis in Children.' *J. Path. Bact.*, 1935, **40**, 489.

S. L. Cummins—
'Pulmonary Tuberculosis in Wales.' *23rd Ann. Rep. King Edward VII Welsh Nat. Mem. Ass.*, 1935, p. 163.
'Problem of the Acute Pulmonary Phthisis of Young Females.' *Brit. J. Tuberc.*, 1935, **29**, 4.
'Contact with Infection in Tuberculosis: Its Rôle in Disease Production and Protection.' *Canad. publ. Hlth. J.*, 1935, **26**, 1.

A. S. Griffith—
'Tuberculous Bacillaemia.' *Quart. Bull. Hlth. Org. L.o.N.*, 1935, **4**, 283.

A. S. Griffith, J. B. Buxton, and R. E. Glover—
'Immunization Experiments on Calves with BCG.' *Lancet*, 23rd Feb. 1935.

A. S. Griffith and W. T. Munro—
'Family Tuberculosis due to Bovine Tubercle Bacilli.' *Brit. med. J.*, 27th July 1935.

A. R. Macgregor, H. J. R. Kirkpatrick, and W. S. Craig—
'Meningeal Tuberculosis: Bacteriology and Pathology.' *Edinb. med. J.*, 1935, **42**, 138.

H. Schwabacher—
'A Case of Spontaneous Tuberculosis in a Goat.' *J. comp. Path.*, 1934, **47**, 214.

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Cell and Tissue Growth

All the work described under this head is being done at the Strangeways Research Laboratory, Cambridge, where the Council continue to provide a large part of the expenses and the salary of Dr. F. G. Spear. Dr. Honor B. Fell, Director of the Laboratory, holds a Messel Research Fellowship awarded by the Royal Society. A personal grant has been made here to Miss C. F. Fischmann. Some general account of the work of the Laboratory has already been given in the Introduction, but a more particular statement of what has been done during the past year may now be made.

In extension of her previous work on the development of bones in tissue culture, Dr. Fell has begun a series of experiments on the mechanism of self-differentiation in the avian breastbone. The shape of the adult bone is attained largely by differential growth in the various parts of the original rudiment, and preliminary work has indicated that similar differentiation occurs in the isolated rudiment in culture, showing that it is independent of any regional distribution of the blood-supply and of the pull of the pectoral muscles. Mr. C. H. Waddington has studied the growth *in vitro* of posterior parts of the chick blastoderm and has found that nerve tissue may develop even in the absence of Hensen's node. With Mr. M. Abercrombie he has examined the effects of grafting fragments of chicken blastoderm into the primitive streak of a second chick. Grafts of ectoderm are not usually incorporated, but remain distinct and may be induced to form nerve tissue. If fragments of primitive streak are grafted, they either disappear owing to their assimilation by the host embryo, or they may lead to the growth of interesting compound embryos.

Dr. W. Jacobson has continued his work on the relationship between growth and development in early embryonic tissues and their glycogen and fat content. Specific micro-chemical reactions for lipoids have been applied to the early fowl blastoderm. Structures able to act as organizers, such as the head process and the primitive streak, have a higher lipoid content than the surrounding tissues, a fact which supports the view that the organizer substances belong to the sterol group.

Miss S. Glasstone has succeeded in cultivating embryonic rat teeth *in vitro*. The artificially grown teeth show remarkable powers of self-differentiation and form plentiful dentine. The dentine is usually of the normal tubular kind, but in some cultures it resembles the scar tissue found in the teeth of animals suffering from vitamin C deficiency. The development *in vitro* of dental enamel has not yet been achieved. Miss J. Hill has begun a series of studies on the cytology and chemistry of the osteoblast cultivated *in vitro* under different conditions of growth.

Dr. A. Glücksmann has examined the influence of environmental factors on the development of bone. It has been found that cultures of undifferentiated osteogenic tissue, when subjected to tension, develop a structure similar to that of avian tendon bone, while similar cultures not subjected to tension form the ordinary 'osteoblastic' type of bone tissue. When embryonic long bones are subjected to pressure and tension in culture, calcification is much more intense on the tension than on the pressure side. Studying the effect of defective nutrition on bone formation *in vitro*, Dr. Glücksmann has shown that when osteogenic tissue is cultivated in medium containing very dilute embryo extract it seldom forms normal osteoid tissue and bone, but produces large masses of soft material which do not calcify and contain very few cells. When these abnormal cultures are transferred to normal media, they usually recover and form typical osteoid tissue and bone. The same worker has investigated the development *in vivo* and *in vitro* of the human lung rudiment. He has maintained cultures of human foetal lung for several weeks, and has found that growth of the air-spaces takes place, not only by terminal branching, but also, and even more frequently, by lateral budding. The branching and budding are effected solely by the epithelial cells.

Dr. A. F. W. Hughes has made further observations on the development of blood-vessels. He is investigating the forces responsible for the differentiation of arteries and veins from a plexus of vessels which are originally similar in size and structure. An apparatus has been devised for measuring the rate of blood-flow in embryonic vessels, and it is being used to compare the rate of flow with the rate of dilatation of the vessel wall, with the object of finding whether any general relation exists between the two.

Miss Fischmann has extended her studies of the influence of vitamin D on bone formation *in vitro*. Her recent experiments have been concerned with the capacity of D-deficient osteogenic tissue cultures to recover when transferred to normal medium. She has found that cultivation for forty-eight hours in a medium deficient in the vitamin is sufficient to affect the culture permanently. Thus, even after prolonged cultivation in a normal medium, the abnormal tissue formed during the period of deficiency remains unaltered in the interior of the culture, although it becomes enclosed by a zone of normal, partially calcified osteoid tissue which has developed after transference to the normal medium.

Dr. P. D. F. Murray has analysed the mechanism of fibrillation in the embryonic heart; Dr. T. D. Day is applying the tissue-culture method to a general study of pathological fibrosis; and Mr. C. W. Wilson has completed an investigation of the lethal effects of gamma rays on young chick embryos in the egg.

Dr. Spear has done further work on the intensity factor in

radiation. With Mr. L. G. Grimmett, measurements have been made of the actual intensities used in earlier tissue-culture experiments. It has been shown that the optimum intensity for reducing cell division in culture is in the region of 77 millicuries. With Dr. Hughes observations are being made on the effects of gamma rays on the circulatory system of the chick embryo *in ovo*. One of the first effects noted in the vascular system after irradiation is a clumping of the red blood-cells, which ultimately leads to obstruction of the circulation in the affected vessel. This result is not seen until a much higher dose has been given than that which affects cell division. Once the effective level has been reached, however, it is found that the dose of gamma rays which just produces clumping varies with alterations in intensity, in a manner closely resembling the tissue-culture results. It is remarkable that alteration in intensity values should affect two widely different types of biological response in a similar manner, and the inquiry is being extended to other kinds of biological response in order to show whether these early findings have a general or only a limited application.

With Dr. K. Tansley, of University College, London, Dr. Glücksmann and Dr. Spear have examined the method by which irradiation produces rosettes in the rat retina *in vitro*. This study has given valuable information bearing directly on problems of radiation in general. The most striking result of an effective irradiation was a degeneration of cells in the outer layers of the retina so that whole areas became necrotic. In these circumstances the outermost layer was deprived of its normal support during growth and rosettes were formed in it as a result of folding. Radiation produces recognizably destructive effects only in those parts of the retina which are undifferentiated at the time of exposure, and this may eventually prove a useful method for determining exactly which cells have differentiated at any given stage of development. Where degeneration occurs it is always preceded by a reduction in cell division. It appears that the first effect of exposure is upon cells which are about to divide; that these cells subsequently degenerate and are permanently lost; and that the formation of rosettes from the residual, unaffected cells is secondary to the degenerative process and is not due to a direct action of the gamma rays. In the course of these experiments a new fibre layer was produced in the retina by radiation: it was formed only if the retina was exposed during one particular stage of development, and its nature and significance is now being examined. While studying the effects of gamma rays on the tissues of the tadpole, Dr. Glücksmann has compared the reactions of lymphoid tissue and blood-cells to radiation, with that of nerve tissue. Lymphoid tissue has proved to be specially radio-sensitive.

H. B. Fell—
'Tissue Culture. I. The Advantages and Limitations as a Research Method.' *Brit. J. Radiol.*, 1935, n.s. **8**, 27.

H. B. Fell and R. G. Canti—
'Experiments on the Development *in vitro* of the Avian Knee-Joint.' *Proc. Roy. Soc.*, B, 1934, **116**, 316.

H. B. Fell and W. Landauer—
'Experiments on Skeletal Growth and Development *in vitro* in Relation to the Problem of Avian Phokomelia.' *Proc. Roy. Soc.*, B, 1935, **118**, 133.

H. B. Fell and R. Robison—
'The Development of the Calcifying Mechanism in Avian Cartilage and Osteoid Tissue.' *Biochem. J.*, 1934, **28**, 2243.

C. F. Fischmann—
'Tissue Culture Experiments on the Relation between the Low Phosphate and Calcium Content of the Blood in Rickets and the Changes Produced in Rachitic Bone.' *J. Soc. chem. Ind.*, Lond., 1935, **54**, *Chemistry & Industry*, 269.

P. D. F. Murray—
'La micro-fibrillation de Léon Fredericq étudiée *in vitro*.' *Arch. int. Physiol.*, 1934, **40**, 243.
'Fibrillation in the Chick Embryo Heart *in vitro*. I. The Effects of Excess Potassium, Calcium, Magnesium, and Sodium, and of High and Low Osmotic Pressures. II. The Character and Mechanism of the Fibrillation.' *Proc. Roy. Soc.*, B, 1935, **116**, 434 and 452.

F. G. Spear—
'Tissue Culture and Radiological Research.' *Brit. J. Radiol.*, 1935, n.s. **8**, 68.

F. G. Spear and L. G. Grimmett—
'The Biological Response to Gamma Rays of Radium as a Function of the Intensity of Radiation.' *Brit. J. Radiol.*, 1935, n.s. **8**, 231.

C. H. Waddington—
'The Development of Isolated Parts of the Chick Blastoderm.' *J. exp. Zool.*, 1935, **71**, 273.
'Cancer and the Theory of Organisers.' *Nature*, Lond., 20th April 1935.

C. W. Wilson, A. F. Hughes, A. Glücksmann, and F. G. Spear—
'Bestrahlungsversuche an Hühnerembryonen *in vitro* und *in vivo* mit Radiumgammastrahlen.' *Strahlentherapie*, 1935, **52**, 519.

Radiology and Radiotherapy

During the year under review, the Council learnt with great regret of the deaths of Sir John McLennan, F.R.S., and of Dr. Helen Chambers, who were both closely connected with their programme of research into the radium treatment of cancer. Sir John McLennan, a physicist of outstanding attainment, was most active in promoting the scheme of inquiry into the curative possibilities of radium beam therapy, of which mention is made below. It was mainly through his influence that the Union Minière du Haut Katanga generously lent the large quantity of radium which is being used for this research, and he was Secretary-Treasurer of the Radium Beam Therapy Research Board (p. 166). Dr. Helen Chambers was a devoted worker on the causation and treatment of cancer. Her foresight and inspiration were in large measure

responsible for the foundation of the Marie Curie Hospital in London, and she made a number of important contributions to the study of malignant disease, on both its clinical and experimental aspects. For the last fifteen years of her life she was in the whole-time service of the Council, working as a member of the cancer research team at the Middlesex Hospital, and acting as honorary pathologist to the Marie Curie Hospital.

The stock of radium held by the Council on behalf of H.M. Government, and distributed on loan to various research centres, is supplemented by further quantities provided by the British Empire Cancer Campaign and by the National Radium Commission. The Campaign contributes towards the working expenses of the Radon Centre at the Middlesex Hospital, where an important fraction of the Government radium is kept in solution as a source of radon. The following centres have taken part in a co-ordinated scheme of clinical research into the radium treatment of cancer and some other diseases: the Middlesex Hospital, St. Bartholomew's Hospital, University College Hospital, the Royal Free Hospital, the Marie Curie Hospital, St. George's Hospital, and St. Peter's Hospital, London; the General Hospital, Birmingham; the Radium Institute, Manchester; the Royal Infirmary, Cardiff; the Royal Infirmary, Aberdeen; the Scottish Branch of the Medical Women's Federation, Edinburgh; and the Irish Radium Committee, Dublin.

Supplies of radium for experimental work have been lent to Dr. J. C. Mottram at the Mount Vernon Hospital, Northwood; to Mr. W. V. Mayneord at the Cancer Hospital, London; to Dr. Joan Ross at the Royal Free Hospital, London; to Sir Leonard Hill and Dr. H. J. Taylor at the St. John Clinic, London; to the Strangeways Research Laboratory, Cambridge; and to Mr. J. J. M. Shaw and other workers in Sir David Wilkie's department at Edinburgh. A few additional workers and institutions have shared in the facilities for the supply of radon. A summary of the reports received from the different clinical and experimental centres on the work done with radium in 1934 has been prepared by the Radiology Committee (p. 166) and published.

Assistance by Miss D. Clephan in the research work at the Middlesex Hospital has again been provided, and a grant for expenses has been made to Dr. Joan Ross at the Royal Free Hospital. Dr. Ross is continuing an experimental inquiry into the effects produced on the blood and tissues by prolonged irradiation of small intensity.

With an expenses grant in Professor A. J. Clark's department at Edinburgh, Dr. C. M. Scott has done further work on the mode of action of X-rays and radium on living cells. Experiments on the eggs of *Calliphora* and the isolated amphibian heart have shown

that the effects of X- and gamma-rays are independent of all the known metabolic functions of the resting cell, and cannot be directly influenced by artificial interference with the cell's metabolism. This finding, together with the known fact that X- and gamma-rays tend especially to destroy actively growing tissues, suggests that both forms of irradiation act specifically on the substances and functions of the cell that are concerned in cell division. There is strong evidence that the substances on which X-rays have their primary action are identical with the genetic factors of the cell. An account of this study is being prepared for publication.

Mention of work at Cambridge by Dr. F. G. Spear and others has already been made under the preceding head.

At the St. John Clinic and Institute of Physical Medicine, London, Sir Leonard Hill and Dr. H. J. Taylor have a grant for expenses. Sir Leonard Hill has extended his work on the physiological effects of infra-red rays, and Dr. Taylor is observing the effects of ultra-short high-frequency waves on normal tissues and in experimental cancer. The claim that a wave-length of 3·4 metres has a specific action on malignant cells has not been confirmed, and tests are now being made of the combined effects of ultra-short high-frequency waves and radium.

Research at the London Hospital on ultra-short wave therapy is noticed at pp. 81 and 162.

The Council continue to provide part of the expenses of the investigation into the treatment of cancer with massive doses of radium which is being made at the Radium Institute, London, under the direction of the Governing Body of the Radium Beam Therapy Research (p. 166) which has the status of a joint Research Board of the Council and of the Department of Scientific and Industrial Research. During the year under review, special attention has been given to the treatment of cancer of the mouth and throat, and the staffs of various London hospitals have helped by sending suitable cases for treatment. Encouraging results have been obtained, and the number of patients referred to the Board has necessitated the installation of another five-gramme radium unit for this form of therapy. The radium used in the research is lent by the Union Minière du Haut Katanga, whose ready co-operation has made the work possible.

'Medical Uses of Radium: Summary of Reports from Research Centres for 1934.' *Spec. Rep. Ser. Med. Res. Coun.*, Lond., No. 204, 1935.

H. Chambers—

'The Histological Classification of Cancers of the Uterine Cervix and the Relation between the Growth Structure and the Results of Radium Treatment.' *Amer. J. Cancer*, 1935, 23, 1.

'Radiotherapy in Cervix Cancer.' *Lancet*, 16th March 1935.

H. Chambers and S. Russ—

'Principles of Radiological Treatment and their Bearing on Hospital X-ray Organisation.' *Brit. med. J.*, 6th July 1935.

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N. R. Lawrie and M. Robertson—
'The Effect of γ-Ray Irradiation upon the Growth and Nitrogenous Metabolism of the Protozoon, *Bodo caudatus*.' *Biochem. J.*, 1935, **29**, 1017.

L. Hill—
'"Nose-opening" Rays.' *J. Hyg.*, Camb., 1935, **35**, 75.
'A Simple Method of Measuring the Air-way of the Nose.' *J. Physiol.*, 1935, **85**, 19 P.
'A Method of Measuring the Airway of the Nose.' *Lancet*, 13th July 1935.

Vision and Hearing

Research on problems of vision is supervised by the Committee named at p. 166.

The Physiology of Vision

At Cambridge Miss M. D. Vernon has received a personal grant in the department directed by Professor F. C. Bartlett. She has continued her inquiry into the factors involved in the binocular perception of distance, with a view to establishing the nature of their interrelationships. A comprehensive account of recent experimental studies in visual perception has been prepared for publication. Dr. H. Banister, of this department, has published the results of work on 'eye-dominance' which was done with support from the Council.

At Manchester Professor D. Katz has again had a grant for assistance. Under his direction Mr. T. Martin has extended the work begun last year by Mr. J. J. Webster on the perception of objects viewed through measured depths of haze and fog under varying conditions of lighting.

With a part-time grant at University College, London, Dr. R. J. Lythgoe has made further observations on the photo-chemistry of the visual purple. The rate of decomposition of this substance under the influence of monochromatic radiation has been measured at various wave-lengths and at various temperatures. The results have been analysed in terms of existing photo-chemical laws. The collected evidence shows, among other things, that visual yellow, the intermediate breakdown product of visual purple, plays no active part in the physiology of sight.

At the Imperial College of Science, London, Dr. W. D. Wright has been provided with the assistance of Mr. F. H. G. Pitt and Mr. J. H. Nelson in work on colour vision: the research is under the general direction of Dr. L. C. Martin. A report by Mr. Pitt on the characteristics of dichromatic vision has been published by the Council: it gives a detailed analysis of the range of colours and luminosities seen and distinguished by persons whose colour vision, unlike the normal, is a function of only two variables; it also provides new data on which a theory of colour vision may be based. An appendix to the report deals with some of the anomalies of trichromatic vision.

H. Banister—
'A Study in Eye Dominance.' *Brit. J. Psychol.*, 1935, **26**, 32.

R. J. Lythgoe—
'Visual Perception under Modern Conditions.' *Illuminating Eng.*, November 1935.

F. H. G. Pitt—
'Report of the Committee upon the Physiology of Vision. XIV. Characteristics of Dichromatic Vision. With an Appendix on Anomalous Trichromatic Vision.' *Spec. Rep. Ser. Med. Res. Coun.*, Lond., No. 200, 1935.

W. D. Wright—
'Intensity Discrimination and its Relation to the Adaptation of the Eye.' *J. Physiol.*, 1935, **83**, 466.

Diseases and Abnormalities of the Eye

Under the direction of Sir Stewart Duke-Elder at University College, London, Mr. H. Davson has had a personal grant to study the physico-chemical properties of the vitreous humour of the eye, with special reference to their bearing on clinical problems such as glaucoma, detachment of the retina, and the formation of vitreous opacities. Mrs. M. C. Bourne, with an expenses grant here, has continued her experimental work on cataract. She has examined the possibility of preventing naphthalene cataract by giving cysteine and other compounds containing sulphur, and is investigating the supposed relationship between cataract and vitamin B_2 deficiency. With Dr. Dorothy Campbell, of the Birmingham Eye Hospital, observations have been made on the sulphur metabolism of a number of patients with cataract: no deviation from the normal was found.

At University College, London, and the Royal Westminster Ophthalmic Hospital, Mr. E. Wolff has received expenses for work on the mechanism by which quinine may cause temporary blindness. No evidence was found to support the theory that this substance acts on the retina by way of the vitreous humour. It was shown, however, that a single subcutaneous injection of quinine might cause a prolonged decrease in the oxygen-consumption of the retina. The parts played by arterial spasm and by retinal haemorrhages in quinine blindness are being further investigated.

Research by Mr. J. W. Tudor Thomas, at Cardiff, on a surgical treatment for blindness due to opacities of the cornea has been noticed at p. 89.

M. C. Bourne and M. Pyke—
'The Occurrence of Cataract in Rats Fed on Diets Deficient in Vitamin B_2.' *Biochem. J.*, 1935, **29**, 1865.

J. F. Danielli and H. Davson—
'A Contribution to the Theory of Permeability of Thin Films.' *J. cell. comp. Physiol.*, 1935, **5**, 495.

W. S. Duke-Elder and H. Davson—
'Studies on the Vitreous Body. II.' *Biochem. J.*, 1935, **29**, 1121.
'The Vitreous Body and Glaucoma.' *Brit. J. Ophthal.*, 1935, **19**, 433.

W. S. Duke-Elder, E. B. Robertson, and H. Davson—
'Studies on the Vitreous Body. I.' *Biochem. J.*, 1935, **29**, 72.

E. Wolff—
'The Causation of Quinine Blindness.' *Lancet*, 29th June 1935.

The Physiology of Hearing

The Committee named at p. 167 supervise research on problems of hearing and on diseases of the ear.

At the Middlesex Hospital, London, Dr. C. S. Hallpike, a Foulerton Student of the Royal Society, has continued to study the physiology of the ear by means of modern electrical recording methods. Part of the apparatus used in his work has been provided by the Council, and they have again made a grant to Mr. A. F. Rawdon Smith for assistance jointly to him and to Professor F. C. Bartlett at Cambridge.

At Manchester University Dr. A. W. G. Ewing and Mrs. I. R. Ewing have had grants for expenses and for assistance by Mr. T. S. Littler, in research on physical problems related to the efficiency of mechanical aids to hearing. They have continued their investigations of auditory adaptation and fatigue, and have made further observations on the response of partially deaf patients to amplified speech. The capacity and effective amplification of different hearing aids in common use have been measured by means of special apparatus installed in a sound-proof room. In October 1934 a clinic for the study and relief of deafness was established under the supervision of Dr. and Mrs. Ewing. Some two hundred and fifty patients have so far attended, the majority having been referred to the clinic by their own physicians or by school medical officers. Tests have been made with pure-tone and gramophone audiometers and with various types of hearing aid. An account of the data obtained is being prepared for publication.

Dr. H. E. O. James, at Manchester University, has completed the work on the physiology of binaural hearing, for which he received a grant.

At Cardiff Dr. J. H. Shaxby has had grants for expenses and for assistance by Mr. F. H. Gage. Mr. Gage has concluded an investigation of the effects of graded stimuli applied to one ear on the auditory threshold of the other, and has made an experimental inquiry into the measurability of visual and auditory sensations.

The Choice of a Hearing Aid. Pamphlet issued by the National Institute for the Deaf, with the approval of its own Medical Committee and of the Hearing Committee of the Medical Research Council.

A. W. G. Ewing and T. S. Littler—
'Auditory Fatigue and Adaptation.' *Brit. J. Psychol.*, 1935, **25**, 284.

I. R. and A. W. G. Ewing—
'Hearing Aids in Schools for the Deaf.' *Report of Conference of National College of Teachers of the Deaf*, 1934.

F. H. Gage—
'A Phase-shifting Transformer.' *J. sci. Instr.*, 1934, **11**, 289.
'Variation of the Unilateral Differential Threshold with Simultaneous Stimulation of the Other Ear.' *Brit. J. Psychol.*, 1934, **25**, 458.
C. S. Hallpike—
'Recent Advances in the Electrophysiology of Hearing.' *J. Laryng.*, 1935, **50**, 672.
C. S. Hallpike and A. F. Rawdon Smith—
'The Origin of the Wever and Bray Phenomenon.' *J. Physiol.*, 1934, **83**, 243.

Anatomical and Anthropometric Researches

At King's College, London, a grant for expenses has been made to Professor D. M. Blair. With Dr. F. Davies he has studied the comparative anatomy of the conducting system which co-ordinates the rhythm of the mammalian heart. A microscopic staining method which has been shown to distinguish the muscular and nervous elements in the system has been applied to serial sections of the hearts of a number of different species.

Dr. Tudor Jones, who formerly had a part-time grant at Liverpool, has completed an investigation of the early development of the nervous system and the nerve-supply of blood-vessels. The results have been prepared for publication.

At the Research Laboratories of the Royal College of Surgeons of England, Dr. Harold Burrows and Miss Parbury are measuring by X-rays the comparative sizes of the pituitary fossae of European and Negro skulls, as an indication of the size of the pituitary gland in different races. The Council have provided expenses. The extensive collection of accurately classified skulls in the Museum of the College offers a good field for this study, and the Curator, Dr. J. Beattie, has given every facility for the work. From measurements of fifty skulls of each type it has been found that the average length and depth of the fossa are greater in the Negro than in the European. The comparative measurements of the width of the fossa have not yet been completed, owing to technical difficulties which have still to be overcome.

Reference has been made at pp. 100 and 108 to the clinical and anthropometric studies made by Dr. Matthew Young of the Council's staff on behalf of the Committees on Iodine Deficiency and Thyroid Disease and on Dental Disease, respectively. Dr. Young continues to work in the Institute of Anatomy at University College, London, by courtesy of Sir Grafton Elliot Smith. In addition to the researches already mentioned he has co-operated with Professor J. C. Brash of Edinburgh in an anthropometric analysis of two large collections of Anglo-Saxon skulls.

General Physiological Researches

Professor G. A. Clark, at Sheffield, who receives a grant for expenses, has extended his work on the action of adrenalin on the

blood-vessels in voluntary muscle. It has been shown that prolonged stimulation of the sympathetic nerves to a limb will temporarily prevent the 'phase of vasoconstriction' which is ordinarily one of the results of injecting a small dose of adrenalin into a limb artery: the 'phase of vasodilatation' after adrenalin is, however, enhanced by sympathetic stimulation, and it is thought that this finding may possibly have a bearing on the phenomena of shock after injury. With Dr. L. B. Winter, Professor Clark has completed a study of the sugar content of lymph. The results have been published.

At Aberdeen Dr. J. M. Peterson, Mr. H. R. Noltie, Dr. D. J. Bell, and others have continued a series of researches on the nervous and biochemical control of carbohydrate metabolism which were begun under the direction of the late Professor J. J. R. Macleod. The Council have provided expenses.

At University College, London, grants for expenses have been made to Dr. F. G. Young and Dr. D. H. K. Lee (p. 160). Dr. Young has examined the method by which extracts of the anterior lobe of the pituitary gland may produce symptoms of diabetes when injected into animals. It appears that crude extracts of this lobe of the gland contain more than one substance capable of influencing carbohydrate metabolism and apparently antagonistic to insulin. Attempts are being made to isolate the substances concerned. Dr. Lee has investigated the bearing of climatic conditions upon human metabolism, with special reference to the effects of tropical humidity on health.

With a grant for assistance to Professor A. V. Hill at University College, Miss B. M. Garrard has made further observations on the problem of water excretion under normal conditions and in Bright's disease, and on the physical mechanism of oedema. Dr. F. H. Smirk, of the Medical Unit, University College Hospital, co-operated in these studies.

In the School of Physiology at Cambridge, Mr. W. G. Walter has had a personal grant. He has co-operated with Dr. Rosenthal, of Professor Pavlov's laboratory at Leningrad, in an inquiry into the changes in conditioned reflexes produced by variations in the oxygen and carbon dioxide content of the blood.

Research by Dr. P. Eggleton and others at Edinburgh has again been assisted by an expenses grant. They have continued to measure the distribution and diffusion of various substances in voluntary muscle. From their data on this subject it is concluded that living muscles consist of two phases which may be called 'cells' and 'interspaces' respectively. Some muscle constituents, such as carnosine, are contained only in the cells, while others, such as chloride, are confined to the interspaces; a third group, including phosphate, lactate, and creatine, is present in both cells and interspaces,

although not necessarily in the same concentration. There may also be a fourth group which can diffuse freely throughout the living muscle, but urea is the only substance which has yet been shown to have this property. Dr. J. McMichael, at Edinburgh, has received an expenses grant for work on the physiology of the portal circulation and on methods for the measurement of cardiac output in man.

At the College of Medicine, Newcastle-upon-Tyne, expenses have been provided for work by Professor D. Burns and his colleagues. They have made further studies in the biochemistry of tetany and allied conditions. Mrs. C. M. Burns and Miss N. Henderson have prepared a paper on the variations in chemical composition between normal and pathological bone. Research on the physiology of the automatic nervous system is being continued here by Dr. J. Secker.

D. J. Bell—
'Liver Glycogen. III. The Molecular Units of Fish and Rabbit Glycogens.' *Biochem. J.*, 1935, **29**, 2031.

D. J. Bell and H. Kosterlitz—
'Liver Glycogen. II. Acyl Derivatives and "Regenerated Glycogens".' *Biochem. J.*, 1935, **29**, 2027.

C. H. Best, M. E. Huntsman, and F. G. Young—
'The Effect of Diets low in Choline, and of Choline Feeding, on the Glycosuria of the Depancreatized Dog.' *J. Physiol.*, 1935, **85**, 8 P.

E. M. Bridge and H. R. Noltie—
'The Action of Adrenaline on the Respiratory Quotient.' *J. Physiol.*, 1935, **85**, 334.

C. M. Burns and F. J. Elliott—
'The Calcium Content of Liver.' *J. Physiol.*, 1935, **84**, 39 P.

C. M. Burns and N. Henderson—
'The Salts of Young Bone.' *J. Physiol.*, 1934, **82**, 7 P.
'The Mineral Constituents of Bone. I. Methods of Analysis.' *Biochem. J.*, 1935, **29**, 2385.

G. A. Clark—
'The Development of Blood-Pressure Reflexes.' *J. Physiol.*, 1934, **83**, 229.
'Adrenaline Vaso-Dilatation in Voluntary Muscle.' *Ibid.*, 1935, **84**, 344.

G. A. Clark and L. B. Winter—
'Lymph Sugar.' *J. Physiol.*, 1935, **83**, 49 P.

M. G. Eggleton—
'Diffusion of Sugars into Muscle.' *J. Physiol.*, 1935, **84**, 59.

P. Eggleton—
'The Place of Phosphagen in Muscle Biochemistry.' *Ergebn. Enzymforsch.*, 1934, **3**, 227.
'The Chemistry of Muscle.' *Ann. Rev. Biochem.*, 1935, **4**, 413.

D. H. K. Lee—
'A Modification of Rehberg's Microtitration Apparatus.' *J. Physiol.*, 1935, **84**, 27 P.

H. R. Noltie—
'Post-mortem Glycogenolysis in Rabbit Liver.' *Quart. J. exp. Physiol.*, 1934, **24**, 261.

'The Effect of Iodoacetate on Post-mortem Glycogenolysis in Liver.' *Ibid.*, 1935, **24**, 377.

J. A. Saunders—

'Guanidine and the Parathyroid Glands.' *Biochem. J.*, 1935, **29**, 1597.

Sex Hormones

Research in this subject is directed by the Committee named at p. 167. Clinical trials of oestrin and progestin are supervised by a special sub-committee of this committee and of the Therapeutic Trials Committee. Work at the National Institute has been noticed at p. 53, and work on the standardization of sex hormones at pp. 23 and 67.

At University College, London, Dr. W. H. Newton has again received an expenses grant for work on the physiology of the uterus and the mechanism of parturition. Observations in mice have shown that the placenta can survive *in utero* after destruction of the foetus and itself be delivered at normal full-term. Oestrus does not occur so long as the placenta is present, and it thus appears that the placenta plays a more important part than the foetus in maintaining the state of pregnancy. This power to prevent oestrus may perhaps provide a useful qualitative test for placental extracts. Further studies have been made of the combined action on the uterus of oestrin and oxytocic pituitary extract: in these experiments oestrin benzoate has been used, since Zondek showed that it was less easily destroyed in the body than other oestrin derivatives. Oestrin benzoate was found to be more active than oestrone or oestriol in initiating parturition, but more extensive tests are necessary before its clinical use can be recommended.

In the Department of Social Biology at the London School of Economics, Professor L. T. Hogben has a grant for expenses and Mr. C. W. Bellerby a personal grant. With Mr. S. S. Alexander work has been continued on the effects of injecting anterior pituitary extracts at successive stages of the ovarian cycle; it has been shown that the physiological effects produced by a single extract may vary considerably with the stages of ovarian activity.

At Edinburgh, expenses have been provided for work by Dr. J. M. Robson, Dr. A. W. Greenwood, and Miss A. M. Hain. Dr. Robson has made further inquiry into the parts played by pituitary and ovarian hormones in maintaining pregnancy and initiating parturition. Observations have been extended on the physiological effects of hypophysectomy, special attention being given to the actions of corpus luteum and other hormones in the absence of the pituitary body. With Dr. Greenwood and Mr. David Band Dr. Robson has also examined the nature and quantity of the hormones excreted by patients with enlarged prostate glands. Dr. Greenwood has continued to co-operate with Professor E. C. Dodds, of the Middlesex Hospital, in studies of the activity in

capons of preparations of male and female sex hormones. Miss Hain is investigating the effects of sex hormones given during pregnancy and lactation upon the development of the young animal.

With an expenses grant at Bristol, Dr. G. H. Bell has examined the content of oxytocic hormone in the foetal pituitary gland at different stages of development. He has also made further observations on the method by which oestrogenic hormones may augment the activity of oxytocin on the uterus. Dr. T. Nicol, who received expenses at Glasgow, has completed a study, by special staining methods, of the detailed anatomy of the female reproductive system in the guinea-pig and the effects of hormones upon it. An account of the findings has been published. Work on the influence of sex hormones on the reproductive cycle in different mammalian species has been continued by Miss M. Allanson, with an expenses grant at King's College, London.

At the Middlesex Hospital, Professor E. C. Dodds (pp. 133 and 136) has had a grant for assistance by Mr. G. M. Hills in chemical and pharmacological studies of sex hormones. With Professor J. W. Cook (p. 133) and Mr. W. Lawson, further work has been done on synthetic oestrus-producing substances. A series of isomers of known synthetic oestrogenic agents has been prepared, and it is hoped that their examination may shed light on the molecular structure responsible for this form of physiological activity.

A grant for expenses has been made to Dr. S. S. Zuckerman at Oxford. He is investigating the interrelationship of neuro-vascular and endocrine factors in the control of menstruation. With Dr. A. S. Parkes (p. 54) experiments are also being done on the effects of different sex hormones on the reproductive system in higher mammals.

At the Lister Institute, London, Dr. V. Korenchevsky has a personal grant. With Mrs. M. Dennison and Dr. S. Levy Simpson, he has continued to study the physiological activity of preparations of male and female sex hormones. It has been shown that the diol derivatives of androsterone have a more powerful physiological action than this preparation itself. Androsterone-diol and its derivatives seem to have no ill effects in male animals, and the abnormal effects produced by them in female animals are insignificant compared with those caused by ovarian hormone in the male. Controlled experiments with preparations of male hormone have failed to show that they have any general 'rejuvenating' power. Dr. Korenchevsky and his co-workers have made further observations on the combined influence of male and female sex hormones on the reproductive system, and on the metabolic and other changes associated with deficiency or operative removal of the adrenal glands.

S. S. Alexander and C. W. Bellerby—
'The Effect of Captivity upon the Reproductive Cycle of the South African Clawed Toad (*Xenopus laevis*).' *J. exp. Biol.*, 1935, **12**, 306.

P. M. F. Bishop, F. Cook, and A. C. Hampson—
'Indications for the Clinical Use of Progestin; Standardized Corpus Luteum Extract.' *Lancet*, 19th Jan. 1935.

G. H. Bell and J. M. Robson—
'Oxytocic Properties of Blood Extracts and their Physiological Significance.' *J. Physiol.*, 1935, **84**, 351.

C. W. Bellerby—
'Termination of Pregnancy in the Rabbit by Intravenous Injection of Anterior Lobe Pituitary Extract.' *J. exp. Biol.*, 1935, **12**, 286.

E. C. Dodds—
'Oestrus-producing Hormones.' *Brit. med. J.*, 29th Dec. 1934.

A. W. Greenwood and J. S. S. Blyth—
'Biological Methods of Diagnosing Equine Pregnancy. II. The Capon Test.' *Proc. Roy. Soc.*, B, 1934, **116**, 247.
'Variation in Plumage Response of Brown Leghorn Capons to Oestrone. I. Intramuscular Injection. II. Intradermal Injection.' *Ibid.*, 1935, **118**, 97.

A. W. Greenwood, J. S. S. Blyth, and R. K. Callow—
'Quantitative Studies on the Response of the Capon's Comb to Androsterone.' *Biochem. J.*, 1935, **29**, 1400.

V. Korenchevsky—
'Effects Produced on Rats by Synthetic Androsteron (Male Sex Hormone).' *Nature*, Lond., 16th March 1935.
'Homology of the Female Periurethral Glands and the Prostate.' *Ibid.*, 3rd Aug. 1935.

V. Korenchevsky and M. Dennison—
'The Assay of Crystalline Male Sexual Hormone (Androsterone).' *Biochem. J.*, 1935, **29**, 1720.
'The Assay of Fat-soluble Androsterone-Diol.' *Ibid.*, 1935, **29**, 2122.
'The Manifold Effects of Testicular Hormones (as extracted from Human Urine or Synthetically Prepared) and of Oestrone on the Male, as judged by Experiments on Rats.' *Proc. R. Soc. Med.*, 1935, **28**, 1265.
'Histological Changes in the Organs of Rats Injected with Oestrone alone or Simultaneously with Oestrone and Testicular Hormone.' *J. Path. Bact.*, 1935, **41**, 323.

V. Korenchevsky, M. Dennison, and S. L. Simpson—
'The Effects of Water-soluble Preparations of Androsterone and Androsterone-Diol on Castrated Rats.' *Biochem. J.*, 1935, **29**, 2131.

G. F. Marrian and W. H. Newton—
'The Synergism between Oestrin and Oxytocin.' *J. Physiol.*, 1935, **84**, 133.

W. H. Newton—
'"Pseudo-parturition" in the Mouse, and the Relation of the Placenta to Post-Partum Oestrus.' *J. Physiol.*, 1935, **84**, 196.

T. Nicol—
'The Female Reproductive System in the Guinea-Pig: Intravitam Staining; Fat Production; Influence of Hormones.' *Trans. Roy. Soc. Edinb.*, 1934–5, **58**, 449.

J. M. Robson—
'Uterine Reactivity and Activity *in vitro* and *in vivo*.' *J. Physiol.*, 1935, **84**, 45 P.
'The Effect of Oestrin on the Uterine Reactivity and its Relation to Experimental Abortion and Parturition.' *Ibid.*, 1935, **84**, 121.
'The Action of Oestrin on the Uterus of the Hypophysectomized and of the Pregnant Rabbit.' *Ibid.*, 1935, **84**, 148.

'The Response of the Uterus of Hypophysectomized Rabbits to Extracts of the Corpus Luteum.' *Ibid.*, 1935, **84**, 296.

'The Action of the Ovarian Hormones on the Uterine Muscle measured *in vivo* and *in vitro*.' *Ibid.*, 1935, **85**, 145.

'The Action of Oestrin on the Mammary Secretion.' *Quart. J. exp. Physiol.*, 1935, **24**, 337.

A. E. Russell and S. Zuckerman—
'A "Sexual Skin" in a Marmoset.' *J. Anat.*, Lond., 1935, **69**, 356.

S. L. Simpson and V. Korenchevsky—
'Histological Changes in the Kidneys of Adrenalectomized Rats.' *J. Path. Bact.*, 1935, **40**, 483.

J. Z. Young and C. W. Bellerby—
'The Response of the Lamprey to Injection of Anterior Lobe Pituitary Extract.' *J. exp. Biol.*, 1935, **12**, 246.

S. Zuckerman—
'Variation in the Sensitivity of Different Species of Monkeys to Oestrin.' *J. Physiol.*, 1935, **84**, 191.

'The Menstrual Cycle of the Primates. VIII. The Oestrin-Withdrawal Theory of Menstruation. IX. The Effect of Oestrin on the Denervated Sexual Skin.' *Proc. Roy. Soc.*, B, 1935, **118**, 13 and 22.

General Biochemical Researches

In the School of Biochemistry at Cambridge, a grant has been made to Dr. E. G. Holmes for assistance by Miss M. C. A. Cross in studies of the metabolism *in vitro* of tissues damaged by various poisons. Miss E. C. Watchorn, who received a personal grant here, has investigated with Dr. R. A. McCance (p. 98) the distribution of inorganic sulphur between the blood-serum, cerebrospinal fluid, and other body fluids in man. The results support the view that the cerebrospinal fluid is not formed simply by ultra-filtration from the blood-serum, but must be regarded as an active secretion. Miss Watchorn and Dr. McCance have also examined experimentally the effects of a chronic deficiency of magnesium in the diet. It has been shown that, although the early acute symptoms of the deficiency quickly subside, lack of magnesium in the diet leads to renal damage, brittleness of the bones, and characteristic changes in the teeth. The nature of the effects produced in different organs is being studied chemically and microscopically.

With a personal grant in Professor E. K. Rideal's department at Cambridge, Dr. J. H. Schulman has continued to examine the actions of enzymes upon monomolecular surface films of proteins, fats, and lipoids. By electrophysical measurements it is possible to follow the course of the chemical reactions concerned, and a series of these reactions has been analysed. Attempts are being made to adapt the methods used in this inquiry to the study of immunity reactions.

The properties of surface films of substances of biological interest have been further investigated by Dr. N. K. Adam at University College, London, with a grant for whole-time assistance by

Mr. F. A. Askew. The work has shed new light on the chemical structure of the sterols and allied substances. Methods which had proved informative in the case of substances of known constitution have since been used to examine various compounds of unknown structure, including vitamin E. It has been shown that many organic compounds lower the air-water interfacial tension of surface films, and are strongly adsorbed to form froths: this principle is being used in the extraction of active substances from biological fluids. Work is also being done on the electrophysical properties of films suspended between two liquids, under conditions resembling those of living membranes.

At the Cancer Hospital, London, Professor J. W. Cook has been provided with the assistance of Dr. A. Cohen and Mr. C. A. Lawrence in work on the chemistry of oestrogenic and cancer-producing compounds, with special reference to the relationship between molecular structure and biological activity. With Dr. C. L. Hewett, Professor Cook and Dr. Cohen have determined the molecular structure of the three oestrogenic hormones, oestrone, equilin, and equilenin. Experiments are being continued in the artificial synthesis of oestrogenic hormones and other substances of similar activity. Professor E. C. Dodds (p. 130), of the Middlesex Hospital, co-operates in these investigations. Research on the synthetic preparation of oestrogenic compounds is being done also by Dr. G. A. R. Kon and others at the Imperial College of Science, London, the Council defraying expenses.

At Manchester University, Dr. B. Cavanagh has had a personal grant for work, under the direction of Professor M. Polanyi and Professor H. S. Raper, on applications of isotopic chemistry to biological problems. He has examined the mechanism by which molecular hydrogen is activated by enzymes of the coliform bacteria, and has begun an investigation of metabolic processes in the animal body, by the use of food materials 'marked' with isotopic hydrogen.

A grant has been made to Professor H. V. A. Briscoe at the Imperial College of Science, London, for assistance by Mr. F. W. James in studies of the concentration and significance of 'heavy water' in biological fluids. The work has been done in co-operation with Professor E. L. Kennaway and Dr. W. Boyland of the Cancer Hospital.

Dr. J. Pryde, at University College, Cardiff, has again had grants for expenses and assistance. He has continued to study the biochemistry of glucuronic acid and allied compounds in relation to the problem of detoxication *in vivo*. Further data have been collected on the fate of the phenyl glucosides in the body, and similar observations are being made on other glucosides. Work on the structure of benzoyl glucuronic acid is being repeated, as the

chemistry of this detoxication product has been the subject of some controversy.

With an expenses grant at Liverpool, Professor H. J. Channon and his colleagues are investigating the role of the liver in fat metabolism, and the method by which choline will prevent fatty liver in animals fed on diets which ordinarily produce it. It has been found that the deposition of glyceride in experimental fatty liver is influenced not only by choline but also by the amount of protein in the diet. Experiments are being done to determine whether this effect is due to a constituent part of the molecule of the protein used, or to some contaminating substance. With Dr. F. X. Aylward and Mr. H. Wilkinson, Professor Channon has examined the changes in amounts of the different lipoids in the liver which follow meals containing fat and cholesterol with and without added choline. The effects on the liver of various homologues of choline, and related compounds, have been studied by Dr. J. A. B. Smith. Dr. O. A. Trowell has investigated the metabolism of liver tissue in artificial culture and the results of adding choline to the culture medium.

N. K. Adam—
'Surface Chemistry.' *Nature*, Lond., 28th Sept. 1935.

N. K. Adam, F. A. Askew, and J. F. Danielli—
'Further Experiments on Surface Films of Sterols and their Derivatives.' *Biochem. J.*, 1935, **29**, 1786.

F. A. Askew—
'Absorption Spectra of Polycyclic Hydrocarbons. Part I. Alkyl-substituted Phenanthrenes.' *J. chem. Soc.*, 1935, p. 509.
'Part II. Partially Reduced Derivatives of Phenanthrene, &c.' *Ibid.*, 1935, p. 512.
'Surface Films of Vitamin E Concentrates.' *Biochem. J.*, 1935, **29**, 472.

F. X. Aylward, H. J. Channon, and H. Wilkinson—
'The Liver and Fat Metabolism.' *Biochem. J.*, 1935, **29**, 169.

H. J. Channon and H. Wilkinson—
'Choline and the "Cholesterol" Fatty Liver.' *Biochem. J.*, 1934, **28**, 2026.
'Protein and the Dietary Production of Fatty Livers.' *Ibid.*, 1935, **29**, 350.

A. Cohen—
'The Synthesis of Compounds related to the Sterols, Bile Acids, and Oestrus-producing Hormones. Part V. The Synthesis of Conjugated Arylhexadienes, and their Behaviour in the Diels-Alder Reaction.' *J. chem. Soc.*, 1935, p. 429.

A. Cohen, J. W. Cook, and C. L. Hewett—
'The Synthesis of Compounds Related to the Sterols, Bile Acids, and Oestrus-producing Hormones. Part VI. Experimental Evidence of the Complete Structure of Oestrin, Equilin, and Equilenin.' *J. chem. Soc.*, 1935, p. 445.

J. W. Cook and E. C. Dodds—
'Chemistry of Oestrogenic Substances.' *Nature*, Lond., 11th May 1935.

J. H. Schulman and A. H. Hughes—
'Monolayers of Proteolytic Enzymes and Proteins. III. Enzyme Re-

actions and Penetration of Protein Monolayers.' *Biochem. J.*, 1935, **29**, 1236. 'IV. Mixed Unimolecular Films.' *Ibid.*, 1935, **29**, 1243.

O. A. Trowell—
'Choline and Liver Respiration.' *J. Physiol.*, 1935, **85**, 356.

E. Watchorn and R. A. McCance—
'Calcinosis Universalis: A Further Note on Dr. J. H. Sheldon's Case Previously Shown.' *Proc. R. Soc. Med.*, 1934, **27**, 1483.
'Inorganic Constituents of the Cerebrospinal Fluid. VI. Sulphur.' *Biochem. J.*, 1935, **29**, 2291.

General Pathological Researches

Dr. A. N. Drury, of the Council's staff, continues to work in Professor H. R. Dean's department at Cambridge. With Miss G. Plaüt, a further study has been made of the biological effects of psychosin and related compounds. All the substances used in this inquiry have been prepared from animal tissues by Dr. H. Weil in the School of Biochemistry. It has been shown that psychosin in a dilution of 1 in 100,000 has a definite bactericidal action upon most gram-positive organisms, but that gram-negative and acid-fast organisms are relatively resistant to it, and spores are unaffected. The bactericidal effects even upon gram-positive organisms are completely inhibited by blood-serum. Experiments with related compounds suggest that the power of psychosin to kill bacteria is lost if the amino-group is removed, and weakened if the same group is in part replaced by a methyl or ethyl grouping: loss of the carbohydrate, however, does not affect this action. Observations of the effects of psychosin on tetanus and other toxins have been extended. The 'fixation' by psychosin of toxins *in vitro* is not specific for tetanus toxin, as diphtheria toxin can also be partially fixed by this means. Mr. J. A. R. Miles, working here, has examined the haemolysis of red blood-cells by psychosin and allied compounds. It appears that in this respect psychosin acts similarly to other known haemolysins. Dr. Drury and Miss Plaüt have studied the effects of psychosin upon blood-vessels and muscle, and have attempted, so far without success, to determine whether the haemolytic substance known to be excreted in urine is chemically related to psychosin. They have obtained no evidence at present that psychosin exists as such in living tissues, although the substances from which it is prepared are widely distributed throughout the body.

With Dr. A. M. Wedd of New York, Dr. Drury has tested the effects upon the coronary blood-vessels of the comparatively stable choline derivatives which are now issued commercially for the treatment of disorders of the peripheral circulation. These substances stimulate the vagus nerves, and by this action the coronary arteries may be constricted. Pharmacological experiments have shown, however, that doses of these substances which are capable

of reducing the general blood-pressure have little or no influence upon the coronary outflow. It seems therefore that their therapeutic use would not necessarily be contra-indicated in patients with disease of the coronary arteries.

Before his appointment to the Chair of Pathology at Oxford, Professor H. W. Florey had an expenses grant at Sheffield. With Dr. H. E. Harding, he has continued his work on the part played by secretin in the function of the digestive glands. The liberation of this hormone into the blood-stream after meals has been shown to stimulate the secretion of Brunner's glands in the duodenum. A similar effect on the glands is produced by the injection of pure secretin into the blood-stream. It appears that the release of secretin into the blood-stream and its action on the glands are independent of the passage of bile or pancreatic juice into the intestine. At Oxford, Professor Florey has grants for assistance by Dr. Beatrice D. Pullinger and Mr. E. A. H. Roberts. The former is studying the structure and functions of lymphatics, and the latter the chemistry of lysozyme.

A part-time grant has been made to Dr. B. G. Maegraith for experimental work, in Professor Florey's department at Oxford, on problems of arterioclerosis and high blood-pressure. Dr. Maegraith is also continuing the studies of toxin-production by meningococci and other bacteria which he began in the Standards Laboratory here.

Dr. H. N. Green, who is now Professor of Pathology at Sheffield, formerly received a grant at Cambridge. He has published the results of an investigation of the vitamin A reserves of women dying in the puerperium: it has been shown that in such cases the vitamin A content of the liver is often much lower than in the normal adult, but the significance of the finding has not yet been finally determined. Dr. Green has also investigated the effects of nutritional deficiencies on the bactericidal power of blood and the influence of choline on disturbances of fat metabolism associated with malignant tumours and with bacterial toxaemia. Observations on the actions of oxidizing and reducing agents on bacterial toxins have indicated that a toxoid of considerable antigenic power may be produced very quickly by partial oxidation of the corresponding toxin.

At the Middlesex Hospital, London, Professor E. C. Dodds (p. 130) has had grants for expenses and for assistance by Mr. P. C. Williams in experimental work in pathology. With Dr. R. L. Noble, it has been shown that injections of an extract from the posterior lobe of the pituitary gland will abnormally stimulate the secretion of hydrochloric acid by the stomach and produce gastric ulcers very similar to those which occur in man. The same extract has a powerful effect on the bone-marrow and reticulo-endothelial

system, causing increased activity of the blood-destroying tissues and leading to a severe and typical anaemia. The chemistry of the substance responsible for these effects, and the bearing of its action on gastric and blood pathology, are being further investigated. It appears, from work already done, that the substance is not associated with the oxytocic principle of the gland.

Professor J. Shaw Dunn, at Glasgow, has continued the experimental studies of renal disease for which he received an expenses grant. It has been found that sodium chloride in large doses causes a notable deposition of fat in the liver and kidneys, the significance of which it is hoped to explain by further work.

At the School of Medicine, Cardiff, Professor J. B. Duguid has had a grant for assistance by Dr. M. R. P. Williams. Observations have been extended on a form of nephritis which is produced experimentally by giving large quantities of orthophosphates by mouth, in the presence of hypervitaminosis D. Although any of the sodium orthophosphates may cause this lesion where there is hypervitaminosis, the changes in the kidney develop most readily when the acid salt is given. Attempts are accordingly being made to determine the method by which the acid phosphates differ from the alkaline in their effects on the kidney and on calcium and phosphorus metabolism. It has been found that this experimental form of nephritis is accompanied in its later stages by arterial changes and enlargement of the heart, which are closely similar to those associated with chronic Bright's disease in man.

Professor D. F. Cappell, who has an expenses grant at Dundee, has co-operated with Dr. Margaret Fairlie in a combined clinical and pathological study of the endometrium in cases of irregular uterine bleeding and in sterility. He has also made further experimental observations on the tumour-producing effects of dibenzanthracene compounds. Dr. G. L. Montgomery has completed, under Professor Cappell's direction, an inquiry into the prognostic value of the urea-clearance test in the toxaemias of pregnancy and in different forms of kidney disease.

With an expenses grant at St. James's Hospital, Leeds, Dr. C. J. Polson has continued his experimental studies of liver and kidney function. He has examined the excretion of urea and amino-acid nitrogen in animals, under normal conditions and in disease of the liver. At the Royal Hospital, Wolverhampton, work by Dr. J. H. Sheldon has been assisted by an expenses grant. He has completed a clinical and pathological study of haemochromatosis, and is co-operating with Professor H. Dingle, of the Imperial College of Science, London, in further spectrographic analyses of the metallic content of human tissues in health and disease. At the Princess Louise Hospital for Children, Kensington, Dr. S. Levy Simpson (p. 130) has been provided with expenses for experimental work on

the action of ephedrine on the blood picture under normal conditions and after splenectomy.

A part-time grant has again been made to Dr. R. G. Macfarlane at St. Bartholomew's Hospital, London. He is examining the physiological mechanism of blood-clotting, with special reference to the causation of haemophilia and other haemorrhagic diseases. With Dr. Burgess Barnett, of the staff of the Zoological Society, it has been shown that the venom of Russell's viper has the power, when applied locally, to prevent or arrest bleeding in haemophilic patients. With the co-operation of the dental surgeons to the hospital, the treatment has been used successfully to prevent excessive haemorrhage from tooth-sockets. Its clinical possibilities are now being further explored at a number of different centres throughout the world.

Under an arrangement with the British Red Cross Society, part-time and expenses grants were made for a final year to Dr. H. F. Brewer, medical officer to the London Blood Transfusion Service. Working at St. Bartholomew's Hospital, Dr. Brewer has continued his observations on problems of blood-grouping and on the effects of repeated bleedings upon the donors. The distribution of the blood-groups in the London area has been ascertained by a statistical survey of nearly 1,700 donors. By periodical examination of more than 300 persons who have each given blood on ten or more occasions, definite information has been obtained as to the safe intervals between bleedings, for men and women. Work has also been done on the potency and stability of stock blood-grouping sera which have been kept in storage under different conditions.

B. Barnett and R. G. Macfarlane—
'On the Relative Potency of certain Snake-Venoms to Coagulate Haemophilic Blood.' *Proc. zool. Soc.* for 1934, Pt. 4, 1935, p. 977.

H. F. Brewer—
'The Medical Administration of a Voluntary Blood Transfusion Service.' Contr. to the First International Blood Transfusion Congress, Rome, Sept., 1935.

E. C. Dodds, G. M. Hills, R. L. Noble, and P. C. Williams—
'The Posterior Lobe of the Pituitary Gland. Its Relationship to the Stomach and to the Blood Picture.' *Lancet*, 11th May 1935.

E. C. Dodds and R. L. Noble—
'Relation of the Posterior Lobe of the Pituitary Gland to Anaemia and to Blood Formation.' *Nature*, Lond., 11th May 1935.
'Effects on the Stomach of a Substance contained in the Posterior Lobe of the Pituitary Gland.' *J. Soc. chem. Ind.*, Lond., 1934, 53, *Chemistry & Industry*, 1026.

E. C. Dodds, R. L. Noble, and E. R. Smith—
'A Gastric Lesion Produced by an Extract of the Pituitary Gland.' *Lancet*, 27th Oct. 1934.

J. Shaw Dunn—
'The Pathogenesis of Renal Oedema.' *Glasg. med. J.*, 1935, **123**, *Trans. Roy. med.-chir. Soc. Glasg.*, **29**, 44.

H. W. Florey and H. E. Harding—
'A Humoral Control of the Secretion of Brunner's Glands.' *Proc. Roy. Soc.*, B, 1935, **117**, 68.
'The Healing of Artificial Defects of the Duodenal Mucosa.' *J. Path. Bact.*, 1935, **40**, 211.

R. G. Macfarlane—
'The Treatment of Haemophilic Haemorrhage.' *St. Bart's Hosp. med. Rep.*, 1935, **68**, 229.

R. G. Macfarlane and B. Barnett—
'The Haemostatic Possibilities of Snake-Venom.' *Lancet*, 3rd Nov. 1934.

B. Maegraith—
'The Toxicity of Filtrates of Broth Cultures of Meningococci.' *Brit. J. exp. Path.*, 1935, **16**, 109.

B. D. Pullinger and H. W. Florey—
'Some Observations on the Structure and Functions of Lymphatics: Their Behaviour in Local Oedema.' *Brit. J. exp. Path.*, 1935, **16**, 49.

H. Ramage and J. H. Sheldon—
'Haemochromatosis. 1. The Content of the Tissues in Iron and Sulphur. 2. The Results of Spectrographic Examination with Especial Reference to Copper and Calcium.' *Quart. J. Med.*, 1935, N.S. **4**, 121.

Bacteriology and Virus Diseases

The Committee on Bacteriology (p. 167) advise the Council in these subjects and in bacterial chemistry (p. 141). Investigations at the National Institute have already been noticed.

Dr. M. H. Gordon, of the Council's staff, has continued his studies of lymphadenoma at St. Bartholomew's Hospital, London. Results obtained in a further series of cases have confirmed the value of the diagnostic test mentioned in previous reports. The encephalitogenic agent responsible for the test has not been found in the lymph glands in diseases other than lymphadenoma, although MacKenzie and van Rooyen have confirmed Friedemann's finding that a substance with similar, or identical, properties occurs in normal human bone-marrow and occasionally in the spleen and leucocytes. Special attention has been given during the past year to the nature and significance of minute 'elementary bodies' which have been found to occur in great quantity in the glands of patients in the acute stages of lymphadenoma. Attempts are being made to develop a serological test for lymphadenoma based on agglutination or precipitation of suspensions of these bodies. A sensitized 'vaccine' made from them has also been tried in treatment. Some of the patients who have received the vaccine have now been under observation for two years, and the results so far have been encouraging.

In Professor T. J. Mackie's department at Edinburgh, Dr. C. E. van Rooyen has had an expenses grant. Further work has been done on lymphadenoma, with special reference to the significance of Dr. Gordon's diagnostic test. The agent responsible for the test

has been compared with a number of proteolytic enzymes, but it appeared to differ from them all. In spite of doubt as to the nature of the active agent, the practical value of this method for diagnosing lymphadenoma has been established during the year in a large number of cases. With Lt. Colonel E. D. W. Greig and Mr. E. B. Hendry, Dr. van Rooyen has extended his inquiry into the chemical nature of the melano-precipitation reaction for diagnosing malaria. It has been shown that the reaction is not specific, but depends on the increase in serum euglobulin which occurs in that infection.

In the same department Dr. H. J. Gibson had an expenses grant for work on streptococcal infections and the relationship of streptococci to rheumatic fever. Attempts to produce experimental infection by injection of rheumatic exudates with and without streptococci have given inconclusive results. Dr. Gibson has now joined the staff of the Royal Mineral Water Hospital, Bath, and is taking part in a scheme of clinical and bacteriological research on rheumatism there.

At Leeds, Dr. L. Hoyle and Dr. K. E. Cooper have again had grants for assistance to Professor J. W. McLeod. Dr. Hoyle has continued his work on the bacteriology of the common cold and other catarrhal conditions of the upper air-passages. He has also compared the changes in the lungs produced by intranasal inoculation with various pathogenic bacteria and with viruses isolated from human and swine influenza: it was found that a typical aspiration pneumonia developed in each case. Virus material for these experiments was supplied by Dr. C. H. Andrewes (p. 38) of the National Institute. With Dr. J. S. Anderson and Dr. F. C. Happold (p. 144), Professor McLeod and Dr. Cooper have made further tests with a tellurite heated-blood-agar medium for the bacteriological diagnosis of diphtheria, and have investigated the type-stability of the *gravis* form of diphtheria bacillus in the human body. They conclude, from trials of the newer and older methods for the cultural diagnosis of diphtheria, that both methods should when possible be used: the newer method is the more reliable, especially for infections with *B. diphtheriae gravis*, but the older in some cases gives the diagnosis more quickly. Other work by Professor McLeod and his colleagues is mentioned at p. 144.

An expenses grant has been made to Dr. R. Cruickshank at Glasgow for work on the type incidence of lobar pneumonia in that city, and on the biological differences between the different types of pneumococci. Dr. Cruickshank is also co-operating in an investigation at the Belvidere Fever Hospital, on the bacteriological diagnosis of whooping cough.

At the Brown Institute, London, Professor F. W. Twort has continued to receive grants for work on the properties and cultiva-

tion of bacteria, filter-passing viruses, and bacteriolytic agents. Many different media have been tried for the cultivation of viruses, and special attention has been given to the possible influence of solar rays and other environmental factors on the growth of different organisms. The results have emphasized certain guiding principles for the successful isolation of forms which grow only with difficulty; and these principles apply also to bacteria which are more easily grown, although the effect may be masked in vigorous cultures which are more tolerant of adverse conditions. From the experiments as a whole, it appears that the comparative extent of bacterial growth in streak cultivation on any two types of media is in no way a true indication of their relative value for isolating the bacterial type in primary culture. This may be shown by making comparative tests on each medium, using in one case a streak inoculation and in the other an inoculation from a diluted fluid culture giving only a few delicate colonies on an ordinary sloped tube of medium. The medium which gives the most vigorous streak growth may frequently be found to give less than a quarter of the number of colonies which occurs on the medium giving a poorer streak growth. Experiments of this kind usually indicate that the medium giving a good streak growth but a small number of colonies contains two opposing substances, one of which is beneficial and allows the vigorous individuals of the implanted bacteria to give a good streak growth, and another detrimental substance which prevents many of the more weakly implanted individuals from growing and forming colonies.

H. J. Gibson and R. O. Muir—
'A Study of the Streptococci from Fifty Cases of Bovine Mastitis.' *J. Hyg.*, Camb., 1935, **35**, 238.

E. D. W. Greig, E. B. Hendry, and C. E. van Rooyen—
'The Chemistry of Malarial Serum, with Reference to the Factors concerned in the Melano-Precipitation Test.' *J. trop. Med. Hyg.*, 1934, **37**, 289.

L. Hoyle—
'The Production of Pneumonia in Mice by Bacteria and Filterable Viruses.' *J. Path. Bact.*, 1935, **41**, 163.

I. MacKenzie and C. E. van Rooyen—
'Relationship of Jochmann's and other Enzymes to the Encephalitogenic Agent in Lymphadenomatous Lymphatic Glands.' *Brit. med. J.*, 2nd March 1935.

J. W. McLeod—
'Recent Observations on the Bacteriology of Diphtheria.' *Leeds med. Soc. Mag.*, 1935, **5**, 26.

Bacterial Chemistry and Immunity Reactions

Work on these subjects at the National Institute has been noticed at p. 46.

As mentioned in the last Annual Report, a special department for the study of bacterial chemistry has been established by the

Council at the Middlesex Hospital. Dr. Paul Fildes, who directs the department, is in the Council's whole-time service, and he has the co-operation of Mr. B. C. J. G. Knight, with a Halley Stewart Research Fellowship, and of Dr. G. M. Richardson and Dr. G. P. Gladstone, with fellowships provided by the Trustees of the late Viscount Leverhulme. Laboratory accommodation and facilities for the work are provided by the Hospital in the Bland-Sutton Institute of Pathology and the adjoining Courtauld Institute of Biochemistry. The work of the department during its first year has dealt with the nutrition of bacteria. Attempts begun by Dr. Fildes and Mr. Knight to define in chemical terms the basic food requirements of strictly anaerobic organisms have been continued by Dr. Fildes and Dr. Richardson, and have been successful in the cases of *Clostridium sporogenes*, *Cl. botulinus*, and *Cl. welchii*. It has been shown that among other nutritional essentials are certain amino-acids, and further that the amino-acid requirements of these bacteria are closely similar to those of animals. The *Cl. sporogenes* growth factor, previously described by Mr. Knight and Dr. Fildes, seems to be necessary for the growth of strictly anaerobic bacteria, but not of aerobes. The chemistry of this substance has been investigated by Dr. A. M. Pappenheimer (p. 47) working at the National Institute in association with the department at the Middlesex Hospital. The growth of *Staphylococcus aureus* has also been studied in the department, and Mr. Knight has isolated in a relatively pure state another growth factor which is essential for staphylococci and probably other bacteria. Dr. Gladstone has examined the effects of carbon dioxide upon bacterial cultures, and has found that the presence of this gas in the nutritive fluids is needed for the growth of all the bacteria tested. This observation has had an important bearing upon the success of other researches in the department.

At the London School of Hygiene and Tropical Medicine, Professor M. E. Delafield has had grants for expenses and for assistance by Miss H. A. Smith. He had previously shown that the intravenous injection into animals of a chemical fraction derived from *Bact. aertrycke* caused characteristic changes in the blood-sugar curve and symptoms of toxaemia. The fraction used was prepared by Professor H. Raistrick: it contained polysaccharides but no unaltered protein. It has since been found possible to produce a state of immunity by repeated intravenous doses of this fraction, so that the metabolic changes and toxic symptoms cease to occur. Parallel tests have been made with a fraction from *Bact. enteritidis*, with the same type of result: moreover, injections of the fraction from one of these organisms give cross-immunity to that from the other. Tests are being made of the antitoxic power of the immune sera thus produced. Professor Raistrick has now been able to

separate the original fractions into polysaccharide and non-polysaccharide components, and the immunological properties of these purer fractions are being examined in a similar way. With a grant for assistance by Dr. V. Glass, Dr. W. R. Wooldridge has studied here the variations in the activity of bacterial enzymes in relation to such factors as age of culture, composition of medium, and the ratio of living to total organisms in a standard suspension. Working mainly with *Bact. coli*, it has been shown that most of the enzymes examined increase in activity during the period of maximum growth, and that their activity runs approximately parallel with the growth curve of the organism. The relative activity of the various enzymes does not, however, remain the same for all ages of the culture, and may be changed by growing the organism upon different media: moreover, there seems to be no clear correlation between the enzyme activity and the proportion of living to dead organisms in the standard suspension. Attempts are being made to determine the effects of immune sera upon the activity of bacterial enzymes.

In the whole-time service of the Council, at Cambridge, Miss M. Stephenson has continued her work on enzyme production by yeast-cells grown in different media. The formation of galactozymase in *Saccharomyces* has been specially investigated. The presence of galactose in the culture medium is essential for the production of this enzyme: substitution of glucose for galactose prevents its development, and the enzyme, once formed, disappears if the yeast-cells are washed and placed in glucose solution. In media containing galactose, however, the enzyme can be produced without cell growth or multiplication, and its activity is in part retained when the cells are killed by ultra-violet light, though it appears not to be formed in sterile cultures or in the presence of antiseptics. Miss Stephenson has also extended her studies of the nutritional requirements of *Streptococcus faecalis*, and has examined some of the biochemical characteristics of *Bact. alcaligenes*.

Professor J. R. Marrack, at the London Hospital, has had grants for expenses and for assistance by Miss B. R. Carpenter in work on chemical problems of immunity. Further studies have been made of the precipitation reactions between Type II antipneumococcus serum and various gums, to decide what details of chemical constitution are responsible for the reactions. Both gums and serum can readily be obtained in sufficient quantity, and their behaviour gives an opportunity to examine the general features of precipitin reactions. Type I antipneumococcus serum does not react with gums in this way. It appears that the gums which give a precipitate with the Type II serum contain a nucleus consisting of a uronic acid linked to a sugar, and it has been shown that the precipitation between gums and serum is specifically inhibited by

glucuronic acid and glucuronides. Dr. B. Woolf, a Mosely Research Student here, has prepared a synthetic compound from euxanthic acid which precipitates strongly with the Type II serum, and the chemical factors determining its activity have been analysed.

At the Lister Institute, London, Miss A. H. Rosenheim has had a personal grant for work under the direction of Professor J. C. G. Ledingham. As part of a study of the chemical nature of antibodies, and of the groups involved in their activity, she has examined the actions of various enzymes on the agglutinins in an antityphoid serum. It has been found that the destruction by proteolytic enzymes of both the flagellar and the somatic agglutinins is a far more rapid process than the hydrolysis of protein. From the results of other experiments, it appears that the resistance of antibodies to attack by proteolytic enzymes may change during the course of immunization.

Professor J. W. McLeod of Leeds, whose other work was noticed at p. 140, has had an expenses grant for studies of the oxidation-reduction potentials in bacterial cultures. Under his supervision, Dr. K. I. Johnstone is examining the possibility of a relationship between these potentials and the production of hydrogen peroxide by bacteria. Dr. J. Gordon and Dr. F. C. Happold received part-time and expenses grants in this department. With Mr. F. C. Thompson, Dr. Gordon has examined the opsonins of normal serum, comparing their properties with those of complement. Dr. Happold has completed his work on selective media for the growth of flagellate organisms, and has investigated with Dr. Hoyle (p. 140) the production of indole from tryptophan by endobacterial enzymes.

Part-time and expenses grants have again been made to Dr. A. Wormall at Leeds, and the assistance of Mr. W. E. Gaunt has been provided. Further work has been done on the immunological behaviour of proteins which have been modified by treatment with phenyl *iso*cyanates. Attempts have been made to link a non-antigenic protein to one which is fully antigenic, in the hope that the injection of the compound protein might produce antibodies which would react with the non-antigenic protein as well as with the compound antigen. Experiments with gelatin linked to the antigenic proteins of horse-serum gave an antiserum which reacted readily with the compound antigen but not with the gelatin itself. Observations have been continued on the inactivation of insulin by phenyl *iso*cyanate: it appears that this is due to an effect of the *iso*cyanate on the free amino-groups, and that these groups must therefore play an important part in the activity of the hormone. It has been shown that carbo-benzoxy-chloride inactivates insulin in a similar way.

P. Fildes—
'Some Medical and Other Aspects of Bacterial Chemistry.' *Proc. R. Soc. Med.*, 1934, **28**, 79.
'The Tryptophan and "Sporogenes Vitamin". Requirements of *B. botulinus*.' *Brit. J. exp. Path.*, 1935, **16**, 309.

P. Fildes and G. M. Richardson—
'The Amino-acids necessary for the Growth of *Cl. sporogenes*.' *Brit. J. exp. Path.*, 1935, **16**, 326.

W. E. Gaunt, G. Higgins, and A. Wormall—
'Action of Benzylcarbonyl Chloride on Insulin and Other Proteins.' *Nature*, 14th Sept. 1935.

G. P. Gladstone, P. Fildes, and G. M. Richardson—
'Carbon Dioxide as an Essential Factor in the Growth of Bacteria.' *Brit. J. exp. Path.*, 1935, **16**, 335.

J. Gordon—
'Some Aspects of the Mechanism of Natural Immunity.' *Leeds med. Soc. Mag.*, 1935, **5**, 49.

J. Gordon and J. M. Robson—
'Some Immunity Experiments on Hypophysectomized Animals.' *J. Hyg.*, Camb., 1935, **35**, 372.

J. Gordon and F. C. Thompson—
'The Relationship between the Complement and Opsonin of Normal Serum.' *Brit. J. exp. Path.*, 1935, **16**, 101.

F. C. Happold and L. Hoyle—
'The *Coli*-Tryptophan-Indole Reaction. I. Enzyme Preparations and their Action on Tryptophan and some Indole Derivatives.' *Biochem. J.*, 1935, **29**, 1918.

F. C. Happold and D. Stephenson—
'The Toxicity of Bactericidal Substances for Flagellate Parasites, with Special Reference to their Application in the Isolation of *Leptomonas* Forms.' *Parasitology*, 1935, **27**, 383.

S. J. Hopkins and A. Wormall—
'The Action of Phenyl *Iso*cyanate on Insulin.' *Biochem. J.*, 1934, **28**, 2125.

B. C. J. G. Knight—
'An Essential Growth Factor for *Staphylococcus aureus*.' *Brit. J. exp. Path.*, 1935, **16**, 315.

A. H. Rosenheim—
'Adsorption and Elution of Agglutinins.' *J. Path. Bact.*, 1935, **40**, 75.

Helminthology

At the Institute of Agricultural Parasitology, St. Albans, Professor R. T. Leiper has again had grants for expenses and assistance in work on the bearing of nutrition on immunity to worm infections. Under his direction, Miss P. A. Clapham, a Lawrence Research Student of the Royal Society, is making observations on the effects of diet on the infection of chicks with the trematode, *Trichostrongylus tenuis*. These have indicated that magnesium and possibly calcium may influence resistance to this parasite: there is no evidence, however, that a diet rich in calcium has any effect on the course of the established infection. In the case of infection with *Heterakis gallinae*, it appears that the degree of infestation depends only secondarily on nutritional factors, the age and breed

of the host being more important. Further inquiries have been made during the year into the pathology and transmission of gapeworm disease. Oil of garlic has been found useful for its treatment. The immunity of young fowls to this infection has been shown to depend, at least in part, upon an adequate supply of vitamins in the diet.

Medical Entomology

As already mentioned in the Introduction (p. 30), the Council have been glad to accede to a request from the Ministry of Health that a special Committee should be appointed to promote research into the health problem caused by the infestation of houses by the bed-bug, and to investigate methods for the eradication of this parasite. The composition of the Committee is shown at p. 167.

On the recommendation of the Committee, grants for work on this subject have been made to Professor P. A. Buxton, at the London School of Hygiene, and to Professor J. W. Munro, at the Imperial College of Science, London. Professor Buxton has been provided with the assistance of Mr. C. G. Johnson in studies of the general conditions of viability of the bed-bug, and Professor Munro has received a grant for expenses and assistance in work on chemical methods for its destruction.

Other work on medical entomology, with special reference to the insect carriers of tropical diseases, is noticed below.

Chemotherapy and Tropical Diseases

The Committee named at p. 168 have continued to direct work on new chemical compounds which are likely to have curative value in infective diseases, and especially in trypanosomiasis, syphilis, and malaria. The members of the Committee representative of chemistry are appointed by the Department of Scientific and Industrial Research. The Department has again supported the purely chemical side of the research, the biological side being supported by the Council.

New compounds for biological tests have been received from: Professor G. Barger, Dr. W. O. Kermack, and Dr. W. McCartney of Edinburgh; Professor G. R. Clemo of Newcastle; Professor J. Kenner of Manchester; Professor T. S. Patterson and Dr. S. H. Tucker of Glasgow; and Professor R. Robinson of Oxford. Others have been provided by Professor G. T. Morgan and his colleagues at the Chemical Laboratory, Teddington, and by Dr. H. King (p. 51) of the National Institute.

One of Professor Morgan's arsenical compounds (S. 107) has been tested in human trypanosomiasis by Dr. Lester, Director of the Nigerian Sleeping Sickness Investigation. Preliminary reports are encouraging. Arrangements are being made for the preparation

of two of Dr. King's arsenical compounds in sufficient quantity for clinical trial. An account of the laboratory tests of Dr. King's compounds has been published by Miss W. I. Strangeways.

Compounds submitted from several different centres have been tested at Glasgow for antiseptic, antisyphilitic, and trypanocidal properties by Professor C. H. Browning and Miss R. Gulbransen, the latter receiving a personal grant. On behalf of the Therapeutic Trials Committee (p. 87), a study has been made of the action of 'prontosil' in experimental streptococcal infections. Research has also been continued here on the tumour-producing properties of a benzoyl-amino-styryl compound prepared in the late Professor J. B. Cohen's department at Leeds.

Professor Warrington Yorke, at the Liverpool School of Tropical Medicine, has had grants for assistance by Dr. F. Murgatroyd and Dr. G. R. Walker in tests of new chemotherapeutic agents and in work on the mode of action of arsenical compounds. Professor Morgan's compound, S. 107, which has been shown to be very effective in the treatment of experimental trypanosomiasis, has been tried clinically in a number of cases of syphilis, with promising results. This substance is now being prepared on a commercial scale which will permit more extensive tests of its therapeutic value in syphilis and trypanosomiasis.

At the Molteno Institute, Cambridge, grants have again been made to Dr. Parr Tate and Miss M. Vincent for work under the direction of Professor D. Keilin on the antimalarial action of synthetic drugs and on the biology of the mosquitoes which carry malaria. During the year, twenty-two new compounds were tested for their curative action in bird malaria. Further work on one of Professor Robinson's compounds has confirmed its high therapeutic index for experimental malaria: it appears to be more efficient even than plasmoquine for treating the induced infection in birds. Research has been continued here on the bionomics of the different races of the mosquito, *Culex pipiens*. An investigation has also been made of the anatomy and physiology of the peri-spiracular glands of mosquito larvae, with special reference to their bearing on the mode of action of paraffin and other oils which are used to destroy the larvae in pools.

At the London School of Hygiene and Tropical Medicine, Sir Rickard Christophers continues to direct a special unit for research in malaria. The establishment of the unit was made possible by a generous donation from the Trustees of the late Viscount Leverhulme, and the Director gives whole-time service as a Leverhulme Research Fellow. The Council provide the assistance of Miss E. Williams and the expenses of the work, and the School provides the laboratory facilities. The work of the unit is closely associated with that done in the Ministry of Health Malaria Laboratory at

Horton under the direction of Colonel S. P. James: Mr. P. Shute, of the staff of the Horton laboratory, receives an honorarium in respect of help given in maintaining contact between the two centres. The work of the unit in the past year has again dealt mainly with the biological principles underlying the curative action of quinine and other antimalarial drugs. All these substances are characterized chemically by the possession of a basic side-chain, and this is apparently an essential factor in their power to combine with cell protein, and probably in their therapeutic activity. The absorption of quinine by the malarial parasite substance and by red blood-cells has been found generally to resemble other protein-base combinations, and a quantitative study has been made of the extent of absorption of various basic and acidic radicles by protein, to determine the precise chemical mechanisms involved. An account of this work has been prepared for publication. It has recently been shown that the strain of monkey malaria maintained in the unit for experimental purposes is readily transmissible to man, giving rise to a condition resembling human malaria. Clinically this strain has proved useful for the malaria treatment of general paralysis of the insane and other diseases, where the patient had become immunized against the malarial parasites more frequently employed. Cases of transmitted monkey malaria have been studied at Horton, at Edinburgh, and elsewhere. Workers in the unit have continued to make observations upon the bionomics and maintenance of the strains of mosquito responsible for the natural transmission of the different forms of malaria.

Dr. A. Clark, who formerly received a grant in London, has continued in Nigeria his research into the poisonous effects of certain native foods. His work there has been supported jointly by the Council, through their special Tropical Medical Research Fund, by the Colonial Office, and by the Nigerian Government. He has shown that albuminuria is common among natives who eat particular forms of 'coco-yam', and has found evidence of a relationship between the eating of various tubers and other toxic symptoms which occur in native populations.

C. H. Browning and R. Gulbransen—
'Combined Treatment of Experimental Trypanosome Infections by Chemotherapeutic Agents.' *J. Path. Bact.*, 1935, **40**, 425.
'Late Relapses and Apparently Spontaneous Cure of Untreated Relapses in Experimental *T. brucei* Infections Treated by Chemotherapeutic Agents.' *Ibid.*, 1935, **41**, 253.
'Variation in Chemotherapeutic Susceptibility associated with Change in Virulence of a Strain of *Trypanosoma brucei*.' *J. Hyg.*, Camb., 1935, **35**, 180.

C. H. Browning, R. Gulbransen, and W. McCartney—
'The Trypanocidal Action of Certain Styryl Selenazole Compounds.' *J. Pharmacol.*, 1935, **54**, 367.

C. H. Browning, R. Gulbransen, and S. H. Tucker—
'The Antiseptic Action of Carbazole-3-Diazonium Chloride and Certain

Other Diazonium Compounds. With a Note on the Preparation of Carbazole-3-Diazonium Chloride.' *J. Pharmacol.*, 1935, **54**, 353.

D. Keilin, P. Tate, and M. Vincent—
'The Perispiracular Glands of Mosquito Larvae.' *Parasitology*, 1935, **27**, 257.

E. M. Lourie, F. Murgatroyd, and W. Yorke—
'Studies in Chemotherapy. XII. The Diffusibility of the Aromatic Arsenicals into Erythrocytes and the Action of the Latter on the Pentavalent Arsenicals.' *Ann. trop. Med. Parasit.*, 1935, **29**, 265.

P. Tate—
'The Larva of *Phaonia mirabilis* Ringdahl, predatory on mosquito larvae (*Diptera, Anthomyidae*).' *Parasitology*, 1935, **27**, 556.

Warrington Yorke and F. Murgatroyd—
'Biological Problems in Chemotherapy.' *Trans. R. Soc. trop. Med. Hyg.*, 1935, **28**, 435.

Epidemiology and Vital Statistics

At the London School of Hygiene and Tropical Medicine, Professor M. Greenwood and Professor W. W. C. Topley have continued their studies in experimental epidemiology. Dr. A. Bradford Hill and Mrs. Joyce Wilson have co-operated in the work: the latter has had a grant from the Council, who also provide the expenses of the research.

During the past year a report has been prepared on the results obtained in these investigations since they began some fifteen years ago. The report, which is being issued by the Council, includes records of several studies not previously published: among these are a description of the epidemic behaviour of the virus disease known as infectious ectromelia, an account of the herd-effect of preventive immunization against this infection, and an investigation of the virulence and infectivity of different strains of a single bacterial species. It has been shown that natural immunization against ectromelia is more effective than natural immunization to a bacterial infection such as mouse-typhoid, and that the same is true of artificial immunization against these diseases. It appears, however, that mice immunized with a partially attenuated ectromelia virus and then infected with a potent virus, although they are themselves resistant, are infective for weeks or months to normal non-immunized mice. If this is a frequent result of antiviral immunization, it is clearly a factor that will have to be taken into account in planning protective campaigns against herd-infections. The experiments on bacterial virulence and infectivity indicate that these two characters vary independently, and seem to give a basis for defining more exactly the nature of the 'epidemic' strains referred to by many field epidemiologists.

The observations recorded in this report provide a comprehensive description of the behaviour of an infected herd in an environment that provides optimal conditions for contact infection.

Experiments have now been begun in which this factor is subject to variation. As an initial study, the fate of mice withdrawn from an infected herd at varying cage-ages, and subsequently kept in isolation, is being compared with that of mice of the same cage-ages that are allowed to pass the whole of their subsequent life in herd. This will be followed by an experiment in which the members of an infected herd are allowed only occasional contact. When the behaviour of herds under these conditions has been determined, it is hoped to study the effect of various methods of immunization when the risk of contact infection is adjusted at different levels, thus providing an environment resembling more closely that to which a human population is commonly exposed.

W. W. C. Topley, J. Wilson, and J. T. Duncan—
'The Mode of Formation of Aggregates in Bacterial Agglutination.' *Brit. J. exp. Path.*, 1935, **16**, 116.

Statistics

The Council's statistical work is directed by the Committee named at p. 168, who also serve the Ministry of Health in the field of medical statistics. A staff provided by the Council works for the Committee in Professor M. Greenwood's department at the London School of Hygiene and Tropical Medicine.

As before, much help has been given by the Statistical Committee to the Industrial Health Research Board and other research committees in the treatment of statistical problems arising in their work, and many individual investigators have been assisted. Members of the staff have also done much independent research.

For the Ministry of Health, Dr. A. Bradford Hill has analysed the trend of mortality in childhood and adolescence in England and Wales: his data were included in the Chief Medical Officer's Annual Report for 1933. He has also examined the recent course of the death-rate from pernicious anaemia in this country.

Dr. J. O. Irwin, in addition to publishing a number of papers on the application of modern mathematical methods to problems of psychology and of general biology, has analysed a large series of experimental results bearing on the tumour-producing properties of various substances. Mr. W. T. Russell has continued to analyse data provided by Dr. W. Gunn, of the Public Health staff of the London County Council, on the value of adult human serum for the prevention of measles in children. He has also made a statistical study of sex-ratio at birth.

Mr. W. J. Martin has co-operated in the work on experimental epidemiology and school epidemics, and has prepared for press an analysis of the mortality-rates of young adults, which throws an interesting light upon some statistical peculiarities of the recent trend. His work relates particularly to the observation made in

some continental countries of a fall in the male mortality curve in the early twenties, which some writers have attributed to the physical benefits of compulsory military service. This fall in mortality limited to a few years in early adult life has lately appeared also in the English experience, and Mr. Martin's analysis indicates that the factor chiefly responsible is the comparatively smaller incidence of fatal road-accidents at these ages. Mr. E. Lewis-Faning has examined the regional changes in mortality-rates, and has made progress with an analysis of the death-rates of diabetics (p. 81).

A. B. Hill—
'The Trend of Mortality in Early Childhood and in Adolescence.' *Ann. Rep. Minist. Hlth. for the year* 1933. Lond. (H.M. Stationery Office), 1934.
'Mortality from Pernicious Anaemia in England and Wales.' *Lancet*, 5th Jan. 1935.

J. O. Irwin—
'Independence of the Constituent Items in the Analysis of Variance.' *J. R. statist. Soc.*, Suppl., 1934, **1**, 236.
'Recent Advances in Mathematical Statistics (1935).' *J. R. statist. Soc.*, 1935, **98**, 83.
'Some Aspects of the Development of Modern Statistical Method.' *Math. Gaz.*, 1935, **19**, 18.
'On the Indeterminacy in the Estimate of "g".' *Brit. J. Psychol.*, 1935, **25**, 393.

W. J. Martin—
'The Decrease in Mortality during early Adult Male Life in England and Wales.' *J. Hyg.*, Camb., 1935, **35**, 375.

School Epidemics

The Committee named at p. 168 have continued to investigate the incidence and spread of epidemics in residential schools. On the retirement of Sir George Newman from the Ministry of Health, Dr. A. S. MacNalty accepted the chairmanship of the Committee in his place.

The fifth year of the inquiry was completed at Christmas 1934, and the data collected during the whole period are now being analysed by Professor Greenwood and his staff. Records are still being maintained for the Committee in thirteen boys' schools and in five girls' schools.

Professor Topley has again been given facilities to do naso-pharyngeal swabbing in one large public school, and sample groups of a hundred boys have been examined twice a term in this way. The object of this study is to obtain data on the carrier-rates of different pathogenic bacteria in a boy population of school age. Bacteriological observations on cases of otitis media, tonsillitis, scarlet fever, and pneumonia have been continued on behalf of the Committee by Dr. F. Griffith, of the Ministry of Health Laboratories.

F. Griffith—
'The Serological Classification of *Streptococcus pyogenes*.' *J. Hyg.*, Camb., 1934, **34**, 542.

Human Genetics

The special Committee (p. 168) on this subject continue to have the co-operation of many hospitals throughout the country in a large-scale statistical inquiry into the incidence of consanguineous parentage among patients suffering from different conditions. The objects of this investigation are to determine the proportion of hospital patients who are the offspring of marriages between blood relations, and to ascertain what morbid conditions occur more commonly among such individuals than among other people. For these purposes it is important that during the period of the inquiry all cases—whether showing relationship or not—should be reported by the participating hospitals, without discrimination as to diagnosis, and the Council are much indebted to the members of hospital staffs who are making this work possible. Some tens of thousands of records have already been received, and a preliminary survey of them indicates that results of considerable interest are likely to emerge from the still larger numbers which it is hoped to obtain.

The collection of records is also being continued in an investigation into the incidence of certain rare congenital defects among school-children, for which facilities are being provided by the London and Lancashire County Councils.

In the Galton Laboratory at University College, London, Dr. Julia Bell gives whole-time service to the Council in studies of pedigrees of hereditary abnormalities and diseases. During the year she has completed a memoir on the peroneal type of progressive muscular atrophy, including an analysis of about six hundred cases of the disease occurring in ninety-five families. She has secured two new and extensive family histories of this condition, one in Somersetshire extending to four generations, and one in Aberdeenshire to seven generations: the information was obtained through the co-operation of Dr. Armstead and Dr. J. Findlay, respectively.

Dr. Bell has begun similar inquiries with regard to hereditary ataxia. She has also continued the search for cases of haemophilia for work by Professor J. B. S. Haldane on problems of genetic linkage, and has done much work in the preliminary examination of the records of the inquiry into consanguinity which has already been mentioned.

In the Department of Social Biology at the London School of Economics, Dr. I. Zieve has received a personal grant for work with Professor L. T. Hogben on the problem of linkage between genes, such as those concerned in the inheritance of the phenomenon known as taste blindness, and of the isoagglutinating characteristics of the blood.

During the year the Council have gladly agreed to administer a grant which has been made by the Rockefeller Foundation in aid of a scheme of research in serological genetics, with ultimate reference to mental disorders, under the direction of Professor R. A. Fisher at the Galton Laboratory. The grant is for a period of five years, and makes provision during that time for the salary of a research fellow, with assistance and expenses. Dr. G. L. Taylor has been appointed under this arrangement, and the work has begun.

Reference has already been made under an earlier head to work which is being done by Dr. L. S. Penrose at Colchester, mainly on the inheritance of different types of mental defect.

M. Gunther and L. S. Penrose—
'The Genetics of Epiloia.' *J. Genet.*, 1935, **31**, 413.

L. S. Penrose—
'The Detection of Autosomal Linkage in Data which Consist of Pairs of Brothers and Sisters of Unspecified Parentage.' *Ann. Eugen.*, Camb., 1935, **6**, 133.

L. S. Penrose and J. B. S. Haldane—
'Mutation Rates in Man.' *Nature*, Lond., 1st June 1935.

VI. INDUSTRIAL HEALTH

Industrial Pulmonary Disease

The Committee named at p. 169 direct inquiries into the effects on health of the atmospheric dusts associated with various industries. More general reference to the work has already been made in the Introduction.

By arrangement with the War Office, Mr. H. L. Green, of the Chemical Defence Research Experimental Station, Porton, has continued to investigate the physical characters of the dust clouds met with in industry. He is assisted in this study by Mr. H. H. Watson, a proportion of his salary and that of Mr. Watson being temporarily provided by the Council, who also defray the special expenses of the work. A report by Mr. Green and Mr. Watson on physical methods for the estimation of the dust hazard in industry has been issued by the Council. This deals especially with the use of a modified thermal precipitator for collecting atmospheric dusts and measuring the concentration and size-frequency of the particles: the practical value of the instrument has been tested under actual industrial conditions and with particular reference to the occupation of stone-mason. Progress has since been made in devising experimental methods to show the relationship between size of particles and the retention of dust inhaled into the lungs, and for the detection and enumeration of particles below 0·2 micron diameter in dust clouds. Gravimetric methods for estimating dust clouds are being standardized.

In complement to the physical studies at Porton, work on the chemistry of dusts associated with silicosis is being done for the Committee by Professor H. V. A. Briscoe and his assistants at the Imperial College of Science, London. The Council are providing the expenses of the work and have made personal grants to Miss H. Bennett and Miss P. M. Sanderson, who are doing the analyses under Professor Briscoe's direction.

In Professor H. B. Maitland's department at Manchester, Dr. Carl Prausnitz has completed an inquiry into the aetiology of respiratory disease in cotton operatives. His work was supported jointly by the Rockefeller Foundation and the Council. It was shown that a protein fraction of cotton dust had a severely irritant effect when injected, and that cotton workers with respiratory disease were particularly sensitive to this fraction. The reactions both in normal and diseased subjects were entirely different from those caused by histamine. Dr. Prausnitz has also made further clinical observations on respiratory disease in cotton workers and its effect on the efficiency of the lungs. A report on his investiga-

tion is being published in the Council's series. Research on the chemistry of the protein and fatty components of cotton dust is being continued under Professor Maitland's direction by Mr. E. Howarth, who has a Dr. Angus Smith Scholarship at Manchester.

At the British Post-graduate Medical School, London, Professor E. H. Kettle has had an expenses grant for work on the pathology of silicosis and allied diseases. Recent work has confirmed his previous conclusions as to the importance of the infective factor in producing silicosis. He is at present studying the reactions produced by the various compounds of silicon, with the object of defining the toxicity of the different forms of combined silica met with in industry.

The relationship of bronchitis to the development of silicosis is being examined experimentally by Mr. F. Haynes at St. Bartholomew's Hospital, London. His expenses are provided from a grant made to Dr. J. S. Haldane, of Oxford, and the research is under Dr. Haldane's general direction.

At Leeds, Professor M. J. Stewart has had grants for expenses and for assistance by Dr. R. C. Page in work on silicosis and asbestosis. With Dr. F. S. Fowweather, a special study is being made of the silicosis of sandblasters: the materials used in sandblasting are being individually examined in the hope of determining the nature of the irritant substance and the bearing of Jones's 'sericite' theory upon this form of pulmonary disease. Dr. Page has completed his observations of the sputum of asbestos workers and the results have been published. At Wakefield, Dr. P. L. Sutherland has continued an investigation of the pathology and chemistry of the lungs from cases of silicosis in coal-miners and sandstone workers. Similar work on the lungs of haematite workers has been done by Dr. J. S. Faulds at Carlisle, and both inquiries have been assisted with some expenses.

Under the direction of Professor S. L. Cummins at Cardiff, Dr. Enid Williams and Dr. P. K. Sen have made further clinical and pathological studies of lung diseases in coal-miners. Their investigations have been noticed at p. 115.

S. L. Cummins—
'Pneumoconiosis.' *Brit. med. J.*, 17th Aug. 1935.

F. S. Fowweather—
'The Silica Content of Normal and Silicotic Lungs and its Bearing on the Problem of Silicosis.' *Refractories J.*, May 1934, p. 173.

H. L. Green—
'Recent Developments in Methods of Sampling Dusts.' *Bull. Instn. Min. Metall.*, Lond., 1934, No. 362.

H. L. Green and H. H. Watson—
'Physical Methods for the Estimation of the Dust Hazard in Industry.' *Spec. Rep. Ser. Med. Res. Coun.*, Lond., No. 199, 1935.

E. H. Kettle—
'The Action of Harmful Dusts.' *Bull. Instn. Min. Metall.*, Lond., 1934, No. 362.

E. L. Middleton—
'Some Methods of Collecting Atmospheric Dusts with a View to Enumeration and Measurement of the Particles.' *Rapports VII^me Congrès International des Accidents et des Maladies du Travail*, Bruxelles, 1935.

R. C. Page—
'A Study of the Sputum in Pulmonary Asbestosis.' *Amer. J. med. Sci.*, 1935, **189**, 44.

The Industrial Health Research Board

A detailed account of the work of the Board is given in their fifteenth Annual Report, published separately last July. To fill vacancies caused by the retirement of Sir Arthur Hall and Dr. L. P. Lockhart, the Council have appointed Professor J. A. Nixon and Dr. R. E. Lane to be members of the Board.

Fifteenth Annual Report of the Industrial Health Research Board. London (H.M. Stationery Office), 1935.

The Physiology of Muscular Work

There was published during the year a report on the inquiry, directed by Professor E. P. Cathcart at Glasgow, into the physique of men in different industrial occupations. The results were of interest in showing geographically and occupationally where the tallest, strongest, and heaviest men are to be found. It was not, however, possible to determine to what extent the heavy manual industries attract men of superior physique, and the report showed that no certain index of physical fitness has yet been attained. Despite the number of remediable defects disclosed by the data, it did not prove possible to make any reliable deduction concerning improvement or deterioration in the national physique.

At the London School of Hygiene Dr. T. Bedford and Mr. C. G. Warner, of the Board's staff, have examined the influence of muscular effort on skin temperature, and Dr. G. P. Crowden has made further observations on the physiological effects of using vibratory tools.

E. P. Cathcart, D. E. R. Hughes, and J. G. Chalmers—
'The Physique of Man in Industry.' *Rep. Indust. Hlth. Res. Bd.*, 1935, No. 71.

Industrial Psychology

At the London School of Hygiene, Professor Millais Culpin, with a grant from the Council, and Dr. May Smith, of the Board's staff, have extended their studies of psychological factors in relation to industrial efficiency and illness. Dr. Smith, for whom the Council provide assistance by Miss M. Leiper, has prepared a report on sickness absenteeism in clerical occupations and light industries. It has been shown that the common cold and 'influenza' account

for nearly 40 per cent. of the total sickness absenteeism in every industrial group: if to these be added operations, gastric disorders, rheumatic affections, nervous break-downs, and accidents, in that order, over 70 per cent. of sickness absenteeism is accounted for. The reasons for occupational variations, so far as they can be ascertained, are discussed in the report, which is being published in the Board's series.

With Professor M. Greenwood (p. 150), Dr. Smith has continued an analytical inquiry into labour wastage, with the object of determining the factors mainly responsible for high wastage rates.

At Manchester, Mr. S. Wyatt and Mr. J. N. Langdon, assisted by Mr. F. G. L. Stock, all of the Board's staff, have completed an investigation into psychological problems of repetitive work in industry, with special reference to the incidence, causes, and alleviation of boredom. The same investigators have begun a study of the nature, value, and limitations of incentives to work. With facilities kindly provided by the London County Council Education Authority, Mr. Langdon has completed a research on the effects of practice in improving manual dexterity.

Work on incentives and efficiency by Dr. C. A. Mace and his assistants at St. Andrews University has been embodied in a report which has been published.

Mr. E. Farmer and Mr. E. G. Chambers, of the Board's staff—assisted in the earlier part of the year by Mr. F. J. Kirk—have continued their work on mental integration, with special reference to accident proneness, and occupational fitness. At the request of the Ministry of Labour, and with its co-operation, a field experiment on the value of selected tests as aids to vocational guidance is now being made. Mr. Farmer and Mr. Chambers are also preparing a further report on the subject of accident proneness, and the former has extended his analysis of the factors affecting juvenile employment: this has involved the examination of a number of subjects whose subsequent careers in industry will be followed.

During the year the Board's opportunities for research in industrial psychology were notably extended by an arrangement made between the Council and the University of Cambridge. As a result of this, Mr. Farmer and Mr. Chambers will in future conduct their investigations for the Board from the Psychological Laboratory at Cambridge, where they have been given the status of Reader and of Assistant Director of Research, respectively. This association between research applied to practical problems on the one hand, and fundamental studies and academic teaching on the other, should be of mutual advantage.

C. A. Mace—
'Incentives: Some Experimental Studies.' *Rep. Indust. Hlth. Res. Bd.*, 1935, No. 72.

Occupation and Gastric Disease

In view of the claim that transport workers run a special risk of gastric disease, representatives of the Council's Statistical Committee, the Industrial Health Research Board, the London Passenger Transport Board, and the Transport & General Workers' Union have been constituted as an *ad hoc* committee to investigate the relevant records and figures.

In the meantime, an inquiry is being made by Professor Culpin and Mr. Harold Dodd (p. 90) into the occupational circumstances and physical types of patients with organic diseases of the stomach and duodenum. Dr. G. Martin is giving voluntary assistance in the work, which is being done at the King George Hospital, Ilford. The examination of fifty cases of peptic ulcer is approaching completion, and will be followed by the examination of a control group.

M. Culpin—
'Temperament and Digestive Disorders.' *Brit. med. J.*, 20th July 1935.

Environmental Conditions in Industry

Heating and Ventilation. Work on this subject is supervised by a Committee (p. 170) appointed jointly by the Council and by the Department of Scientific and Industrial Research.

Dr. T. Bedford and Mr. C. G. Warner, members of the Board's staff working at the London School of Hygiene, have completed a field investigation of the physiological basis of comfortable working conditions for light work. The limits of the 'comfort zone', and the optimum conditions of warmth have been determined. The influence of each separate thermal factor on the warmth of the environment has been studied, and an examination has been made of the reliability of different instruments or scales of warmth as indices of comfort. The relations between comfort and skin temperature, and between skin temperature and the warmth of the environment, have also been analysed.

Noise. Mr. H. C. Weston, of the Board's staff, has continued his inquiry into the effects of noise on industrial health and efficiency. A special sub-committee of the Board has been appointed to direct this work. A further study of the influence of noise reduction on the performance of cotton weavers has been completed and published: the results showed that the performance of those weavers who wore ear defenders was appreciably better than that of the control group. It is hoped to extend the investigation to a number of factories where noisy machines are used and, if possible, to collect additional data on the effects of noise reduction in mechanized offices.

Lighting. In co-operation with the Illumination Research Committee of the Department of Scientific and Industrial Research,

Mr. Weston has completed an inquiry into the degrees of illumination required for satisfactory performance of different types of work. The results have been published in a joint report of the Board and the Illumination Research Committee. He is now examining the effects of contrast in work on the quality of performance at different levels and intensities of lighting.

An account of work by Mr. S. Adams, late of the Board's staff, on the influence of good lighting on efficiency in tile pressing, has also been published as a joint report of the Board and the Illumination Research Committee.

S. Adams—
'The Effect of Lighting on Efficiency in Rough Work (Tile Pressing).' *Joint Rep. Indust. Hlth. Res. Bd. and Illum. Res. Com.*, 1935.

T. Bedford—
'Body Heat-Loss by Radiation and Convection in relation to Room Temperature.' *J. Physiol.*, 1935, **84**, 17 P.
'The Effective Radiating Surface of the Human Body.' *J. Hyg.*, Camb., 1935, **35**, 303.
'Skin Temperature in relation to the Warmth of the Environment.' *Ibid.*, 307.

T. Bedford and C. G. Warner—
'The Globe Thermometer in Studies of Heating and Ventilation.' *Ibid.*, 1934, **34**, 458.

H. C. Weston—
'The Relation between Illumination and Industrial Efficiency. I. The Effect of Size of Work.' *Joint Rep. Indust. Hlth. Res. Bd. and Illum. Res. Com.*, 1935.

H. C. Weston and S. Adams—
'The Performance of Weavers under Varying Conditions of Noise.' *Rep. Indust. Hlth. Res. Bd.*, 1935, No. 70.

VII. TRAVELLING FELLOWSHIPS

The Rockefeller Medical Fellowships

As already mentioned in the Introduction, the arrangement under which the Council have awarded Rockefeller Fellowships in the medical sciences to candidates in Great Britain ceases with the current academic year. The following were awarded fellowships in the thirteenth and final annual group: Dr. D. F. Anderson, Professor of Midwifery and Gynaecology, Anderson College of Medicine, Glasgow; Mr. N. R. Barrett, Chief Assistant to the Surgical Unit, St. Thomas's Hospital, London; Dr. A. C. P. Campbell, Clinical Tutor in Medicine, Royal Infirmary, Edinburgh; Mr. J. E. A. O'Connell, Demonstrator in Anatomy, St. Bartholomew's Hospital Medical School, London; Dr. R. Walmsley, Assistant in Anatomy, University of Edinburgh. All these fellows are working at centres in the United States.

In addition, grants from the fellowships fund have been made to Dr. D. H. K. Lee, Dr. F. Warden Brown, and Dr. W. H. Bradley. The grant to Dr. Lee was in supplement to a Sharpey Scholarship of University College, London, that to Dr. Brown in supplement to a Radcliffe Travelling Fellowship of the University of Oxford, and that to Dr. Bradley in supplement to an Arthur Durham Travelling Fellowship of Guy's Hospital, London. Dr. Lee worked in Professor Laurence Henderson's laboratory at Boston, on the effects of climate on human metabolism; Dr. Brown has studied psychiatry at Baltimore, under Dr. Adolf Meyer; and Dr. Bradley is investigating the bacteriology and epidemiology of acute rheumatism, under Dr. Alvin F. Coburn in New York.

Of the fellows of the twelfth annual group (1934–5), Mr. I. Aird studied problems of intestinal surgery under Dr. Evarts A. Graham at St. Louis; Dr. I. A. Anderson worked on diabetes and other metabolic diseases under Dr. G. A. Harrop at Baltimore; Dr. E. G. Oastler worked in Dr. J. H. Means's department at Boston, studying the properties of the thyrotropic pituitary hormone; Dr. W. H. Owles and Dr. C. Wilson also worked at Boston: the former investigated problems of gastro-intestinal secretion under Dr. G. R. Minot and the latter co-operated with Dr. S. Weiss in pathological studies of arteriosclerosis and nephritis; Dr. H. Sheehan made experimental observations on nephritis and diabetes, mainly under Dr. E. K. Marshall and Dr. W. G. MacCallum at Baltimore.

The Dorothy Temple Cross Research Fellowships in Tuberculosis

The Council have awarded a sixth series of these fellowships, which were established under a generous endowment by Mrs. Odo

Cross. The fellowships are open to suitably qualified British subjects who intend ultimately to devote themselves to the advancement, by teaching or research, of the curative or preventive treatment of tuberculosis in all or any of its forms: they are awarded preferably to candidates who wish to make their studies or inquiries outside Great Britain.

Of the fellows of the fifth annual group, Mr. W. S. Creer has studied the treatment of tuberculous disease of the bones and joints at different centres in America; Dr. A. W. Franklin has examined the problem of tuberculous contact infection in children: he worked mainly under Dr. E. A. Park at Baltimore; Dr. P. A. D'Arcy Hart has investigated the methods used in America for the early diagnosis and treatment of pulmonary tuberculosis; Dr. A. Landau has worked mainly with Dr. Leroy U. Gardner at Saranac Lake, New York State, on the relationship between silicosis and pulmonary phthisis; Dr. A. H. T. Robb-Smith has done experimental research under Dr. L. Aschoff at Freiburg, Germany, on the reactions of the lung tissue to infection with tuberculosis.

For the academic year 1935–6, fellowships have been awarded to the following: Dr. G. B. Brook, Uttoxeter District Veterinary Officer, Doveridge, Derby; Dr. J. W. Craig, Assistant Medical Officer, King Edward VII Sanatorium, Midhurst; and Dr. A. H. B. Rhodes, House Physician, Brompton Hospital, London. All these fellows are studying problems of tuberculosis at centres on the continent of Europe.

VIII. CONCLUSION

Reference has already been made to the impending retirement of Lord Linlithgow from the chairmanship of the Council. At the end of the period under review, the ordinary system of rotation made necessary the retirement of Lord Dawson of Penn, who had completed his term of four years as a member of the Council. At the same time, Professor A. E. Boycott felt obliged, for reasons of health which the Council greatly regret, to relinquish his membership after only three years of service. The two new scientific members appointed to fill these vacancies are Professor John A. Ryle, now of the Regius chair of Physic in the University of Cambridge, and Professor Matthew J. Stewart, of the chair of Pathology in the University of Leeds.

Last March the Council heard with very deep regret of the death of one who had until quite recently been a member of their body, Professor J. J. R. Macleod, of the Regius chair of Physiology in the University of Aberdeen. Of his distinguished researches, which were made particularly in the field of carbohydrate metabolism, it is unnecessary to speak here. The part which he played at Toronto in the work leading to the discovery of insulin, and in its subsequent development, is well known: for that he was awarded the Nobel Prize in 1923, jointly with Sir Frederick Banting. By his colleagues on the Council, during his period of office, he was held in high esteem for his wide knowledge of physiology and for the soundness of his judgement on questions of many kinds. He was also a man who inspired the warmest personal regard, and not least during the long and painful illness which he met with such cheerful courage.

The Council have also suffered heavy losses in other directions. The deaths have occurred during the year of Dr. H. W. Dudley, of their staff at the National Institute for Medical Research; of Dr. G. A. C. Gough, an attached worker there; of Dr. Helen Chambers, for many years engaged in cancer research on their behalf; and of Sir John McLennan, who had lately been associated with them through his part in the activities of the Radium Beam Therapy Research Board. Fuller reference to each of these has already been made at an appropriate point in the main text of this report.

The public funds expended by the Council have received further important augmentations from private sources during the year. A grant of £4,000, during a period of three years, was made by the Stock Exchange Dramatic and Operatic Society for investigations at the London Hospital into the therapeutic value of short-wave radiations: the Council have been entrusted with the administration of this special fund, which has been named by the Society in

honour of its secretary, Mr. Hugh Queckett. An annuity of £350 for twenty-five years was entrusted to the Council by the late Mr. E. M. Schlesinger and by Mrs. Schlesinger, to endow a research fellowship for work on cysts of the brain or allied conditions, tenable at the National Hospital for Diseases of the Nervous System, Queen Square, London, or elsewhere: this is to be known as the Kathleen Schlesinger Research Fellowship, in memory of the founders' daughter, and is to be administered by the Council with the assistance of a special advisory committee. The Council have again been entrusted by the Rockefeller Foundation, of New York, with the administration of various grants for specific items of work closely related to their own programme, particularly in the field of mental disorders and genetics.

In addition, the Council have continued to receive grants made for various specified purposes by the Dental Board of the United Kingdom, the British Empire Cancer Campaign, the Sir Halley Stewart Trust, the Trustees of the late Lord Leverhulme, and the Nitrate Corporation of Chile, Limited. The Council have also had the disposal of endowments and capital funds resulting from earlier benefactions.

As on previous occasions, the Council wish gratefully to acknowledge all the assistance which their work has received, whether in the form of supplementary financial provision or in other ways. They have had, as always, the ready co-operation of the Universities, and of medical schools, hospitals, and research institutes throughout Great Britain; and the greater part of their own expenditure has been for the assistance of research work which is made possible by these institutions. Finally, the Council are once more deeply indebted to the members of the numerous standing committees, shown in the Appendix, who give so freely of their time and expert knowledge in advising on technical questions arising in particular parts of the wide field of medical science.

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EDWARD MELLANBY,
Secretary of the Council.
38 Old Queen Street,
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London, S.W. 1.

17th January, 1936.

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