1931-32 [Cmd. 4008] **Committee of the Privy Council for Medical Research. Report of the Medical Research Council for the year 1930-1931**

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COMMITTEE OF THE PRIVY COUNCIL FOR MEDICAL RESEARCH

REPORT OF THE MEDICAL RESEARCH COUNCIL FOR THE YEAR 1930—1931

Presented by the Lord President of the Council to Parliament by Command of His Majesty February 1932

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THE MEDICAL RESEARCH COUNCIL

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REPORT

OF THE

COMMITTEE OF THE PRIVY COUNCIL FOR MEDICAL RESEARCH

FOR THE YEAR 1930–1931

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 1931.

1. A grant-in-aid of £148,000 was provided by Parliament for the expenditure of the Medical Research Council during the present financial year.

2. 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 £10,000.

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 £52,000.

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 the investigations of the Industrial Health Research Board, we have provided in all £86,000.

3. In accordance with the provisions of the Royal Charter, as amended in 1926, we determined, by an Order dated 21st July 1931, that Professor T. R. Elliott, C.B.E., D.S.O., M.D., F.R.S., and Professor J. B. Leathes, B.M., F.R.C.S., F.R.S., should be the members of the Medical Research Council to retire on 30th September 1931.

By the same Order, after statutory consultation with the Medical Research Council and with the President of the Royal

Society, we appointed the Right Hon. Lord Dawson of Penn, G.C.V.O., K.C.B., M.D., President of the Royal College of Physicians and Physician to the London Hospital, and Professor Edward Mellanby, M.D., F.R.S., Professor of Pharmacology in the University of Sheffield, to be members of the Medical Research Council from 1st October 1931.

4. We have received a Report from the Medical Research Council upon the progress of their work during the year ending 30th September 1931 which is submitted herewith. This is the Seventeenth Annual Report upon the research work falling now to their duty and formerly to that of their predecessors, the Medical Research Committee.

5. The Council have again received important additions to their resources from various public bodies interested in research work within the medical field. It will be seen that payments towards the cost of particular investigations have been made by the Empire Marketing Board, the Dental Board of the United Kingdom, the British Empire Cancer Campaign, the Distemper Research Council of the *Field* newspaper, and the Foot-and-Mouth Disease Research Committee. The developments of research work that have been aided in this way will be found in the Report under the appropriate headings.

Valuable assistance has again been given to their work, as the Council acknowledge, by gifts of material from various manufacturing firms. They have received help also from funds coming to them by bequest or by donation from private benefactors desiring to promote medical progress, and of these some have been expressly assigned to particular directions of work. The Council refer in their Report to a suggestion lately made to them that many of those interested in the advance of medical science who may be unable to give any large financial aid might desire to contribute relatively small annual sums. Help of that kind would be gratefully welcomed by the Council, as they indicate here, and if subscribers are multiplied the results might add notably to the possibilities of progress. The standing organization of the Council would allow gifts of this kind to be applied directly to the support of research work without any part being absorbed in administrative or other 'overhead' expenditure. They would be applied to the best effect at any given time, moreover, in considered relation to work already undertaken or planned. We desire to make it plain here that it has never been the practice, and is never likely to be the desire, of Your Majesty's Government to allow that any addition to the funds of the Council from private benefactions should affect adversely instead of favourably the amount of grant-in-aid for medical research recommended annually to Parliament.

6. As in previous years the Council's Report shows that the

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research work they support has had useful relations at many points to the administrative services of various other Government Departments, and especially to those of the Home Office and Mines Department, of the Ministry of Health, and of the Department of Health for Scotland. For the assistance of the Defence Services inquiries have been undertaken in numerous scientific fields. These have been directed to increasing the safety of deep diving, to improving the methods of selecting recruits for tasks requiring special physical or mental qualities, and to following the results of selection as shown by increased proficiency and by the diminution of accidents. The Council have co-operated also in the specialized study of vision as a factor in numerous problems of naval, military, or aerial defence.

The Council have maintained at many points their active relations to the international work of the League of Nations, and they continue to be represented directly upon the permanent International Commission for Biological Standards. They mention particularly the valuable work done during the past year in preparation for the international Conference upon standards for therapeutic sera and for the factors of diet known as vitamins, which was held in London last June under the auspices of the League.

7. In July 1930 Your Majesty was pleased by Order in Council to appoint a Committee of Privy Council for Agricultural Research, and upon their advice to grant a Charter in July 1931 incorporating an Agricultural Research Council appointed by that Committee. This Charter is closely similar in its terms to that by which you were pleased to incorporate the Medical Research Council twelve years ago.

The appointment and incorporation of the Agricultural Research Council have been under the consideration of successive Governments for more than ten years. Its formation has been postponed from time to time by a variety of circumstances. Now that it has been attained it may confidently be expected, as the Medical Research Council have represented on several occasions to the Lord President of Council, to do much to facilitate co-operation in work at the numerous common boundaries between the adjacent fields of medical and agricultural science and so to promote both economy and scientific efficiency. As part of the provision for this, Your Charter ordains that one of the scientific members of the Medical Research Council shall at all times be one of the members of the Agricultural Research Council.

A primary function and the chief ultimate aim of all agriculture is to yield bodily sustenance to mankind. The right direction of that function and effort must always therefore be the close concern of medical science. But a more intimate tie than this com-

munity of general aim subsists between the two fields of activity. Each deals with living organisms and each is served by many of the same disciplines of scientific study. The laws of nutritional science, and no less the methods and results by which they are to be further known, make common foundations on which both agriculture and medicine base their powers and must build their progressive arts. The study of infective human disease, again, not only uses the sciences applicable to animal disease, and even indeed to plant disease, but owes its chief progress to the study of disease in the animal kingdom. For these reasons a close community of method and of ideas between the systems of agricultural and of medical research must always be a condition likely to serve the best interests of economy and fertility.

With the formation of the Agricultural Research Council under the direction of the Privy Council Committee for that subject, the full triad of research organizations under Your Majesty's Privy Council is now completed. They deal together with the three main departments of man's activities with material things.

The Agricultural Research Council deals with the production and protection of plant and animal life needed for human use. The Scientific and Industrial Research Department deals with the materials and methods used in all forms of manufacturing industry. The Medical Research Council deals with the proper development and right use of the human body in all conditions of activity and environment, as well as with its protection from disease and accident, and its repair.

The present Report, like those that have preceded it, illustrates at very many points the gain that comes from a free interchange of ideas and methods among the workers within the various fields of science that serve the practical needs of the community.

STANLEY BALDWIN,
Lord President.

WALTER M. FLETCHER,
Secretary to the Committee of Privy Council for Medical Research.

25th January 1932.

REPORT
OF THE
MEDICAL RESEARCH COUNCIL
FOR THE YEAR 1930–1931

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 1930 to 30th September 1931.

I. INTRODUCTION

Few years in their experience have brought a better harvest of fruitful or encouraging results than this, the seventeenth year of their work. This successful activity in research work, gratifying as it has been, has put a heavy strain upon the resources of the Council, a strain quite independent of the results of the national financial crisis during last autumn.

A statement of the measures taken by the Council to meet the demands upon them and to reduce their expenditure in view of the increased necessity for national economy will be given at the close of this Report, on pp. 128, 129.

New Advances in Nutritional Science

As in almost all the past years of their work, a relatively large part of the expenditure of the Council has been claimed by the rapidly progressive work being done in the new fields of nutritional research, as will be seen at many points in this Report. They have referred to this in so many of their previous Reports to Parliament that special reference to it now may seem unnecessary. But both the scientific interest and the immediate practical value of this part of their work are so great, and seem so clearly to justify any effective expenditure upon it, that the Council could not well omit to draw attention here to some notable progress that the past months have seen.

In their Annual Report for 1926–27 the Council put together an account of the successive advances in knowledge that followed in rapid but irregular sequence the discovery by Professor Mellanby, made in the first years of their work, that rickets was a deficiency disease, preventable or curable by the presence in the diet of a substance now known as vitamin D. The story was traced through its remarkable course up to the discovery made early in 1926 by Dr. Rosenheim and Mr. Webster at the National Institute for

Medical Research, Hampstead, that not cholesterol, as had been supposed, but a substance closely related to it and inseparable from it by ordinary means, is the parent of the essential vitamin, which can be derived from it by the action of ultra-violet light. The subsequent identification of ergosterol as this parent substance was made by them here, and at the same time by Professor Windaus at Göttingen. Since ergosterol can be readily obtained in quantity from yeast, this work led at once to the commercial preparation and supply of vitamin D in highly concentrated form upon a large scale, to the great potential advantage of the public and the medical profession. Meanwhile a group of workers at the National Institute have been continuously engaged on behalf of the Council in studying the process by which the vitamin is produced from ergosterol by the action of ultra-violet radiations of particular wave-lengths, with the aim of preparing the vitamin itself in pure form and examining its chemical nature. The problem has needed for its solution the close co-operation of physicists and chemists concerned with the improvement of methods, and of biologists attending to the estimation of the actual dietetic results produced by the different fractions of active product. A more detailed reference under the heading of the National Institute, p. 43, will be made to these workers, to the great technical difficulties they have successfully overcome, and to the relations of their work to that lately done in other countries.

This team of investigators under the general leadership of Dr. Bourdillon succeeded early in the year in obtaining from the products gained by the irradiation of ergosterol under special conditions a crystalline compound with constant and very high vitamin D activity and with well-defined chemical and physical properties. This they provisionally named 'calciferol'.[1] During last autumn a further advance was made. It had been realized that 'calciferol' as thus obtained, though it had an intense vitamin D activity, probably contained an inactive component. Chemical means were found for confirming this view, and for isolating in stable crystalline form what is apparently vitamin D itself or, if not, the nearest approximation to it yet obtained.

This crystalline calciferol has astonishingly intense biological activity. Weight for weight it has 400,000 times the value of a good sample of cod-liver oil in preventing or curing rickets. A certain daily ration of vitamin D is needed for the proper development and growth of every child. Lacking this, though it has otherwise abundant food, the child becomes stunted, deformed, and enfeebled. A single ounce of calciferol, dissolved in suitable liquid,

[1] This name has reference to the most conspicuous body function in which vitamin D plays an essential part, namely, that of calcareous hardening of the bones and teeth.

could provide the necessary daily ration for more than a million children.

It seems almost incredible that a particular addition to the food so infinitesimal in amount, taken into the child's body for distribution to every part of it, should be so potent in its deep-seated activity as to make all the difference between crippling and disease on the one hand, and healthy life and development on the other. Similar instances of the significance in nutrition of the 'infinitely little' are provided of course by the other vitamins. We now have for the first time the description of a vitamin, or at least of a very close approximation to it, in terms of known chemical and physical characters. This is a notable advance, and high credit should be given to the ingenuity, skill, and perseverance that have led to this new stage of knowledge.

It need hardly be said that the attainment of accurate knowledge of vitamin D in terms of its chemical structure and physical properties is not merely a matter of academic interest. This information will in time, early or late, be needed for gaining insight into the processes within the body by which this substance fits into the intimate biochemical machinery of the growing cell and the developing organs. A more immediate practical advantage, moreover, may come from our possession of a fixed stable substance by reference to which the vitamin D activity of any foodstuff or remedy can be measured. For some time past a standard of this kind has been held at the National Institute for distribution on request to any workers seeking it. This is a standard preparation of irradiated ergosterol which can be kept stable under right conditions. One unit of vitamin D is defined as equivalent to one milligram of this solution. It will be seen on a later page that, by international agreement attained last summer under the League of Nations, this standard is to be maintained at the Institute for world-wide reference. It has been agreed that if, as seemed then not unlikely, the vitamin D itself should be isolated in pure crystalline form 'during the next few years', the international unit is to be redefined in terms of the pure substance. The isolation of calciferol at Hampstead and the practically simultaneous isolation of the same substance by Professor Windaus and his colleagues, who refer to it as 'Vitamin D_2', have, with great probability, already fulfilled this indication. One milligram of it is equivalent to about 40,000 international units, as defined in terms of the present standard.

The attainment of accurate standards of measurement for the vitamins is a matter of direct public interest. Obviously it is desirable for the guidance of the physician or medical officer, in order that what he intends to give shall be given accurately, and in order that the observations by which his skill is to advance may be based on measurable data. Obviously, again, it is of the

first importance that estimation in terms of accurate measurement should be made of the various diets actually available to, and used by, the people. As soon as knowledge makes it practically possible, the public should have effective guarantee that given foods, whether brought from a distance or not, have the vitamin value which is claimed for them and in respect of which purchase is made. To a poor nursing mother it is of vital importance, for instance, that the fatty substances which she is able to buy for food should have an effective vitamin D value. Deficiency in this invisible quality is of far greater importance to her and to her children than some shortness of weight in the total quantity, against which she is already protected by law.

Another direction in which any accurate knowledge of the physical chemistry of the production of calciferol has practical usefulness is in relation to the commercial aim of improving and cheapening large-scale production. We have good reason to believe that the great majority of the population living under urban conditions are living very near the minimum of adequate vitamin D supply, or below it. This applies especially to the young and actively growing, and it has been made apparent by evidence of many kinds, direct and indirect. Work in the National Institute during the last few years has already led to the large-scale artificial production of vitamin D in this country. This has brought within sight the possibilities of great national saving in health and money. The question of how far and how soon these can be realized does not lie within the sphere of the Council's responsibilities. The possibilities, however, are plain, and seem to the Council to demand every effort on their part to increase the valuable stock of knowledge which is already available for use.

The Relation of Vitamin D to Dental Decay

Ten years ago the Council observed in their Annual Report (1920-21) that though we were then wholly ignorant of the chemical nature of any 'of those elusive substances' the vitamins, and of the mode of their action, nevertheless the empirical study of the parts which they severally play in nutrition had already brought results of great practical utility. It has been seen that intensive investigations by highly technical methods in the laboratory have brought us stage by stage to a definite physico-chemical identification of one of these substances, vitamin D. Not less active than these have been various practical studies, in very different settings, of the possibilities of exploiting for the public benefit the known biological properties of this vitamin. One part of these has reached a stage calling for special mention here.

It is now securely known, as the result of Mrs. Mellanby's work, that proper development of the teeth and the jaws is impossible in

the absence of vitamin D, and that full health and normality are attainable only when vitamin D is given with close approach to the optimum. This was established several years ago by converging testimony drawn both from animal experiment and from observations of human dentition. To these the Council have referred on previous annual occasions. Full summaries of the published evidence are given in two special Reports already issued by the Council, and in a third now in the press. The health and beauty of the mouth are found to be directly dependent on the vitamin D supply. Much evidence has also supported the view, made probable by many analogies, that the attacks of micro-organisms causing decay (dental caries) in the teeth after their formation are more easily resisted by well-formed than by ill-formed teeth, and that the incidence of caries might be diminished by adding vitamin D to the diet.

Four years ago the Council thought it well, on the advice of their Dental Committee, to make a large-scale trial of the effects of giving vitamin D to groups of children living under urban conditions and supplied with diet believed to be fully adequate. The results collected after unbroken observation for two years were so significant as to call for an interim publication, made in September last. The children, all living under similar institutional conditions, were divided into groups of from 65 to 86 in each group. Each group received a specific addition to the standard diet. All the children were regularly examined and the progress of dental decay in the permanent teeth recorded. It was found that there was a striking difference in the rate of increase of decay between the groups receiving vitamin D either in the form of cod-liver oil or of artificially manufactured vitamin D, given as 'radiostol', on the one hand, and those, on the other hand, not receiving additional vitamin D, but only receiving either treacle or olive-oil for purposes of comparison. As between the first inspection of the teeth and the final inspection after two years, the percentage increase in decay for the olive oil or the treacle group was close to 46 per cent. That for the cod-liver oil (natural vitamin D) group, or the radiostol (artificial vitamin D) group was in each group close to 10 per cent. Corresponding results had been previously obtained in a more limited trial undertaken at Sheffield by Mrs. Mellanby and by Dr. Lee Pattison.

It should be noted particularly that these results apply only to teeth which had already been formed at the beginning of the trial. The final report which the Council hope may appear during next year will include the results shown by the teeth that have been in the course of development since the beginning of the trial, and it is natural to expect that these will bring out the value of a full vitamin D supply in an even more striking degree.

Here, again, another vista is being opened of great benefits

attainable by the people when these new discoveries in preventive medicine are followed up effectively. Attention must be drawn particularly to the fact that in this remarkable trial at Birmingham we have been dealing with children receiving a dietary that was believed by both the medical and the lay authorities concerned to be perfectly adequate for normal health and growth. The diet had obtained full official sanction. Plainly, however, it was qualitatively deficient. We have to reflect that results of the kind gained here are more fully to be expected, by *a fortiori* argument, if proper supplies of vitamin D can be brought to those not already enjoying a regular and approved diet. We are here given a warning, moreover, that many dietaries hitherto regarded as adequate, either by medical or by 'common-sense' standards, may not in reality be adequate qualitatively for full health and resistance to disease.

It is worthy of remark here, too, that only first-hand experience can teach how numerous and varied are the practical difficulties that may arise at any point when a trial of this kind is being designed and begun. If it is to be conducted under conditions of strict control that will allow sound conclusions to be drawn, difficulties will persist throughout the whole course of the work. Apart from those of maintaining strictly controlled conditions, the necessary periodic observations require skilled and uninterrupted service. The work, therefore, is necessarily costly, though the money expended is utterly insignificant, of course, in comparison with the vast expenditure, direct and indirect, which dental deformity and disease inflict on the community year by year—and this still leaves out of account any calculation of suffering. A large part of the necessary money has been provided by a grant to the Council from the Dental Board of the United Kingdom, and it should be remembered here that this comes from a fund to which every registered dental practitioner contributes annually. It seems right that the attention of Parliament should be drawn to the generous willingness with which the dental practitioners of the nation have accepted terms of registration under which the whole profession contribute a large annual sum for the support of research work.

Progress in the Study of Virus Diseases

In their Annual Report of two years ago the Council gave a brief general review of the state of our knowledge of the invisible agents, 'viruses', of numerous destructive diseases in mankind, animals, and plants, and of the current progress made in their study. They explained then the policy they had followed since the first equipment of the National Institute after the War, in promoting inquiry into this subject by a group of investigators there.

One of the main parts of this policy has been to aim at the improvement of the technical means of handling, seeing, and measur-

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ing these extremely minute particulate agents of disease. The viruses, e.g. of yellow fever or foot-and-mouth disease, are called filterable' because they can pass through porcelain and other finely porous filters that hold back the ordinary bacteria, such as those, for instance, that cause diphtheria or typhoid fever. Anything like uniform retention will obviously be effected only in so far as the holes in the filter are below a given size, and regularly so. For several years Dr. Elford has been engaged upon the purely physical problem of making filters of which the pores have both a uniform and a measurable size and which have the needful strength and simplicity for the work of the bacteriologist. In the past year he has published an account of his new series of graded collodion membranes (called 'gradocol' membranes) which meet these requirements. They have now been in regular use for many months in the Institute and have already been of great service to the studies of the different viruses under investigation there. The pores through which the filtrate passes are closely uniform in size, and within each grade of filter, obtainable at will, the pores vary in diameter within only a very narrow range. It is possible, therefore, by use of these filters to gain a close estimate of the absolute and relative dimensions of the infective particles for each virus examined. A given virus, moreover, can be separated from other particles, whether of another virus or not, that are coarser than its own, by a first filtration, and then be itself concentrated and washed free from finer particles on the surface of a second, higher graded, filter membrane. By this kind of selective concentration the chance of finding and identifying the particles of a specific virus by special microscopic methods has been greatly increased. Examples of the new usefulness of these gradocol filters, and of the sorting out of some of the best known viruses for the first time by their order of size, will be given in more detail when the work of the Institute is summarized in a later section.

These results have been achieved in close association with Mr. Barnard and his staff, whose progress in the design of new microscopic apparatus and the improvement of optical methods for the examination by ultra-violet photography of sub-microscopic organisms in the living condition has been noted in many successive Annual Reports. This also will be mentioned again below in further detail. It may be said here in general that all the evidence now being accumulated by the use of these refined new methods of ultra-filtration and ultra-microscopy tend to reinforce the opinion, already widely held, that some, at least, of the viruses examined are definite self-reproducing organisms, differing from the bacteria visible by the ordinary microscopic methods chiefly in being so minute that their diameter is much less than the wave-length of visible light rays.

Side by side with this application of physical methods to the improvement of the laboratory armament, the Council have followed another line of general policy. This has been to leave complete freedom to skilled workers in this field to select particular virus diseases for study. A more detailed account will presently follow of recent work at the National Institute which is giving promising and interesting results over a wide range of virus diseases. These include the newly recognized mouse disease, infectious ectromelia, which was discovered and first described in a stock of mice received at the Institute. The arrival of this disease seems to have been a most fortunate accident, because the virus here happens to offer features that make it especially convenient for the pursuit of clues to its intimate nature and behaviour. Other subjects under investigation include foot-and-mouth disease, vaccinia, encephalitis lethargica, herpes, distemper in dogs, and transmissible malignant tumours of birds. They include also the virus-like agents known as bacteriophages which destroy bacteria, each 'phage' having a highly specific action upon a particular race of bacteria towards which it behaves like the agent of a specific disease, enormously multiplying itself as it destroys the object of its attack.

It will be seen at a later page below (p. 117) that this virus disease of mice has given Professors Topley and Greenwood at the London School of Hygiene and Tropical Medicine an opportunity of studying its epidemic form. They have obtained the interesting result that the processes of herd immunization appear to be essentially different in this virus infection from those of the bacterial infections they have long had under observation and study. This line will be followed up and may lead to conclusions of much importance.

The Virus of the Common Cold

It has often been made a reproach to the medical world that no effective control has been gained over the plague of the 'common cold' that inflicts such a burden of inconvenience, with many added risks of death, and brings heavy annual expense to the country through loss of time and work. There has long been reason to believe that the infective agent of 'colds' is primarily a virus that may open the way for the secondary invasion of various kinds of bacteria. The chief bar to progress in this direction has hitherto been the absence of a satisfactory experimental method, for neither the domestic animals nor the smaller rodents commonly used for laboratory work appear to be susceptible to the causal agent of this form of illness in man. There has recently been made available in the United States a large fund provided by a business organization which has made it possible for Dr. Dochez of New York and his colleagues to use chimpanzees for experiment, under conditions of rigid quarantine, unceasing attendance, and control. It was

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found possible to transmit 'colds' to these apes in nearly a half of the attempts by the use of material derived from persons in the early stages of catarrh, and filtered so as to exclude bacteria. Clear evidence was obtained that the causal agent belonged to the virus group. The next stage of the work, undertaken in the light of the knowledge thus gained, showed parallel results in the use of human volunteers. It was found, moreover, that the catarrhal virus could be cultivated outside the body in living cells from a chicken embryo, and could be passed through a series of sub-cultures. From these cultures the virus could be recovered, and could again produce typical catarrh in a susceptible individual. Dr. Andrewes, of the National Institute staff, visited this work in the past year by the courtesy of Dr. Dochez, and an arrangement is now being made to confirm it here and if possible extend it. A generous supply of human volunteers has been forthcoming from among the students at St. Bartholomew's Hospital. These, and the availability of the new culture method, will provide, it is hoped, a sufficient experimental field to allow the costly use of chimpanzees to be avoided. The methods of study already worked out at the Institute will be applied to the virus and its products.

It should be noted here that the chimpanzees under experiment showed, just like their human cousins, that only a brief immunity succeeds infection by this catarrhal virus. In this respect it differs notably from other well-known viruses of disease, such as those, for instance, of measles or smallpox, where immunity after a first attack is long and commonly life-long. The brevity of catarrhal immunity diminishes the prospect of any rapid attainment of the means of practical control.

Work complementary to direct studies of this virus has been supported by the Council during the past two years in Professor McLeod's laboratory at Leeds, where Dr. Hoyle has been engaged in studying the secondary bacterial invaders during 'colds' both in different individuals and in successive attacks in the same individual.

Virus Studies and Cancer

For the past eight years Dr. Gye has been engaged in the study of the causation of the malignant tumours that can be produced in fowls by the injection of cell-free filtrates from a pre-existent tumour. These filtrates have infective properties closely parallel to those containing acknowledged filterable viruses of other diseases, and indeed this work at its inception was designed as part of the general programme of virus studies to be promoted within the National Institute. Dr. Gye's claim to have obtained two separate factors in tumour formation by suitable treatment of filtered tumour extracts, one an extrinsic virus-like infective agent, the other a cell-specific chemical adjuvant, and his interpretation of the

causation of cancer in terms of these two kinds of factor, have been discussed by the Council in previous Annual Reports. They have also recorded Dr. Gye's later difficulties in reproducing the apparent separation of the two factors with regularity. Two years ago they indicated that he was turning to study the immunity reactions of these tumour-producing agents with his colleague Dr. Purdy, and that Dr. Andrewes at the same time was bringing to bear on the same problems the results of his work upon the immunity reactions of other known viruses. An outline of the main experimental results lately achieved is given below at p. 34. In general it may be said here that the evidence from both sets of experiments converges to support the view that in these tumour filtrates we have to deal with an infective virus which, as regards the immunity reactions it can elicit, is similar in many respects to some of the acknowledged viruses causing specific diseases. Dr. Gye and Dr. Purdy have now put together an account of their work in a book, recently published, in which they set out fully Dr. Gye's hypothesis of the causation of malignant disease, in the light of which their work has gone forward. Dr. Andrewes is publishing his results in the technical journals. It is unnecessary to point to the extreme interest and potential significance of this direction of inquiry. The Council have given it every facility and encouragement in their power from the beginning.

Maternal Mortality and the Study of Puerperal Fever

In their last Annual Report the Council explained the circumstances in which they had arranged to co-operate in the systematic study of puerperal fever with Queen Charlotte's Hospital at Hammersmith, where the Hospital authorities have built a new Isolation Block for treatment, and Research Laboratories in close association with it. The new wards were opened for use in September, 1930, and the laboratories in February last. Dr. Leonard Colebrook, of the scientific staff of the Council, is honorary Director of the laboratories, and co-operates with the clinical staff of the Hospital. The Council also provide the services of Dr. Ronald Hare as bacteriologist. Other workers in pathology and biochemistry are supplied by the Hospital. For the completion of this team of workers and the provision of full facilities and materials for their investigations the Rockefeller Foundation of New York have generously offered a grant of £3,000 a year for a period of seven years to be paid to the Council for the fuller development of this work at Queen Charlotte's Hospital. This benefaction has been gratefully accepted by the Hospital and the Council. A summary of the work done during the past year will be found on p. 73 below.

The Council attach great importance to this effective concentration of puerperal fever cases at one centre and the organized study

of the disease by clinicians and laboratory workers in intimate association. The chances of recovery for each patient are much increased by the proper concentration of special clinical experience, combined with appropriate laboratory work. It may be noted here that 200 patients have been received at this special hospital in the first twelve months; these have in general been grave cases, and many of them were received at a late stage in their malady. Of these, 30 have died, though the usual death-rate of such cases is much higher.

Arrangements have been made to link this work as closely as possible with the inquiries that are made from time to time by the Ministry of Health into local occurrences of puerperal fever in various parts of the country. Dr. Dora Colebrook, in the service of the Council, after a period of work under Dr. F. Griffith at the Ministry of Health Laboratories, will act on suitable occasion with officers of the Ministry in local inquiries, while her work will be based at the Queen Charlotte's laboratory at Hammersmith.

Status Lymphaticus

Readers of newspapers are familiar with the term 'status lymphaticus' used very often at coroner's inquests into cases of sudden death to indicate a state of disease not recognized in life which is supposed to account for death when no other cause is apparent. The term has reference to a supposed over-development in the young, or abnormal persistence in the old, of the thymus gland in the neck, perhaps with a corresponding undue development of lymphatic tissue elsewhere. It has long been suspected that this supposed disease of 'status lymphaticus' has no real existence. It was suggested that medical men in many instances have been misled by the absence of properly recorded data of the normal size of the thymus gland, and of common variations about the normal, during healthy life. A man accustomed to the diminished thymus commonly seen in hospitals after death from fever or wasting illness might readily take as abnormal the size of the gland after sudden death in normal states of health and nutrition. Coroners from time to time have publicly expressed their doubts whether any real meaning can be attached to 'status lymphaticus' as providing an adequate cause of death. Even if such an abnormal condition does exist, it has not yet been adequately explained in what manner it can account for sudden death. There is an obvious danger lest the facile use of a verbalism of this kind may serve only to divert attention from the need for fuller inquiry into the actual cause of death. In 1926 the Council, in conjunction with the Pathological Society of Great Britain and Ireland, organized a collective investigation of 'status lymphaticus'. In making arrangements for this they received important assistance from the

Home Office and from the Coroners. The main objects of the investigation were two: first, to establish by a large series of weights and measurements the standards of weight for age, and proportion to body-weight, of the normal thymus at all ages, and, second, to investigate closely the precise cause of death in persons dying suddenly from unexplained or trivial causes where the only apparent abnormality was the presence of a large thymus. This scheme involved the appointment of a number of investigators in large centres of population in Britain to collect detailed records upon special cards prepared and issued for the purpose. The work has been directed throughout by a Committee of pathologists whose names are given below at p. 139. An analysis of the data collected by this Committee has been made by Professor Turnbull of the London Hospital and Dr. Matthew Young in the service of the Council, and has been published during the past year. This analysis shows that the inquiry may be regarded as having definitely established within narrow limits the average weights of the normal thymus for the several ages from one year upwards. These are in close accordance with figures based upon data published in recent years by other observers elsewhere. The mean percentage proportions of thymic weight to the body-weight for the different age groups have been similarly established. In the opinion of the Committee, the facts elicited in the inquiry agree with the classical reports published by Hammar in 1926 and 1929 from Sweden, which have met with surprisingly little attention in other countries. They agree also with the statistical results based upon London material supplied by Professor Turnbull and published by Greenwood and Woods in 1927. They provide, as the Committee conclude, 'no evidence that so-called "*status thymico-lymphaticus*" has any existence as a pathological entity'.

Results of Insulin Treatment

In their Report last year the Council examined in some detail the extent to which the benefits of insulin treatment had been actually brought to sufferers from diabetes in the population at large since its beginning in 1923, and the results of the treatment in reducing mortality from the disease. From data in their possession for the national demand and supply of insulin they were able to show that, although there had been abundant supplies almost from the beginning of manufacture in 1923, the general use of the remedy throughout the country had been advancing only gradually and was still much below the level of maximum need. They had also reason to believe that many patients were not receiving insulin under the conditions of biochemical control and dietetic balance that are necessary to secure results equal to those obtained at the chief medical centres.

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Attention was also drawn to the difficulties of interpreting the official figures given for death-rates from diabetes in successive years since the introduction of insulin. These death-rates were already subject to much fluctuation before that time, and there was evidence that the incidence of the disease had been rising since the war. It was pointed out that the figures were based upon death-certificates giving the diagnoses of contributory as well as of immediate causes of death, and that all deaths of diabetic patients, even if actually due to intercurrent illness or occurring at an advanced age, tended to find a place under the head of this disease.

A more important difficulty was that the effect of insulin is not to give radical cure but to prolong life. The results of the treatment, therefore, were to be sought not in a reduction of the total recorded mortality but in a decrease in the deaths from diabetes in the earlier age groups. This decrease was indeed found to be a large one, although not yet so great as might possibly have been expected. The Registrar-General's figures for England and Wales in 1928—the most recent available—showed that since the introduction of insulin in 1923 the mortality of male diabetics under 55 had been reduced by 37 per cent. and of females by 21 per cent.: in the age group 25–45 the rate for males had fallen by as much as 45 per cent. This important result, however, was masked in the total figures by the concurrent increase in the mortality at ages over 55, due in part to the rising incidence of the disease and in part to the prolongation of lives of diabetic patients who without insulin would have died at an earlier age.

The Council concluded by stating their intention of making special inquiry into the results of insulin treatment at special centres, with a view to determining more precisely the standard of success attainable under the best conditions. This has since been done, and a series of over a thousand cases of diabetes, under treatment at one centre in the period 1925–31, is now being submitted to statistical analysis. Almost all these patients have been receiving insulin, except in the highest age group where many of the cases are of the mild and slowly progressive type which is commonly found in elderly subjects and which can often be more conveniently controlled by dietetic measures alone.

The evidence and findings of this inquiry will be published separately at an early date. It must be remembered that the whole period of experience in treatment by insulin covers only eight years at the most. It may be said here, however, that the figures for young and middle-aged subjects show a great preponderance of cases where good health is still maintained against all expectation based on previous experience. The real gain is much greater than any figures can show. Without insulin the patient, during his brief period of survival, fell soon into a state of ever-increasing and

distressing invalidism, under dietetic restrictions amounting almost to starvation. The patient receiving insulin now retains or recovers, in the great majority of cases, a close equivalent of normal health, a full measure of bodily and mental vigour, and the capacity to enjoy a useful and active life.

Organized Trials of New Remedies

The Council have long had before them the problem of securing in the most rapid and effective way the trial, under competent clinical direction, of new substances or preparations which laboratory experiment may have shown to give promise of therapeutic value. On special occasions in the past, as for instance upon the first introduction of insulin for the treatment of diabetes, of liver extracts for the treatment of pernicious anaemia, or again of 'sanocrysin' and of 'diaplyte vaccine' for the treatment of tuberculosis, the Council have made special arrangements for suitable trials and reports by clinical observers invited to act for them in this way. They think that advantage was brought both to the profession and to the public upon each of these occasions, in different degrees, either by the systematic and rapid confirmation of results gained elsewhere, or by the early appraisement of claims found to have been exaggerated.

The production of new therapeutic agents seems certain to increase rather than to diminish, and the Council have proceeded in the last year to set up a more regular machinery for the organization of clinical trials as need for them may arise from time to time.

The Chemotherapy Committee, originally appointed jointly by the Council and by the Department of Scientific and Industrial Research, have been engaged in promoting the production of new synthetic substances of therapeutic importance, and in their biological examination. From this Committee new synthetic compounds are put forward from time to time for biological study in the laboratory, or for clinical trial. Other Committees under the Council, for instance, the Sex Hormones Committee, may also be expected to bring to notice biological products for which laboratory experience may call for early clinical appraisement under controlled conditions.

This subject has been approached also from another point of view. The Council have recently had under discussion with representatives of the Association of British Chemical Manufacturers the problem of securing trustworthy clinical trials of products produced by manufacturing firms. It has been urged, and the Council think with much truth, that in this country the work of University laboratories, as well as that of chemical manufacturers, has sometimes failed to gain its proper reward in clinical usefulness because of the practical difficulties that have hitherto prevented early and

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effective clinical trials. In some other countries and conspicuously in Germany, where the production of new synthetic substances is most active, physicians of good reputation are ready to publish the results of clinical trials of new and patented substances over their own names. In Great Britain, professional men, for reasons that seem obvious here, have not in the same way been willing to use their names. It has been not uncommon, indeed, for a new substance first produced in this country to come into general recognition and use by way of clinical reports published in German or other foreign journals. Members of the medical profession in Great Britain have on more than one occasion had pressed upon their notice, under foreign names by the medium of foreign literature, substances which were British in first production but which have escaped notice and trial by clinicians in their country of origin.

A number of distinguished clinical observers accepted last year the invitation of the Council to form a standing Committee, the Therapeutic Trials Committee, under whose supervision and authority clinical trials of new substances may be organized. The constitution of the Committee is given on p. 138. It contains representatives of general medicine and surgery, who have been empowered to call in the aid, as occasion may demand, of specialists in particular branches. This Committee works in close touch with the Chemotherapy Committee (p. 115), who may be responsible for the experimental work with the drugs or preparations submitted that may be necessary or desirable before their use in man. As a result of earlier consultation between the Chemotherapy Committee and the Association of British Chemical Manufacturers, agreed conditions had been accepted under which new substances may be submitted to the Therapeutic Trials Committee for clinical study.

Clinical trials of substances that have been submitted to the Committee and approved for this purpose have already been organized at suitable hospital centres, and are now in progress.

The Relations of the Council to Manufacturing Firms

It has always been laid down and accepted as among the primary functions of the Council not only to promote the stages of scientific discovery as such within the medical field, but also to facilitate the 'availability' of the results of discovery in the interests of the public and the medical profession. It rarely happens that the discovery of a new substance or a new method allows immediate practical use to be made of one or the other. Very often much time and labour must be given, not seldom involving a new series of researches, before the yield of a new substance can be brought into the phase of large-scale production, or a new method be adapted for widespread use. In these intermediate stages of work it is often necessary for rapid and economic progress that close

co-operation should be established between the original scientific investigators and those whose work lies in finding the adaptations needed for large-scale production and use. The general social and political reasons that make it obviously desirable for State-supported work like that of the Council to be brought into the field of co-operative effort with British manufacturing firms are reinforced by the intimate relations of this kind of manufacturing to health and life within the country. Apart from any other reasons, it will be accepted as desirable for this nation, as for any other, that all the essential materials for good medical work should be readily procurable within the national boundaries.

The Council have just referred to what they hope will be improved machinery for assisting the British production of new therapeutic substances. They conceive of this as only an added phase of what has been their normal relationship to manufacturing production for many years. Earlier reports of the Council provide several examples of this. The Council assisted by special research work the rapid development in this country of methods of manufacturing insulin, and these led not only to a greatly increased rate of output but also to a rapid fall in cost. They have given assistance in a similar way by the study of methods for the production of vitamin D by the irradiation of ergosterol, for the production of various organic extracts used in medical work, and for the production of material for inoculation against distemper in dogs. At the same time, and from the beginning of their work, the Council have received reciprocal aid in generous measure from the chief manufacturing firms. These have always been ready to offer the results of their experience, the supply of raw materials, or help in other forms.

Besides this co-operation in work of common interest, the Council have received from time to time direct gifts from commercial firms in aid of their work, and these are in fact gifts to the nation. The firm of British Drug Houses, Ltd., have generously and confidentially supplied materials for experimental studies promoted by the Council upon a scale which could not have been attained otherwise without heavy added expenditure. The necessary preparations of individual vitamins were thus given for the experiments at Birmingham and at Sheffield upon the control of dental decay by diet, to which reference has just been made. Similar materials have been supplied to Professor Mellanby for his work on the dietetic control of puerperal fever, and to Professor Davidson at Aberdeen for a study of the relations between diet and the clinical course of pneumonia. Other materials have been supplied to Dr. Helen Mackay at the Queen's Hospital for Children and to Miss Hume and Professor Korenchevsky at the Lister Institute, all in the service of the Council. A supply of crystalline oestrin

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has been accumulated for work now being planned by the Sex Hormones Committee. Various chemical organic compounds have been given to Dr. Drury working for the Council at Cambridge and to other workers at the National Institute for Medical Research. Special forms of liver extract have been supplied to Dr. Esmé Gilroy, working for the Council at Edinburgh.

The Council reported last year that Messrs. Lever Bros., Ltd., had most generously placed at the disposal of the Council for medical and scientific purposes the whole available supply of their concentrate of vitamin A, and reference will be made later in this Report to some of the uses to which that gift has already been put. Messrs. Burroughs Wellcome & Co. have repeatedly assisted the work of the Council for many years by the confidential and free supply of new forms of sera and other new products for the assistance of particular research workers. The Council have also received from Messrs. Bovril, Ltd., the generous gift of a large quantity of dried meat, required as a constituent of an artificial diet in vitamin investigations at the National Institute.

In other instances manufacturers have provided quantities of costly materials for research, at or below the bare cost of production. The large amount of ergosterol, for example, that has been used in the search for pure vitamin D was thus supplied in equal share by Messrs. Boots Pure Drug Co., Ltd., the British Drug Houses, Ltd., and Messrs. Burroughs Wellcome & Co. During the past year, also, Messrs. Boots Pure Drug Co., Ltd., Messrs. Burroughs Wellcome & Co., and Messrs. Parke, Davis & Co. have given valuable assistance to the investigation the Council have been promoting into the curative value of concentrated sera in the treatment of pneumonia.

For all the gifts of this kind that have been put at the disposal of their workers, as well as for much friendly interchange of facilities and information, the Council would here express their grateful acknowledgements.

Publication of 'A System of Bacteriology'

During the past year the publication by the Council in nine volumes of a *System of Bacteriology*, to which more than a hundred British bacteriologists have contributed articles, has been completed. This undertaking was first planned in 1926, after the Council had brought to a close the publication of the monthly journal *Medical Science: Abstracts and Reviews*, which they had previously supported for six years after the war. It was strongly represented to them that pathology would gain by the production of a comprehensive series of concise monographs in bacteriology, each written by an expert dealing with his own subject. In 1929 the Council were able to announce the issue of this projected

system, and the publication of volumes began in that year. It fell out that Lord Balfour's last act as Chairman of the Council was his writing the short but brilliant general preface to the whole series, which is printed in Volume I. The Council would express here again their strong hope that the publication of this system may do good service to many workers in many countries who are advancing the sciences of bacteriology and immunology or applying them in the practical fields of human and of animal pathology.

Dr. Paul Fildes, of the London Hospital, and Professor J. C. G. Ledingham, of the Lister Institute, have acted as general editors of this symposium, and they have received other editorial aid in particular sections of the work that has been acknowledged in the several volumes. All those who have so generously given their aid to this project would acknowledge with the Council that by far the heaviest burden of preparation for the work and of other tasks of organization throughout its progress has been borne by Dr. Fildes. Without his devoted work the plan could hardly have been brought to fruition, and certainly the System could not have been published punctually within the allotted time. Dr. Edgar Schuster, of the Council's Publications Department, has given indispensable aid throughout at many points. To all these the Council would offer thanks, both on their own behalf and in the name of the innumerable workers who will benefit by this production.

Publication of 'Nutrition Abstracts and Reviews'

The Council have been enabled, by the completion of the *System of Bacteriology*, to bring financial aid to another publication. They have joined with the Imperial Agricultural Bureaux Council and the Reid Library of the Rowett Institute, Aberdeen, in supporting a new periodical, to be known as *Nutrition Abstracts and Reviews*. The preparations made earlier in the year allowed the production of the first number to be announced for November 1931. The results of scientific work in the field of nutrition are contained within a great variety of technical journals. Some appear in journals of biochemistry, others again in those of physiology and other biological subjects, others again in the medical press and various trade periodicals. That is true of papers relevant to human nutrition, and the same dispersement is even more characteristic of papers directly or indirectly related to the nutrition of live-stock. On purely scientific grounds it is obvious that all workers in this field, whether from the medical or from the agricultural point of view, have greatly to gain by the free communication of ideas, methods, and results. Since the primary object of agriculture is to provide nutriment for human beings, there is an even closer practical *nexus* to be observed between the two directions of work. The Council feel confident, therefore, that this new periodical will do

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much to facilitate the advance of knowledge in this large common field of activity, of which the proper development has unsurpassed interest and practical value among biological subjects.

The British Patent Law in relation to Medical Research.

During the past few years the Council have had to deal with many questions arising from the operation of the patent law in the field of medical discovery, and they have thus been led to give careful consideration to the whole subject of patenting in its relation to research work within their province. That exceptional legislation is justified for the operation of patent law within the medical field is already widely recognized. In some countries medical patents are not allowable: in British law patents applicable to drugs or foods are given exceptional safeguards. It became evident to the Council, more particularly in the light of some recent events, that there are considerations that call for further amendment of the British patent law, and that the importance of these is likely to increase in the near future rather than to diminish.

In 1928, the Council embodied their views in a reasoned statement which the late Lord Balfour, then their Chairman, proposed to bring to the notice of the Government for consideration by a special committee, which would have included representatives of medicine and of biological science as well as those expert in the patent law and its administration. It was subsequently learned, however, that the President of the Board of Trade was appointing a Departmental Committee on the Patents and Design Acts and Practice of the Patent Office, and it was thought desirable to refer the matter to this body, although it had in fact been constituted to deal mainly with questions of quite a different kind. The statement was therefore reaffirmed by the Council in 1929, and submitted to the President of the Board of Trade for consideration by the Departmental Committee. Later, in 1930, representatives of the Council gave evidence before the Committee in support of the memorandum. The Departmental Committee reported in 1931, and published the Council's memorandum in the Minutes of Evidence, but no recommendation was made for any change in the existing law as to medical patents.

In the view of the Council, the questions at issue have wide importance beyond the field of patent law administration, and are of serious concern to all who are engaged in medical research work or in its promotion. They believe it to be unlikely, therefore, that these questions will for long await renewed attempt towards their solution. They have accordingly thought it well to take this first opportunity of more publicly expressing their views, reaffirmed by their present members, and they print their memorandum in full as an Appendix (p. 130) to this Report.

THE NATIONAL INSTITUTE FOR MEDICAL RESEARCH

Hampstead, London

(With Farm Laboratories at Mill Hill)

Academic Year 1930–31

Physiology, Pharmacology and Biochemistry

Staff—

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

Attached Workers—

T. C. Angus, D.F.C.
F. A. Askew, B.A., B.Sc.
Miss H. M. Bruce, B.Sc.
R. K. Callow, M.A., D.Phil.
A. Cohen, B.Sc., Ph.D.
Miss C. F. Fischmann, B.Sc.
G. A. C. Gough, Ph.D., B.Sc., A.I.C.
J. St. L. Philpot, B.A.
O. Rosenheim, D.Sc., F.R.S.
Miss W. Strangeways, B.A.

Visiting Workers—

Dr. T. S. Hele, Cambridge
Dr. Peter Holtz, Greifswald.
Dr. A. J. Klisiecki, Lwow.
Dr. Alex. Marble, Boston, U.S.A.
Mr. S. M. Orlic, Zagreb.
Dr. L. T. Poulsson, Oslo.
Dr. D. W. Richards, New York.
Dr. U. S. von Euler, Stockholm.

Experimental Pathology and Bacteriology

Staff—

Capt. S. R. Douglas, M.R.C.S., 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.S., D.V.H. (*Farm Superintendent*).
W. E. Gye, M.D.
P. P. Laidlaw, B.Ch., F.R.S.
Miss J. E. Marchal.
J. R. Perdrau, M.B.
W. J. Purdy, M.B.
Wilson Smith, M.D.
P. Bruce White, B.Sc.

Attached Workers—

I. A. Galloway, B.Sc., M.R.C.V.S.
G. E. S. Jeffery, L.D.S.
Mrs. B. E. Holmes.
Mrs. A. Pirie.
Charles Todd, O.B.E., M.D., F.R.S.

Visiting Worker—

Dr. Slavko Palmovic, Zagreb.

Microscopy and Physical Methods

Staff—

J. E. Barnard, F.R.S. (*Hon. Director*).
W. J. Elford, B.Sc., Ph.D.
John Smiles, A.R.C.S.

Biological Standards

Staff—

Percival Hartley, M.C., D.Sc. (*Director of Biological Standards*).
J. H. Gaddum, M.A., M.R.C.S.
H. P. Marks, B.Sc.
Miss J. E. Marchal.
Wilson Smith, M.D.
P. Bruce White, B.Sc.

Visiting Workers—

Prof. H. T. Baggesgaard-Rasmussen, Copenhagen.
Dr. E. Cuboni, Milan.
Mr. A. M. Hemmingsen, Gentofte.
Dr. R. S. Sandhu, Punjab.

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II. THE NATIONAL INSTITUTE FOR MEDICAL RESEARCH

The work done at the National Institute, Hampstead, and at the associated Farm Laboratories at Mill Hill, has proceeded in the main along the same lines of inquiry as those described in recent Annual Reports. Work on biological standards will be grouped together in the next section (p. 51) and the investigation into canine distemper will be given under a separate heading in section V (p. 113).

The Council have been highly gratified to learn that His Majesty the King has been pleased to confer the honour of knighthood upon Dr. Dale, Director of the Institute, in recognition of his distinguished and many-sided services to science and medicine.

Virus Diseases

A large part of the pathological investigations at the Institute has continued during the past year to be devoted to the study of the viruses causing diseases in man and animals. Progress has been greatly aided by the co-operative application of general biological methods for the study of such infections, by several investigators, with the advanced microscopical methods developed by Mr. Barnard and his staff, and the methods of differential filtration through accurately graded membranes devised by Dr. Elford.

Ultra-filtration. Reference has already been made to the new series of graded collodion membranes prepared by Dr. Elford for bacteriological use, and especially for the study of viruses. He has described these in a paper published during the year, and they have now been for many months in regular use. The part they have played in specific inquiries will be noticed in the accounts given of other work within the Institute.

Ultra-microscopy. The object of the work of Mr. Barnard and his staff, for many years past, has been the design of apparatus and discovery of methods in which the natural refractile properties of extremely minute particles are used for the production of images recognizable both by direct vision and by photography, so that sub-microscopic organisms can be examined and photographed in the living condition. If real photographic images of the particles constituting a virus are thus obtained, direct measurements can be made of them and the result compared with the data obtained by filtration. Such accurate estimates of size could not be obtained with fixed and stained particles. Mr. Barnard and Mr. Smiles have produced a dark-ground illuminator in which quartz is used

for the refractive elements and magnalium for the reflecting surfaces. This illuminator can be used either with visible light, for preliminary visual observation, or for subsequent photography, with ultra-violet rays, of the particles thus chosen. The illuminator differs from all hitherto made in transmitting the whole of the primary illuminating beam, and allowing the use of quartz monochromatic objectives of the highest attainable apertures. With ultra-violet rays of a single wave-length, and only short exposures, it has thus been possible to obtain accurate photographic images of objects so small that real images of them cannot be formed by visible light, which can be used only for their provisional identification and location, as a preliminary to ultra-violet photography.

Infectious ectromelia. The nature of the infecting agent was shown by Miss Marchal, who has continued her studies of the immunity acquired by mice which survive an attack. The virus, which is easily maintained by artificial transmission, has proved to be valuable for the study, elsewhere, of certain features of the disease of which it is the cause. Professor Greenwood and Professor Topley have used it for an experimental study of the epidemiology of a virus disease (see p. 117). At the Institute it has provided a convenient and regularly available source of material for investigation by Dr. Barnard and Dr. Elford, who have applied to it the methods just described. A description of the size and morphology of its ultimate units has thus been obtained, probably more complete than any which is yet available for any other virus.

Dr. Elford's experiments show that the virus in an infective organ-extract is allowed to pass freely by one, and completely stopped by another, membrane of his series, proving that the virus is composed of particles which are uniform in size within narrow limits. From the respective pore-dimensions of the membranes he calculated that the virus-particles have a diameter not less than 0·1 or more than 0·15 μ. Mr. Barnard's microscopical methods have revealed, in similar extracts, minute bodies of a uniform diameter of about 0·13–0·14 μ. These have a uniform appearance and are shown in ultra-violet photographs to have the form and aspect of submicroscopic cocci. Some forms have been seen which suggest the manner of multiplication by fission. It is of particular interest that the so-called 'inclusion bodies', which appear in epidermal cells infected with this, as with many other viruses, are closely packed with minute bodies, indistinguishable from those found in the infective extracts made from other organs. From these observations and those of other workers, who have been able to use only direct microscopic examination for identification of the virus particles, and only ordinary bacterial filters, there appears to be no reasonable doubt that this typical virus consists of

definite, self-reproducing organisms, and that these, as has already been remarked, differ from the bacteria visible by ordinary microscopical methods chiefly in being so minute that their diameter is much less than the wave-length of visible light rays. The combined observations by ultra-violet light photography and refined filtration methods have defined more accurately than was possible before the exact shape and size of the particles, and have established their intimate and apparently inseparable connexion with the virus. This conclusion reinforces, with more detailed and definite evidence, the indications obtained in recent years, in other centres and with different viruses, that these also consist of extremely minute organisms. Captain Douglas has co-operated on the biological side throughout the course of these investigations on infectious ectromelia.

Foot and Mouth Disease. Mr. I. A. Galloway has continued his work at the Institute on behalf of the Ministry of Agriculture Committee on this virus disease. Apart from a study of the course of the infection in the cat, he has co-operated with Dr. Elford in a determination of size of the infective units in a number of different strains of the virus. These strains have been adapted to the infection of guinea-pigs, in which species their virulence has been maintained at a uniform level. Three types of the foot-and-mouth virus are known, distinguishable from one another by the fact that recovery from an attack by any one of them leaves the animal immune to renewed infection by that one, but not immune to the others. It had been stated that these types of the virus differ also in the size of their infective particles. Dr. Elford and Mr. Galloway have filtered the virus through the graded membranes, using five strains including the three different types, without finding any evidence for this alleged difference of magnitude. All the strains pass through membranes of pore size down to an identical minimum, which is such as to indicate that the virus particles, in all three types, have the minute diameter of about 0·008–0·012 μ. It will be seen that it is not more than one-eighth to one-twelfth of the estimated diameter of the ectromelia organism. The particles are smaller than those of any other of the viruses infecting animals which have yet been subjected to such measurement. The fact that this estimated diameter is only about three times that accepted for the colloidal aggregate of oxy-haemoglobin in solution raises the interesting question whether particles so minute can be regarded as living organisms. They are certainly far below the range of any method of microscopic demonstration which can yet be foreseen. An account of these experiments is being prepared for publication.

Bacteriophages. These transmissible lytic agents, which cause the disintegration of certain bacteria and are themselves reproduced in

the process, are so similar to acknowledged viruses in their characters that it is difficult to frame a definition of a virus which will not include them. Dr. Elford and Mr. Galloway, in many of their filtration experiments, compared a bacteriophage for the colon bacillus with the foot-and-mouth virus. Some observers have regarded a bacteriophage as a toxic principle in solution and its particles as smaller than those of any true virus. Dr. Elford and Mr. Galloway find, on the contrary, that the bacteriophage which they studied is retained by a membrane which allows the foot-and-mouth virus to pass completely. Its particles are estimated to have a diameter of 0·02 to 0·08 μ. Dr. Andrewes has studied the mode of action of the same bacteriophage on the colon bacillus. The only phase of its action hitherto studied has been the occurrence of actual bacteriolysis—the disappearance of the bacilli into solution. This action of the bacteriophage can be arrested by the removal of calcium ions from its fluid surroundings, and this procedure has enabled Dr. Andrewes to show that addition of an excess of the bacteriophage to a culture of the colon bacillus will kill the organisms with great rapidity, long before any lysis has occurred. Dr. Andrewes has also studied the interaction between the bacteriophage and the antibody contained in the serum of a rabbit artificially immunized against it. Working with Dr. Elford, he finds that the addition of the serum to the bacteriophage, in insufficient quantity to abolish the lytic or dissolving action, prevents the bacteriophage from passing through a filtering membrane, through which either bacteriophage or antibody alone will pass freely. The phenomenon might suggest that the antibody prevents the action of the bacteriophage by some aggregating effect which renders its units too large to enter the bacillus. On the other hand, whereas in the case of several viruses the antibody appears to be ineffective on virus which has once entered and infected a cell, the antibody for a bacteriophage is found, under appropriate conditions, still to arrest the action of bacteriophage which has already become attached to, or has entered, the body of the susceptible bacillus.

Vaccinia. The infective agent of vaccinia, though generally acknowledged to be a virus, could not until recently be obtained in such a form that it would regularly pass a bacteria-proof filter. Using a suitable preparation of the virus, Dr. Andrewes and Dr. Elford have now determined the limits of its filtration through graded membranes with sufficient accuracy to justify an estimate of the size of its units, which appear to have a diameter of 0·125–0·175 μ. There is a strong probability, therefore, that the vaccinia virus will be proved to consist, like that of ectromelia, of submicroscopic organisms. Since the data indicate that these should be somewhat larger than those of ectromelia, it ought to be possible to obtain photographs of them, if they can be obtained in a suspen-

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sion sufficiently rich in the virus and relatively free from other particles. Progress in this direction is being made by experiments in differential filtration, in which Dr. Wilson Smith is co-operating with Dr. Elford. Preliminary trials by Mr. Barnard give promise of a successful demonstration of the living virus in ultra-violet photomicrographs.

Dr. Wilson Smith has succeeded in preparing, from material containing the vaccinia virus, a substance which causes a precipitate when mixed with the serum of an animal immune to the virus and which is stable on boiling. This substance is not itself capable of producing immunity, and some of its properties are similar to those of certain carbohydrates involved in analogous precipitations of visible bacteria.

Viruses affecting the nervous system. Dr. Perdrau has continued his investigations, mentioned in earlier reports, of diseases of the central nervous system characterized by loss of the myelin sheaths in tracts of nerve-fibres. Though in some cases, as in that of the so-called post-vaccinial encephalitis, this follows infection with a known virus, the relation of the nervous disease to the virus is still obscure. Neither the virus of the preliminary infection nor any other, previously latent, which the infection might have aroused to activity, has yet been recovered from the brain after death. Even in the disease of this group occurring in dogs, where attempts at transmission into the same species could be made, no infective agent has yet been discovered. The possibility that a virus may be present, but in a condition rendering it incapable of transmitting an experimental infection, owing to the presence of an antibody or other adverse influence, is still under investigation. Meanwhile, the possibility remains open that the demyelinating diseases are not due to infection of the nervous system with a virus but to conditions of toxaemia and malnutrition associated with the antecedent infection. Professor Mellanby has observed at Sheffield somewhat similar conditions in dogs deprived of vitamin A and subjected to chronic poisoning with ergot (see p. 65); and Dr. Perdrau is co-operating in the neurological study of the results.

Virus of herpes. Last year's Report mentioned Dr. Wilson Smith's observation that passage of the virus of herpes, the cause of a common skin disorder, through the tissue of a glandular organ appeared to change its tissue affinity. It has now been found that the change was due to a quantitative enrichment in virus by the method of passage employed. Using these active preparations of the herpes virus, Dr. Wilson Smith has demonstrated its power of producing specific necrotic lesions in the adrenal glands.

Dr. Perdrau, working with a strain of herpes virus recovered from the brain, and investigating the nature of conditions possibly depressing its infectivity, has made the unexpected observation

that it is completely inactivated by exposure to oxidizing influences and regains its power of infection on subsequent reduction. Taken by itself this finding might appear to give support to the view, held by some authorities, that the herpes virus is an unorganized toxic principle reproduced by the infected cells. Some filtration experiments, however, which Dr. Elford has carried out on Dr. Perdrau's preparations, already indicate that the units of the herpes virus are of a size comparable to that of viruses such as those of vaccinia and ectromelia, which the microscope now shows almost certainly to be distinct organisms.

Dog Distemper. Dr. Laidlaw and Mr. Dunkin have continued their work on dog distemper antiserum, and the results have now been published. It has been shown to be possible to secure a hyperimmune serum of decided potency with fair regularity. Serum of standard quality will protect against distemper in dogs at any stage in the incubation period of the disease. Simultaneous side to side inoculation of serum and virus has been shown to be a satisfactory method of immunizing susceptible dogs. Hyperimmune serum may be concentrated and purified by recognized methods, and the greater bulk of the activity is found to be associated with a small fraction of the globulins of the whole serum. This fraction corresponds closely with the globulin fraction which Felton has described as containing the effective antibody in antipneumococcal serum. The concentrated and purified distemper antibody has given some highly favourable results in the treatment of uncomplicated distemper in privately owned dogs, but its value has yet to be tested on a large series of unselected cases. It seems clear, in any case, that serum treatment can have only a limited value in complicated distemper and in distemper encephalitis.

Efforts are being made to increase the native potency of the serum, and to devise a simpler method of isolating its most active fraction, with a view to the production of a highly active preparation with less labour and cost. The methods already described by Dr. Laidlaw and Mr. Dunkin have provided the basis for large-scale production of anti-distemper serum by the Lederle Laboratories in the United States of America and the Wellcome Foundation in this country.

Inquiry has been made into the after-history of 1,090 foxhounds inoculated in 1928 and 1929 with the distemper vaccine and virus prepared by Mr. Dunkin and Dr. Laidlaw. The results of the inquiry, which have been published, are highly satisfactory. Further reference is made to this on page 113.

Viruses of avian tumours. As mentioned in earlier Reports, the infective cell-free filtrates of avian tumours have properties characteristic of viruses. The chief difficulty in the way of regarding them simply as viruses is their remarkable specificity, not only

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for the particular species of bird bearing the tumour, but for the cell-type of the particular tumour yielding the infective extract. Reference has been made (p. 17) to Dr. Gye's hypothesis framed to explain this difficulty. His attention has more recently been directed to the immunology of these tumour-producing agents; and last year's Report made preliminary mention of two sets of his investigations. Dr. Gye and Dr. Purdy, at the Institute's Farm Laboratories, Mill Hill, have worked with the antibodies that appear in the sera of animals of different species in response to injections of tumour filtrates containing the infective agents. Thus they have produced 'antisera' for the infective agent from a fowl tumour by injecting its cell-free filtrate into a goat or a duck. Concurrently, Dr. Andrewes, at the main Institute, Hampstead, has investigated the natural occurrence, in the sera of birds carrying tumours of the more chronic types, of antibodies for the infective agents extracted from more rapidly growing tumours. Certain results are common to the investigations made by these different methods. In the sera obtained by artificial immunization Dr. Gye and Dr. Purdy find evidence of two kinds of antibodies, each capable of suppressing the infective action. Those of one kind, being absorbed by the tissues of a normal embryo of the species from which the tumour was obtained, are apparently directed against a factor in the infective agent which is specific to the cells of the host. The other antibodies, of which two, acting in different ways, have been detected, have no such relation to cells of the tumour-bearing bird, and are apparently adapted to an extrinsic factor of the infective agent. The antibody found by Dr. Andrewes, in the serum of a fowl bearing a slowly growing tumour, has, naturally, no affinity for the cells of the fowl; but it neutralizes the infective agent in filtrates from other fowl tumours. This antibody appears to be identical in its affinities with one obtained by Dr. Gye and Dr. Purdy, both being specific for some extrinsic constituent of the infective agent, which, considered by itself, has the properties ordinarily associated with a virus.

Both sets of experiments, further, reveal the same immunological identities and differences between the filtrates from different tumours. The viruses from most of the fowl tumours examined, irrespective of their histological types, are serologically identical, being neutralized by the antibodies for the Rous virus and by that obtained by Dr. Andrewes. On the other hand, the fowl tumour discovered by Fujinami, remarkable for the fact that it can be transmitted also to the duck, is shown, in both sets of experiments, to yield a virus immunologically distinct from the others, though the histological character of the tumour is practically identical with that of the Rous sarcoma. Fujinami's discovery of a tumour transmissible from fowl to duck had already shown that the action

of the infective agents is not always, as had been supposed, confined strictly to the species in which the tumour arose. Dr. Andrewes has now produced another example of such interspecific transmission, by showing that a filtrate from the original fowl sarcoma of Rous will produce a similar tumour in the pheasant.

Dr. Gye and Dr. Purdy have incorporated an account of their more recent experiments, together with details of many of their earlier ones, in a book in which they survey the whole problem of the malignant tumours, and expound a theory of the nature of these growths to which they have been led by their work on the bird tumours. Dr. Andrewes is publishing his results in separate technical papers.

Mrs. B. E. Holmes and Mrs. A. Pirie (p. 94), of the Institute of Biochemistry, Cambridge, have continued during the past year their biochemical investigations of the infective filtrates from avian tumours, receiving material for study from Dr. Gye and Dr. Purdy, and working partly in the Farm Laboratories of the National Institute. They have examined the nature of enzymes in tumour filtrates causing spontaneous inactivation, and have published evidence in support of the view that the loss of infectivity is due to an oxidative, and not to a proteolytic action. When the filtrates are purified by absorption, the infective agent, though obtained with a very low nitrogen content, remains liable to spontaneous inactivation, and is apparently associated with the oxidative system. Attempts are being made to concentrate and to separate the antibodies described by Dr. Gye and Dr. Purdy.

Protistology

In continuation of his researches into the protozoa found in the intestines of monkeys and of man, Mr. Dobell has completed his experimental study of *Entamoeba coli* and *Endolimax nana*. The chief result is to show that several known forms of both these species are identical in man and in the macaques, as was previously shown for *Entamoeba histolytica*. The three common intestinal amoebae of man are thus shown to occur naturally in this genus of monkeys. The results are being prepared for publication.

The experimental work with *Entamoeba histolytica*, mentioned in earlier Reports, has given opportunity for studies, still in progress, of the morphology and behaviour of various strains of the organism under different parasitic and cultural conditions. It has already been shown that its life-history can be profoundly modified by the nature of the associated bacterial flora. In cultures, at any rate, encystment can be induced or prevented by appropriate changes of the accompanying bacteria. These phenomena, with their bearing on the life-history and control of this dangerous human parasite, offer problems of great complexity and interest,

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towards the solution of which promising progress has been made.

An intestinal species of *Trichomonas* from macaques has been shown to be capable of living in man, and it seems probable that, as in the case of the amoebae, the same species is common to both. This intestinal flagellate has also been shown to be capable of living in the vagina of *Macacus sinicus*, and this supports the view that the trichomonads of the human intestine and urinogenital organs are really all of one species, though different specific names (*T. hominis* and *T. vaginalis*) have been applied to them. A paper on these flagellates will be published shortly.

Mr. Dobell has also continued his work on the ciliate *Balantidium coli*, from man, and its conjugation in artificial cultures, and has completed his study of the development *in vitro* of another intestinal amoeba, *Dientamoeba fragilis*.

Dr. Ruth Svensson, who has been for some years engaged in a survey of the human intestinal protozoa in Sweden, has spent some weeks in the Institute during the year, for consultation with Mr. Dobell during the preparation of a report on her results.

Properties of Dental Enamel

The study of the permeability of the enamel of teeth by the method of kataphoresis devised by Dr. Laidlaw, as mentioned in last year's Report, has been undertaken by Mr. G. E. S. Jeffery, who is working at the Institute with a whole-time grant under Dr. Laidlaw's supervision. Further reference to this will be made at p. 84.

Animal Individuality

Dr. Todd has continued his experiments, mentioned in earlier Reports, on the chemical differences between the blood corpuscles of individual closely related fowls by means of the isoagglutination test. These individual differences are found to be quite independent of the race of fowls. A 'polyvalent' isoagglutinating serum acting on the cells of a particular fowl of the Plymouth Rock breed agglutinates the corpuscles of other Plymouth Rocks as readily as those from a Dorking or a Leghorn fowl. The individual specificity seems, therefore, to be quite independent of such heritable characteristics as are recognizable in the form and plumage of the bird. The factors determining the individual blood reaction have been further studied. A large family from one pair of fowls contained some members with corpuscles practically indistinguishable by the test, and others which could be sharply differentiated. A pair with closely similar corpuscles were immunized in parallel with corpuscles of a fowl from another family; and after immunization the sera of both were found to be practically

identical in their reactions with the corpuscles from a number of different fowls. Two others, however, from the same family, whose own corpuscles were sharply distinguished by the test, yielded, when both were treated with the corpuscles of a third fowl, sera differing widely from one another in their reactions with the corpuscles from a further series. The affinities of the individual antibody, therefore, depend not only upon the corpuscles injected but also upon the individual character of the particular bird receiving the injection. The point is of theoretical importance as not being covered by any of the existing theories of immunity. Further progress has been made in the study of the inheritance of these individual characters. The offspring from a pair of fowls with indistinguishable corpuscles have been found in all cases to have corpuscles indistinguishable among themselves or from those of either parent. No exception has yet been found to the rule that removal from a polyvalent serum of agglutinins for the corpuscles of both father and mother deprives the serum of action on the corpuscles of any of their offspring.

Apart from the light which it throws on the inheritance of personal characteristics, more subtle than any that can be detected by ordinary methods of observation or measurement, the knowledge gained in these experiments may be of direct practical importance in connexion with reparative surgery by grafts and transplantations. The possibility of preventing the formation of iso-antibodies, which normally hinder the survival of grafts from another individual, remains to be explored.

Immunochemistry of Bacteria

Work on bacteria and their products in relation to biological standards is mentioned elsewhere. Apart from this, investigations are being centred on the separation and chemical characterization of the constituents of bacteria connected with their immunity reactions, and, in some instances, with their pathogenic properties.

Salmonella. The bacteria to which this generic name is now applied include the typhoid bacillus, the paratyphoid bacillus B, the food-poisoning bacteria associated with the names of various discoverers or scenes of outbreak—Gärtner, Aertrycke, Hirschfeld, Newport, &c.—and other less familiar organisms. They are distinguished from one another, when obtained in culture, largely by their specific reactions with artificially produced immune sera—sera which agglutinate suspensions of the entire organisms, or form precipitates with dissolved substances obtained from them by chemical methods. In this way it is becoming possible to recognize constituents in the bacillary bodies, of which some are apparently common to the whole group, while others, by virtue of differences in their intimate chemical structure, are closely 'specific' for one

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or two members of it, as tested by their reactions with immune sera. The chemical nature of several of these 'antigens' and 'haptenes' is already known in general terms, some being complex carbohydrates, of a type shown by recent work to be associated with the finer immunological differences between allied races or species of bacteria, while others are protein substances of different types.

The Salmonella organisms have for some years past been the subject of intensive study by Mr. P. Bruce White. He had previously shown that the type of an organism of this genus found in freshly isolated cultures, in which it retains its pathogenicity and grows in 'smooth' colonies, has a carbohydrate constituent of the type concerned in the specific reaction to agglutinating sera. The type growing in granular or 'rough' colonies, on the other hand, which arises as a variant in artificial culture, has lost this specific carbohydrate, and therewith most or all of its disease-producing qualities. He had earlier supposed that the rough type contained no characteristic carbohydrate; but, confirming an observation of Landsteiner, and by the use of less drastic methods, he has now prepared a carbohydrate 'haptene' from the rough types of many species of Salmonella. This, however, is identical in its reaction with immune sera from whatever member of the genus it has been prepared; it is concerned with an antigenic property common to the whole genus, so that, for example, if it is obtained from a rough strain of the typhoid bacillus, it will produce a precipitate with the serum from a rabbit immunized against the rough strain of any Salmonella. In some cases, however, where a strain has been kept for many years growing in artificial culture, Mr. Bruce White has found certain rough colonies in which the organisms appear to be free from the carbohydrate component common to the genus, as well as from that characterizing the separate species. There is thus an interesting biological series, produced by the abnormal conditions of laboratory culture, from the normal 'S' form, producing smooth colonies, through the intermediate 'R' form, which has lost a specific character, to the degenerate type which Mr. Bruce White terms the 'ρ-form', in which a component responsible for a generic character has also disappeared.

In the course of these observations direct evidence has been obtained for the view that certain of the agglutinin reactions are connected with the carbohydrate haptenes, since the latter in solution, when mixed with sera agglutinating the corresponding organisms, neutralize the action on the bacterial bodies. Further study is now being made of the antigenic proteins of the Salmonella group, and Mr. Bruce White has obtained a new substance of this kind, different from the proteins prepared by other investigators,

and peculiar in the fact that it is readily soluble in strong (96 per cent.) alcohol in the presence of weak hydrochloric acid; it is little soluble in neutral water, but dissolves when the reaction is made acid or alkaline. This so-called 'Q' protein is common to the organisms of the whole genus, and behaves as a complete antigen; but the antiserum prepared by its use agglutinates most strongly the ρ-forms. The complex question of the parts played by these different factors in the ordinary phenomenon of agglutination, as used in routine diagnosis, is under investigation. There is a clear prospect, however, of a restatement in chemical terms of the intricate differences and relations among these organisms, as regards their reactions with immune sera, which till recently could only be expressed by a purely empirical nomenclature.

Tubercle Bacillus. In the case of the tubercle bacillus, the existence of a specific carbohydrate haptene was discovered by Dr. Dudley and Dr. Laidlaw in the National Institute some years ago. Large quantities of the tubercle bacillus have now been grown on a medium composed of chemically pure substances by Captain Douglas; and Dr. Gough has made chemical studies of the bacillus and its products with the advice of Dr. Dudley. The carbohydrate haptene has been prepared by an improved technique from the culture medium and from the bacilli and in sufficient quantity for chemical analysis. By mild hydrolysis Dr. Gough has split it into a mixture of sugars, of which arabinose, mannose, and galactose have been isolated and identified, and a complex sugar acid. Crystalline salts of this acid with an alkaloid have been obtained and are still under investigation. The results suggest that the carbohydrate, as obtained from the organisms or the medium in which they have been grown, may be a mixture of substances having similar general properties. Whether the whole complex, or only one constituent of it, is responsible for the specific property of forming a precipitate with immune sera must be the subject of further inquiry.

Dr. Gough is also examining the protein substances derived from the bacilli, and found in the synthetic culture medium after their removal, with particular reference to their part in the 'tuberculin' reaction. Applying the method of precipitation with picric acid, formerly used by Dr. Dudley in work on the pituitary principles and on insulin, and fractionally recovering the proteins from the picrate with hydrochloric acid and wet alcohol, he has obtained evidence of the presence of two distinct proteins. One of these, from its phosphorus content, is likely to be a nucleoprotein, and the other may be a derivative of it. Both, apparently, have the characteristic tuberculin activity in the intradermal test, used for the detection of tuberculous infection in human beings or cattle.

Johnin. Mr. Dunkin, whose time for this work has been

restricted by a visit to the United States of America on behalf of the Distemper Research Committee, has continued experiments with the object of obtaining the diagnostic reagent from Johne's bacillus in a condition free from non-specific constituents, the presence of which complicates its application in the field. Various synthetic media, and methods of fractional precipitation of the product, are under trial.

Chemical Control of the Circulation

Acetylcholine. The interest aroused by the demonstration that acetylcholine is a natural constituent of various organs of the body, particularly of the spleen of certain animals, and its apparent intervention in the action of the parasympathetic nerves, has led to extensive trial of this substance as a remedy and diagnostic agent in various states of disease, especially of the circulation. The announcement by Kapfhammer and Bischoff, that they could regularly isolate acetylcholine from the perfectly fresh blood of the ox in quantities sufficient, if free in the circulation, to produce an intense physiological reaction, appeared to be highly significant. In a series of experiments, however, many following in exact detail the procedure adopted by the German workers, others with additional precautions to secure the preservation of any trace of acetylcholine that might be present, Dr. Dale and Dr. Dudley have failed completely to detect its presence in the blood of oxen or horses, whether during life or just after death. A friendly interchange of experience having revealed no explanation of the discrepancy, it has been necessary to leave this to the future and to publish the negative finding.

With Dr. U. v. Euler of Stockholm, who visited the Institute with a Rockefeller Travelling Fellowship, Mr. Gaddum has extended the investigation of 'pseudomotor' reactions of parasympathetic nerves, mentioned in last year's Report, to an analogous phenomenon described by Rogowicz, in which a pseudomotor reaction is produced by stimulation of the cervical sympathetic nerve. It has proved to be due to the nerve-fibres which, though they run in this true sympathetic nerve and make connexion with cells in the superior cervical ganglion, produce effects of the type elsewhere produced by parasympathetic fibres as a result of a local liberation of acetylcholine. The results have been published.

Other vasodilator substances. Dr. v. Euler and Mr. Gaddum have shown that the vasodilator effects produced by the extracts of certain organs, and particularly by those made from intestinal plain muscle or the basal nuclei of the brain, are only partly accounted for by the known vasodilator substances histamine, acetylcholine, and adenosine. Another active substance has been recognized by its physiological effects, and an approximate

separation of it has been effected, though it has not yet been isolated or chemically identified.

Control of Liver Circulation. Mention has been made in earlier Reports of experiments showing that the circulation through the liver is controlled by nervous and chemical influences causing variations in the rate at which blood flows into the organ, and, by an independent mechanism, of the rate of its outflow. These were begun some years ago by Dr. Dale with Dr. Bauer and Dr. Dickinson Richards from the United States. They have been resumed, after an interval, with Dr. L. T. Poulsson of Oslo, who spent part of the year at the Institute, and the results are now being published in full. Dr. P. Holtz of Greifswald, who has worked at the Institute with a Rockefeller Travelling Fellowship, has been able, by use of the same methods, to find an interesting participation of the post-pituitary gland in this control of the liver circulation.

Surface Tension Phenomena

A method has been described by Mr. Gaddum for measuring the surface tension of solutions and for following the progressive changes of tension which occur after the formation of the surface film. The apparatus, which is simple, allows such measurements to be made with only a fraction of a cubic centimetre of solution. Apart from the practical use which the method may have for measuring the surface tension in small samples of body fluids, for physiological and medical purposes, the observations made have a wider interest. It was found that stretching of the surface of a solution such as that of saponin causes changes suggestively similar to those in a stretched muscle. The phenomenon of 'after-extension', known in the study of muscular contraction, may have its cause in the properties of internal surfaces in the muscle-fibre.

Intermediary Carbohydrate Metabolism

The now well-known discovery of Lundsgaard, that the muscles of animals poisoned with iodoacetic acid contract without the usual production of lactic acid, raised the question of the link in the chain of carbohydrate metabolism at which this interruption occurs. The tissue-enzyme glyoxalase, discovered by Dakin and Dudley, produces lactic acid from methylglyoxal, which is a possible intermediate between glycogen and lactic acid. Dr. Dudley has found that iodoacetic acid has, indeed, a powerful and specific inhibiting action on this enzyme; and the observation supports the suggestion that the action of glyoxalase on methylglyoxal may be an essential stage in the normal carbohydrate changes in muscle. The details have been published.

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Relation of Gases to the tissues of the Body

Dr. Argyll Campbell has developed, in several different directions, his studies of the gas tensions in the body tissues.

Deep Diving. At the request of the Deep Diving Committee of the Admiralty he has co-operated with Sir Leonard Hill in finding the rate of saturation of the fatty bone-marrow of animals (goats) subjected to varying high air pressures. The results give valuable information as to the precautions needed in bringing back to the normal air pressure divers who have been at great depths in the sea for different periods.

Tissue oxygen and Tetanus.. With Dr. P. Fildes (p. 108) he has studied the effects of varying the oxygen tension in the tissues of an animal upon the germination of injected spores of the tetanus bacillus. The proportion of animals in which germination occurs is reduced by exposure to air greatly enriched with oxygen, and increased by keeping the animals in air deficient in oxygen, or by treating them with carbon monoxide in concentrations which they can tolerate.

Effects of Drugs. An interesting contrast has been noted between the actions of ephedrine and adrenaline, in many directions so similar. A hypodermic dose of ephedrine is found to cause a slight fall in the carbon dioxide tension and slight rise in the oxygen tension of the tissues; adrenaline raises the tension of carbon dioxide and lowers that of oxygen.

Gas Treatment of Cancer. It had been claimed by Fischer-Wasels, in Germany, that exposure to a gas mixture of 95 per cent. oxygen and 5 per cent. carbon dioxide, combined with administration of certain chemicals and radiation with different rays, caused complete disappearance of malignant tumours in 50 per cent. of the animals treated. The experiments have been repeated with a transmissible mouse carcinoma without any confirmation of the alleged deterrent effect of the gas mixture, with various chemicals, on the growth of the tumours. The preparation from parathyroid gland, stated by Thompson to contain a growth-retarding hormone, was tested incidentally, by itself and in association with the Fischer-Wasels gas mixture, without any evidence of an effect on the growth of the mouse tumour being obtained. Of methods hitherto tried, the only one that definitely retards the growth of the transmissible tumour is exposure of the mice to carbon monoxide in quantities enough to lower the oxygen tension of the tissues.

Vitamin D.

Reference has already been made to the identification of ergosterol as the parent substance of the anti-rachitic vitamin D by Dr. Rosenheim and Mr. Webster at the Institute. A group of

workers at the Institute have been continuously engaged in investigating the process by which vitamin D is thus produced under the action of ultra-violet radiations of certain wave-lengths, with the ultimate aim of preparing the vitamin itself in pure form, and examining its chemical nature. Subsequent Reports have dealt briefly with stages in the progress of this work, of which more detailed accounts have also been published. The problem has aroused a world-wide interest, and investigations with the same object have been concurrently undertaken in several other countries: of these may be specially mentioned those made in Göttingen under Prof. Windaus, and those made by Reerinck and van Wijk in Holland. The investigation involves unusual difficulties and complexities. Ergosterol, though now easily obtainable in large quantities, is, like other sterols, very difficult to purify from accompanying substances of a similar kind. The different parts of the ultra-violet spectrum differ in their efficiency in producing the vitamin from ergosterol; they also produce other substances, of different kinds and in different proportions, in the total irradiation product. They differ also in the rates at which they effect a further conversion, into an inactive substance, of the vitamin which is first produced. Other changes leading to loss of vitamin, and addition of impurities, occur if oxygen is not elaborately removed from the irradiated solution, and if the products of irradiation are not carefully protected from its action. The product, under the best conditions, is a mixture, and new problems are met in the separation of its sensitive constituents. The preparation by such methods, and isolation from such a mixture, even of a substance easily recognized and measured by a characteristic chemical reaction, would present serious difficulties. The attempt to isolate the vitamin D has been met besides these by a more formidable difficulty, in the fact that the vitamin could only be certainly recognized and measured, in fractions separated from the mixed product, by a laborious and relatively inaccurate biological test, though spectrographic measurements might give an additional check. There was, moreover, a possibility that more than one derivative of ergosterol contributed to the anti-rachitic activity of the total product. The whole course of the search, accordingly, has involved a series of contributory studies of different kinds, often involving the design and construction of special apparatus. One such research was undertaken to improve the biological measurement of anti-rachitic activity. A method was evolved in which X-ray photographs of the rachitic joints, before and after treatment, were assessed by comparison with a standard series of skiagrams, representing degrees of rickets of graded severities. A detailed account of this, with a statistical evaluation of the accuracy of measurement attainable with it, and a full examination of the precautions and

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controls needed in its application, has been published during the year. The procedures used in purifying the ergosterol, irradiating it in solution in the complete absence of oxygen, and separating the anti-rachitic constituent from the mixed product, have required the regular and close co-operation of physicist, physical chemist, and organic chemist, with other workers giving their whole attention to the breeding, dieting, and dosing of large numbers of experimental rats for the estimation of the curative results produced by the different fractions. A team of investigators was accordingly required, and during the past year the following have been engaged in this work, under the general leadership of Dr. R. B. Bourdillon: Mr. T. C. Angus, Mr. F. A. Askew, Miss H. M. Bruce, Dr. R. K. Callow, Miss C. F. Fischmann, Mr. J. St. L. Philpot, and Mr. T. A. Webster. The following items contributory to the main investigation may be mentioned. Dr. Callow worked on the purification of the parent substance, ergosterol, and by benzoylation and fractionation of the resulting esters succeeded in freeing the approximately purified ergosterol from a substance which ordinary methods fail to remove. The latter was obtained pure and identified as α-dihydroergosterol, and its removal enabled ergosterol of high and constant purity to be obtained. For the more rapid measurement of ultra-violet absorption spectra, a new type of photo-electric microphotometer has been devised by Dr. Bourdillon and Mr. Philpot. Dr. E. Schuster, as on so many earlier occasions, has rendered invaluable voluntary service to his colleagues at the Institute by constructing the instrument and fitting it with numerous and ingenious mechanical accessories. It is estimated that the new instrument will effect a fivefold increase in the speed of performing the very numerous measurements of this kind which the work on vitamin D demands.

Mr. Philpot has also designed a new type of spectrograph, the construction of which is again being undertaken by Dr. Schuster, while the Research Department of the Air Ministry have given valuable help by allowing the accurate logarithmic stop required by the instrument to be made in their workshops.

There is good reason to hope that the main object, that of isolating the Vitamin D as a chemical entity, has now been achieved. Professor Windaus with his co-workers has again arrived at the same point as the group at the National Institute, at about the same time but by a different route. In a paper published early in June, Dr. Bourdillon and his associates described a crystalline anti-rachitic substance, having many properties suggesting a single compound, which they had obtained by fractionally distilling in a high vacuum the mixture of products which ergosterol yields on irradiation. They provisionally named this substance 'calciferol', with reference to its characteristic activity,

though they clearly foresaw that it might contain a proportion of inactive material. At the end of the same month Professor Windaus, visiting London for the International Vitamin Conference, brought with him and described a crystalline substance, which he had obtained from the mixed irradiation products by a selective chemical reaction, and which he has later referred to as 'Vitamin D_1'. The two substances were closely similar in many properties, including their anti-rachitic activities, but differed rather widely in their effects on polarized light. Neither was much more active than the best samples of mixed irradiation products from which it was obtained.

The next step was again taken by different methods in the two laboratories. At the National Institute Dr. Callow discovered that the dinitrobenzoyl esters of the sterols of this group are distinctive compounds which crystallize well; and, by good fortune, two esters which were obtained from the distilled calciferol had crystals differing both in shape and colour, so that they were separated without difficulty. One of them yielded a sterol having about twice the anti-rachitic activity of the most potent substance hitherto obtained, and to this, accordingly, the name calciferol has now been applied. The other ester gave an inactive sterol, which the heat used in distillation had formed from calciferol; and this was accordingly named 'pyro-calciferol'. The suspicion that the original preparation contained inactive constituents was confirmed, though the proportion in which these have proved to be present is greater than had been expected. It was then possible to obtain the ester of calciferol free from the inactive product of heat, directly from the original irradiation mixture, without preliminary distillation. Meanwhile Dr. Linsert, working in association with Professor Windaus, had obtained, by an entirely different method, another active substance, which they termed 'Vitamin D_2'. They had not at first observed that this new substance was much more active than the earlier Vitamin D_1, but comparison soon established its identity with the pure calciferol. Professor Windaus was then able, by means of Dr. Callow's method of obtaining the dinitrobenzoyl esters, to separate his vitamin 'D_1' into vitamin 'D_2' (=calciferol) and another sterol, presumably inactive. The special tendency of these sterols to crystallize together as molecular compounds had produced obvious points of similarity in the experience of the two groups working independently, and, up to the final stage, by entirely different methods.

As the evidence now stands, there seems good reason to believe that the substance calciferol (or vitamin D_2) is the true anti-rachitic vitamin in practically pure form. The evidence, indeed, would be regarded as conclusive for most substances, but growing experience of the peculiar difficulties of the sterol group imposes

an unusual caution. Calciferol itself, and the different inactive concomitants that so readily crystallize with it, all appear to have the same empirical formula as the parent ergosterol. They must differ from it, and from one another, in the details of molecular structure, and these offer a problem of much interest, though of great difficulty, for future investigation.

Chemotherapy

Dr. King and Dr. Cohen have continued to investigate the relation between the structure, the physical and chemical properties, and the therapeutic activity in experimental trypanosome infections, of new organic compounds containing arsenic. The biological work has been done by Miss Strangeways. Work with Dr. Gough had previously shown that benzamide *p*-arsonic acid has a promising therapeutic action, and the preparation and testing of numerous allied amides has failed to show superior activity among these analogous derivatives of arsonic acid. The data obtained, however, have enabled important generalizations to be made as to the mode of action of arsenicals, and the effects on it of changes in structure which modify solubility. Valuable evidence for this purpose has been obtained from histochemical observations by Miss Strangeways, with parallel microchemical determinations of arsenic in the different tissues. In the preparation of nicotinic acid, with a view to the synthesis from it of certain arsenical compounds, Dr. King and Dr. Gough had formerly obtained an undescribed by-product. The structure of this, which they have now determined, shows it to have unusual interest from a purely chemical point of view, as its formation involves a nuclear conversion hitherto unknown.

LIBRARY AND PUBLICATIONS DEPARTMENT

During the year 552 bound volumes have been added to the Library. The additions include: *Annales de l'Institut Pasteur*, volume 6, 1892, completing the series except for volumes 2, 3, 4, and 5; *Journal of Clinical Investigation*, starting with volume 1, 1924–5; *Zeitschrift für physikalische Chemie*, Series B, starting with volume 1, 1928, and also three volumes by J. L. W. Thudichum given by Dr. Rosenheim, namely, 'A Treatise on the Pathology of the Urine, including a complete guide to its Analysis', 2nd edition, 1877, and the author's own copies of 'Grundzüge der anatomischen und klinischen Chemie', Berlin, and 'Die chemischen Konstitution des Gehirns des Menschen und der Tiere', Tübingen, 1901. These three volumes, together with three others by the same author, which the Council owe to the generosity of Dr. Rosenheim on previous occasions, form an interesting collection.

The Council welcome this opportunity of thanking Lady Murphy

for her voluntary help and continued interest in the Library. They also thank those who have kindly given books, periodicals, and reports:

Basic Science Research Laboratory, University of Cincinnati; Sir Henry Dale; Mr. C. Dobell; Captain S. R. Douglas; Dr. Dubreuil; Dr. H. W. Dudley; The Eugenics Society; Mr. I. A. Galloway; Mr. Stephen Gaselee; Mr. O. J. R. Howarth; Dr. P. P. Laidlaw; Medical Officers of Health, Aberdeen, Birmingham, Glasgow, Jersey, Newcastle-on-Tyne, Paddington, Preston; Merck & Co.; Metropolitan Water Board; Mond Nickel Co.; National Research Council of Japan; Neurological Institute of New York City; Registrars-General, Northern Ireland and Scotland; Dr. O. Rosenheim; Sir Charles Sherrington; Prof. C. R. Stockard; United Fruit Co., Boston, Mass.; Mr. P. Bruce White; and Miss H. Woods.

Approved persons engaged in medical research are allowed free use of the Library by arrangement with the Librarian.

The Library Committee are glad to receive offers of books and periodicals, and the Librarian will forward a list of desiderata on request.

The publication of the *System of Bacteriology*, to which earlier reference has been made at p. 25, has been completed, and such information as has been received about sales has been most encouraging and indicates that the work has been widely welcomed by bacteriologists. Ten numbers of the Special Report Series have been issued (Nos. 150–159), and one report of the Industrial Health Research Board (No. 62). Assistance has been given, as in previous years, in the sorting and indexing of *Physiological Abstracts*.

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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

Recent Annual Reports have mentioned the increasing volume of investigations made by the Institute, and the growing responsibilities of the staff, in connexion with the Standards for the important remedies that can be tested and standardized only by biological means. Several systematic surveys have been undertaken during the year by Dr. Hartley, with Dr. Wilson Smith and Miss Marchal, of the different brands, on sale in this country, of certain of the substances scheduled under the Therapeutic Substances Act. Sterilized surgical catgut may be mentioned as an example of a substance thus subjected to scrutiny during the past year with a view to finding the effects of the control, first applied to it in 1930. The results indicated that the regulations made to control its sterility are, in general, being effectively applied. They revealed at the same time, in several cases, the need for their enforcement.

A large part of the work, however, has been undertaken in preparation for the meeting of the Permanent Commission on Biological Standards (Health Organization of the League of Nations), held in London at the end of June. With this meeting were associated technical Conferences dealing respectively with standards for sera and bacterial products, and with standards for the vitamins. For the former, Dr. Dale, as British representative on the Commission, had accepted for the Institute the task of organizing international investigations of the standard for gas-gangrene (perfringens) Antitoxin, and of the diagnostic test dose of diphtheria toxin (Schick test). The Institute also co-operated with the Council's Committee on Accessory Food Factors in organizing international trials of preparations suitable as standards for vitamins A, B_1, and D, with a view to their consideration by the Conference on vitamin standardization.

Dr. Hartley and Mr. Bruce White, as reported last year, had already prepared in dry, stable form a quantity of an antitoxin for the toxin of *B. welchii* (perfringens), and had accurately determined its value in terms of the U.S.A. unit. For the international trial they prepared a supply of the corresponding toxin in dry form. They investigated the properties of the toxin, and found improved methods for its preparation in a relatively pure and highly active state, which are being published. Samples were

distributed to seven experts in five countries, together with samples of the U.S.A. standard and of an antitoxin of unknown strength. Reports from the different centres were received, analysed, and presented to the Conference by Dr. Hartley. The results so clearly demonstrated the high degree of accuracy obtainable with the method of assay suggested, and showed such a remarkable concordance among the estimates made by the different participants in the trial, that the Conference had no hesitation in recommending the international adoption of a standard and unit for this serum, based on those already used in the U.S.A. An offer was made to put at the disposal of the international organization a substantial quantity of the dried standard antitoxin prepared by the Institute. This was accepted by the Permanent Commission, and the material will be held and distributed for international use by the State Serum Institute, Copenhagen, under Dr. Th. Madsen, President of the Permanent Commission and of the League of Nations Health Committee. Meanwhile the preparation of this standard, and the verification of its value, had enabled the Licensing Authority under the Therapeutic Substances Act to include in its revised Regulations, made in July, a schedule dealing with this serum, and the first issue of the standard therein defined has already been made. This serum, the value of which was first shown in the treatment of grossly infected wounds during the war, has now a promising application in abdominal surgery; the official prescription of a standard and unit for the measurement and indication of its activity, having an international validity, should further enhance its value in practice.

Dr. Hartley also organized the distribution, to eleven investigators in eight countries, of two samples of diphtheria toxin for use in the Schick test. They were chosen, with the valuable co-operation of the Wellcome Laboratories, as differing widely in constitution, so that their comparative trial would produce evidence as to the relative merits of the methods used in the United States and in England, respectively, for finding the standard dose to be used in the test. The results were again collected and analysed by Dr. Hartley, and the Conference recommended the acceptance, for international use, of a definition embodying the tests already officially prescribed for this country under the Therapeutic Substances Act.

Dr. Hartley also co-operated in a preparatory investigation, organized by Dr. Madsen, on the methods of standardizing the antigenic potency of preparations used in active immunization against diphtheria. The results of these trials, as considered by the Conference, enabled the Permanent Commission to frame a programme of further research with a view to an international standard.

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Before the Conference on Vitamins the Institute distributed three preparations, to fourteen investigators in seven countries, for trial of their suitability as standards. These were: (1) the oily solution of irradiated ergosterol, earlier prepared at the request of the Accessory Food Factors Committee, and already for some months in use as a provisional standard for vitamin D in research institutions and manufacturing laboratories of this country and in some abroad; (2) a preparation of carotene, specially purified by Dr. Dudley and Dr. Rosenheim, and sealed in ampoules completely freed from oxygen, for trial as a standard for vitamin A; and (3) a dried adsorption product, on Fuller's earth, of the active constituent of rice polishings, supplied by Professor Jansen of Amsterdam, for trial as a standard for Vitamin B_1.

The International Conference, of which Professor Mellanby of Sheffield was Chairman, and Dr. Harriette Chick and Dr. W. R. Aykroyd of the Lister Institute were co-secretaries, fully considered the reports from the different investigators. They unanimously decided to recommend the adoption (in some cases for a period of two years in the first instance) of preparations similar to those submitted for trial, as international standards for the respective vitamins, and the definition, in terms of each standard, of an international unit of the activity of the corresponding vitamin. They further recommended that the National Institute for Medical Research should be requested to act for this purpose, on behalf of the League of Nations Health Organization, as the central laboratory for the preparation of two and preservation of all three of these standard preparations, and for their distribution to the different countries requiring them. The Institute accordingly has accepted, with regard to these new standards for the vitamins, a responsibility similar to that which it holds already in relation to the international standards for insulin, digitalis, strophanthin, and certain organic arsenical preparations. This is in addition to its task of preparing and maintaining for this country all the standard preparations required for substances scheduled under the Therapeutic Substances Act, and its prospective similar function in relation to certain requirements of the new British Pharmacopoeia, now in preparation.

Insulin. Mr. Marks during the year has brought under review the correctness of the unit values indicated for the different makes of insulin available in this country. In certain cases the control tests, against the official standard preparation, gave results showing definite, though not serious, differences from the labelled strengths. These discrepancies were found, in each case, to be attributable to the strength assumed for the subsidiary standard used by the manufacturer, and suitable corrections were made. In the course of these tests further evidence was obtained as to

a small discrepancy, long suspected, between the results got by the principal current methods of testing insulin—the test based on hypoglycaemia in mice, and that based on blood-sugar changes in rabbits—when the highly purified insulins, now produced in manufacture, are compared with the relatively impure dried material, which still serves as the international standard on which the unit is based in all countries. The discrepancy, if it exists, is small enough to be easily concealed by the range of the error to which both forms of test are liable. For its certain detection a large number of parallel tests are required, with a statistical examination of the results. To gain more exact information, visits have been exchanged by Mr. Marks with Mr. Hemmingsen of Copenhagen. They have accumulated a large array of data in collaboration, and will join in an analysis of the results. If the reality of this suggested difference is established, it will be desirable to accelerate action for the replacement of the insulin standard, prepared in 1924 at the Institute, and still kept there for distribution, by a new standard, made from insulin of the high purity now easily attainable.

The issue of the new Regulations under the Therapeutic Substances Act has raised the question whether insulin solutions without artificial disinfectant are capable of acting as culture media and so permitting the growth of bacteria. This was investigated by Dr. Hartley, who found that the acidity prescribed for such solutions is by itself lethal for staphylococci, but that, when neutralized or made slightly alkaline, as it may be during the withdrawal of repeated doses in practical use unless precautions are taken, the insulin solution becomes a favourable culture medium for organisms that may have been accidentally introduced. The details have been published, and have provided a basis for an official warning that has been issued.

Thyroid preparations. Mr. Gaddum and Miss Hetherington have published the results of their estimations of the activities of a series of preparations of thyroid gland, comparing them with chemical estimations by Dr. Harington of the content of thyroxin. The biological measurements were made from continuous records of the respiratory metabolism of mice, to which the different preparations were given by the mouth. The two sets of results showed a general correspondence, but some exceptions showed the possibility that thyroxin may sometimes be present in a form not readily absorbed from the alimentary canal.

Other standards. Mr. Gaddum has also done work preparatory to the adoption of a standard tincture of strophanthus, and a standard strophanthin, which are to be maintained at the Institute to meet the needs of the forthcoming new British Pharmacopoeia.

The investigations and tests required in relation to standards

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are done, not by the staff of an isolated department, but by members of the general research staff, each having also his own field of independent research. Their work in relation to standards is under the general control of Dr. Hartley for purposes of organization. For him, and for the Director of the Institute, these national and international duties also entail much work of an administrative and advisory kind. Experience, however, continues to support the view that the studies needed in connexion with standards and their application are better made by workers taking an active part in researches over a wider field, than by those in whose hands the work might tend to follow an unprogressive routine. On the other hand, a share in research into standardization problems gives valuable experience in methods of quantitative precision, and in the statistical evaluation of results; it not infrequently gives points of departure for advances in knowledge of a more fundamental kind.

The National Collection of Type Cultures

The National Collection of Type Cultures continues to be accommodated at the Lister Institute of Preventive Medicine, London, by the courtesy of the Governing Body. Dr. R. St. John-Brooks and Miss M. Rhodes, both in the whole-time service of the Council, continue to act as Curator and Assistant Curator respectively.

During the year 1930–31 over 200 strains were added to the Collection, and over 5,000 cultures were distributed to workers at home or abroad.

Among the types added to the Collection were the following:

Salmonella: 'Bombay', 'Tokyo' and 'Moscow' types from Dr. W. M. Scott, Ministry of Health; 'Potsdam' or 'Brandenburg' types from Dr. Fritz Kauffmann, Institut für Infektions-krankheiten 'Robert Koch' Berlin; and 'Bareilly' type from Major Bridges, R.A.M.C.

B. polymorphus-suis isolated by Dr. H. Magnusson, Malmoe, Sweden, from focal necrosis in kidney of pig.

B. felsineus, flax-retting, butyl-alcohol-forming organism, from Dr. A. C. Thaysen, Royal Naval Cordite Factory, Dorset.

B. macerans from Prof. A. J. Kluyver, Technical High School, Delft, Holland.

Actinomyces somaliensis isolated from case of mycetoma at the Wellcome Tropical Research Laboratories, Khartoum.

Actinomyces madurae isolated by Dr. F. Marsh, Anglo-Persian Oil Co., Persian Gulf, from case of mycetoma.

B. lactis-viscosus, cause of 'ropy' milk, from the American Type Culture Collection.

B. pseudotuberculosis-rodentium isolated by Prof. Krishnamurti, Madras Veterinary College, from bovine lymphangitis.

Actinomyces asteroides isolated by Prof. W. J. Tulloch, University College, Dundee, from a fatal human case.

B. erysipelatis-suis from polyarthritis of lambs, from Dr. Seddon, Government Research Laboratory, New South Wales.

Pseudomonas solaniolens isolated from internal rust spot of potato by Dr. G. S. Paine, Imperial College of Science, London.

Periconia felina, isolated from English soil, from Mr. C. G. C. Chesters, Botany Department, Birmingham University.

Organism of pleuropneumonia of cattle from Dr. P. P. Laidlaw, National Institute for Medical Research.

B. purifaciens isolated by Dr. H. Magnusson, Malmoe, Sweden.

B. morax-axenfeld from Dr. D. Thomson, Pickett-Thomson Laboratories, St. Paul's Hospital, London

Salmonella abortus-ovis from Dr. Fritz Kauffmann, Berlin.

Pseudomonas malvacearum from the Wellcome Tropical Research Laboratories, Khartoum.

Collection of microfungi from Mr. W. H. Wilkins, Department of Botany, Oxford University.

B. alvei and *B. orpheus*, isolated from foulbrood of bees, from Dr. A. G. G. Lockhead, Dominion Agricultural Bacteriologist, Ottawa, Canada.

Cultures of microfungi from Central Bureau voor Schimel-cultures, Baarn, Holland.

Leishmania species from Dr. S. Adler, Hebrew University, Jerusalem.

Cultures of *Neisseria intracellularis* from Dr. W. M. Scott, Ministry of Health.

Salmonella eastbourne, from Mr. Patrick H. Leslie, Standards Laboratory, University of Oxford.

Streptococcus from strangles abscess in horse, from Prof. Tom Hare, Royal Veterinary College.

Leuconostoc mesenteroides and *L. dextranicus* from Dr. G. Hucker, N.Y. Agricultural Experiment Station, Geneva, U.S.A.

For all these donations the Council desire to make their grateful acknowledgements.

During the summer of 1930 the hospitality of the department was given to Miss Blodwen Lloyd of the Royal Technical College, Glasgow, for work on denitrifying organisms. Dr. A. Felix and Miss Rhodes have completed their studies of the serological varieties of typhus fever.

A new edition of the catalogue of the Collection, revised and greatly extended, was published in June 1931.

'Catalogue of the National Collection of Type Cultures.' *Spec. Rep. Ser. Med. Res. Coun.*, Lond., No. 64, Third edition, 1931.

R. St. John-Brooks and M. Rhodes—
'A List of the Fungi &c. maintained in the National Collection of Type Cultures, 1930.' *Trans. Brit. Mycol. Soc.*, 1930, **15**, 155.

A. Felix and M. Rhodes—
'Serological Varieties of Typhus Fever.' *J. Hyg.*, Camb., 1931, **31**, 225.

The Standards Laboratory, Oxford

The work of producing standardized suspensions and sera for the diagnosis of enteric, dysenteric and *Brucella* infections has been maintained at the Standards Laboratory, in the Institute of Pathology, University of Oxford. In this Dr. A. D. Gardner has the assistance of Miss E. F. Stubington, both of them being in the whole-time service of the Council. Valuable help has also been given from time to time by Mr. P. H. Leslie, who has been collaborating with Dr. Gardner in researches in whooping-cough, with a part-time grant from the Council (p. 112).

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Some changes have been made in the methods of issuing agglutinating sera, to make their manipulation easier. A constant 'titre' of 1 in 250 is used, and a more convenient type of phial. The output of the Laboratory has shown a large increase, of about 16 per cent., over that of the preceding twelve months.

Dr. Gardner and Miss Stubington have investigated the development of agglutinins for the heat-stable or 'O' antigen in paratyphoid fever, and their results will soon be published.

To meet a need that became urgent during the recent epidemic of cerebrospinal meningitis, the Laboratory has undertaken the preparation of type-agglutinating sera for the meningococci, and these are now ready for issue. This has involved much experimental work, related to the significance and identity of Gordon's four 'types', which are still subjects of controversy. Great help has been given by Dr. M. H. Gordon, by Dr. W. M. Scott of the Ministry of Health Laboratories, and by several officers of the Royal Army Medical College. These have provided cultures of various types, sera, and practical advice.

P. H. Leslie and A. G. Shera—
'A New Serological Type of Salmonella.' *J. Path. Bact.*, 1931, **34**, 533.

IV. THE DEPARTMENT OF CLINICAL RESEARCH, UNIVERSITY COLLEGE HOSPITAL, LONDON

Sir Thomas Lewis continues to give whole-time service to the Council as Director of the Department, and in this he has been assisted during the year by Dr. R. T. Grant, Dr. W. H. Craib, and Dr. G. W. Pickering, all full-time workers in the same service. Dr. W. H. Craib resigned his post early in the year to return to South Africa, and Dr. E. J. Wayne of Leeds has recently been appointed by the Council as a full-time worker in the department. Dr. E. F. Bland (Virginia), Dr. E. M. Landis (Boston), Dr. P. Rothschild (Frankfürt a/Main), Dr. K. E. Harris, Mr. J. H. Bentley, and Mr. P. H. Himsworth (all of London) have been attached as voluntary workers for various periods during the year.

Observations upon the peripheral circulation, and especially upon disturbances of this seen in patients, have continued during the year. Sir Thomas Lewis, with Dr. Landis, has investigated acrocyanosis and concludes that this condition is due not to obstruction on the venous side as some have thought, nor to structural change, but essentially to obstructive spasm in the arterioles of the affected area of skin. The spasm is shown to be brought about locally, and is not due to increased vasomotor tone. Dr. Landis has extended his readings of micro-capillary pressure to Raynaud's disease and has been able to show that, during the stage of spasm, the capillary pressure is low. The pressure rises, however, when the veins of the arm are deliberately congested, and falls abruptly when this venous pressure is abruptly released. These observations supplement previous evidence that the obstruction in Raynaud's disease lies on the arterial and not on the venous side.

Supplementary observations on the reactions of the vessels of the human skin to cold have been made by Sir Thomas Lewis. The relative cooling of different parts of the skin of the hands and face in subjects exposed out of doors has been ascertained, and the expectation realized that the degree to which a part cools corresponds in general with its susceptibility to maladies attributable to cold, such as frostbite and chilblain. It has been shown, further, that the vasodilatation which occurs as a local response to considerable cooling in laboratory experiment, also occurs under more natural conditions of cooling out of doors; the reaction therefore tends, in natural circumstances, to guard exposed parts from injurious cooling. The reaction is more certain if the body as a whole is kept warm.

Sir Thomas Lewis and Dr. Landis have published a long series of observations upon a type of Raynaud's disease complicated by

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scleroderma. These observations show that, as in uncomplicated Raynaud's disease, the vascular defect is a local one and is not brought about by vasomotor influences of the nervous system. Special tests applied to the living subject indicate that in many cases of Raynaud's disease structural change has occurred in the digital vessels, a change that contributes to the circulatory manifestations of the disease.

A report has been made by Sir Thomas Lewis upon cases of angina pectoris of a peculiar type, in which the blood-pressure and the pulse-rate rise during the attacks of pain. It has been found that the pain in these attacks succeeds the circulatory disturbance and does not cause it; at the same time there seems to be no precise relation between the work of the heart and the occurrence of pain in the attack, which indicates that the coronary vessels of the heart themselves participate in the general vasomotor storm. This form of angina is particularly susceptible to the action of amyl nitrite; the effects of the drug are not to be ascribed to simple lowering of blood-pressure, but in part, if not in chief part, to dilatation of the coronary vessels. This type of angina is contrasted with the totally distinct 'vasomotor angina' described by Nothnagel.

Sir Thomas Lewis, Dr. Pickering, and Dr. Rothschild have investigated the production of a variety of pain associated clinically with 'intermittent claudication'. They have been able to reproduce a precisely similar pain by exercising a normal limb with its circulation arrested, and to show that vascular spasm, often regarded hitherto as the cause of the pain, does not occur. They have found that the times of beginning and intolerance of the pain are remarkably constant under given conditions of exercise. Using these times as indices, they have shown that the stimulus to pain is related to the amount of exercise undertaken, and that the severity of the pain continues unchanged if exercise is stopped but the circulation remains arrested. On the basis of these and other facts, they put forward the hypothesis that the stimulus to pain is a chemical or physico-chemical one arising from muscular contraction. Further observations and analysis have shown that the stimulus to pain acts in the tissue spaces, and that events occurring within and without the muscle fibre must be considered separately. The cumulative process occurring in the working muscle fibre occurs whether the circulation is free or arrested, but only when the circulation is arrested or is inadequate does the stimulus concentrate in the tissue spaces sufficiently to give rise to pain.

The observations are of interest in strongly suggesting that pain arising spontaneously in the human body may result primarily from a chemical or physico-chemical stimulus. The explanation obtained, though first applicable to pain occurring in somatic

muscle, is clearly relevant also to that of angina pectoris, a point which it is hoped to develop later.

Dr. Grant has studied the reactions of arteries in the intact animal to various mechanical and chemical stimuli, using for this purpose the rabbit's ear, where the vessels can be directly observed. He has found that the arteries respond to increasing degrees of mechanical stimulation of the overlying skin by increasingly complex local reactions. While some of these reactions are attributable to the action of a histamine-like substance released from the tissues by injury, others cannot be explained in this way, as, for example, the transient dilatation in response to light touch. The vascular reaction to injury is essentially the same as that in human skin, though the flare is much less distinct and more limited in extent; an extract of rabbit's skin was found to contain a histamine-like substance which called forth the same vascular responses as histamine itself. The effect of histamine on the arteries differs according to the size of the vessel examined; applied to the larger arteries, histamine caused constriction followed by oscillations in calibre, while applied to the smaller arteries it produces dilatation alone; these reactions are independent of the nervous system.

In the course of these observations Dr. Grant also noticed, in the living ear, relatively large direct communications between the arteries and veins, and he has since studied their response to different stimuli. These observations are of interest, for, although arterio-venous anastomoses have been recognized anatomically for many years in the peripheral regions of man and of several animals, they have not so far been observed during life, and there has been no conception of their function based on experiment. By use of a special method of intravascular staining after fixation, the channels can be demonstrated readily and clearly in microscopic preparations of the ear, where they are very numerous. Dr. Grant has found that these communicating channels dilate under the influence of mechanical stimulation, of histamine or of acetylcholine, while adrenaline constricts them. They contract vigorously and quickly under the influence of the sympathetic nerves; moreover they are shown to possess an unusually rich supply of these nerves. Dr. Grant concludes that in the rabbit the anastomoses serve two functions, local and general. Locally, it is mainly through their agency that the temperature of the ears is maintained when they are exposed to cold. Generally, they are important factors in regulating body temperature, aiding the dispersal of heat by allowing an enormous blood-flow through the ears. Dr. Grant has found, further, that the temperature reaction of the rabbit's ear to cold is similar to that previously described in man by Sir Thomas Lewis, and he brings forward evidence to show that in the human extremities arterio-venous anastomoses not only take a part in

this reaction but are chiefly responsible for the increased blood-flow. Applying the method devised for the rabbit he has found, with Dr. Bland, that in man many communicating channels are present in the sole of the foot and palm of the hand; they are particularly numerous at the ends of the digits, as many as five hundred underlying one square centimetre of surface area. It is pointed out that because of their activity under various conditions, and their presence in large numbers in some parts of the animal body, arterio-venous anastomoses must be taken into account in dealing with the peripheral circulation, for example in experiments on the blood-flow through the limbs, and especially in relation to the action of drugs.

Dr. K. E. Harris has studied spontaneous eruptions of urticaria ('nettle rash') in patients. He has shown that the individual lesions behave in detail as do urticarial lesions produced by artificial stimuli. The manner in which a spontaneous eruption appears has been studied; it is shown that the skin is in a susceptible condition —whealing to strokes—before the eruption comes, and that it is left refractory by the fading lesions of the spontaneous rash, so that these lesions do not usually appear twice upon the same area of skin. It is also shown that serum from patients with spontaneous urticaria, when given intradermally, makes wheals in the skin of normal persons to an unusual degree.

Dr. Craib, shortly before leaving for South Africa, completed a full report of his work on the interpretation of electrical records of active tissues from the standpoint of its application to human problems. He showed that the distribution of potential set up by impulse-conducting tissue is the same in the cases of cardiac muscle, somatic muscle and nerve, and that the field of current-flow around a strip of excited tissue may be ascribed to 'doublets of invasion' and 'doublets of retreat'. His new observations are further directed to explain the 'monophasic' response, and, in the electrocardiogram, the significance of the end deflection T and of changes in the curve resulting from myocardial infarction. His report, beginning with a clear statement of the physical principles involved, is especially relevant to the effects recorded from tissues immersed, as they are in the body, in a fluid medium. The Council are glad to learn that Dr. Craib has recently been appointed Professor of Medicine in the University of Witwatersrand.

The study of after-histories of cardiac patients is being continued by Dr. Grant and Miss L. M. Searle. It is hoped that this work will be completed, and the final report issued, within another year.

T. Lewis—
'Angina Pectoris Associated with High Blood Pressure and its Relief by Amyl Nitrite; with a Note on Nothnagel's Syndrome.' *Heart*, 1931, **15**, 305.

T. Lewis—
'Supplementary Notes upon the Reactions of the Vessels of the Human Skin to Cold.' *Heart*, 1931, **15**, 351.

T. Lewis and E. M. Landis—
'Observations upon the Vascular Mechanism in Acrocyanosis.' *Heart*, 1930, **15**, 229.
'Further Observations upon a Variety of Raynaud's Disease with Special Reference to Arteriolar Defects and to Scleroderma.' *Ibid.*, 1931, **15**, 329.

T. Lewis, G. W. Pickering, and P. Rothschild—
'Observations upon Muscular Pain in Intermittent Claudication.' *Heart*, 1931, **15**, 359.

W. H. Craib—
'The Electrocardiogram. An Investigation of the Principles underlying the Interpretation of the Electrical Responses of Muscle and Nerve, with Special Reference to the Electrocardiogram.' *Sp. Rep. Ser. Med. Res. Coun.*, Lond., No. 147, 1930.

R. T. Grant—
'Observations on Local Arterial Reactions in the Rabbit's Ear.' *Heart*, 1930, **15**, 257.
'Observations on Direct Communications between Arteries and Veins in the Rabbit's Ear.' *Ibid.*, 1930, **15**, 281.

R. T. Grant and E. F. Bland—
'Observations on Arteriovenous Anastomoses in Human Skin and in the Bird's Foot with Special Reference to the Reaction to Cold.' *Heart*, 1931, **15**, 385.

K. E. Harris—
'Urticaria: Some Observations upon the Vascular Reactions in the Skin.' *Quart. J. Med.*, 1931, **24**, 347.

E. M. Landis—
'Micro-injection Studies of Capillary Blood Pressure in Raynaud's Disease.' *Heart*, 1930, **15**, 247.

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V. EXTERNAL RESEARCH SCHEMES.

Clinical Medicine

At St. Bartholomew's Hospital, London, part-time grants have again been made to Dr. R. Hilton (p. 121), Dr. E. A. Carmichael, and Dr. E. N. Allott, in the Medical Unit. Professor F. R. Fraser and Dr. Carmichael (p. 86) have continued to study the action of acetylcholine on human circulation and blood-pressure. They have shown that eserine enhances the action of acetylcholine in man, as has been found experimentally by Dale and others. Dr. G. C. Linder and Dr. Carmichael have continued their studies of the cerebrospinal fluid in nephritis and in conditions of acidosis. It has been found that the normal relationship between the constituents of arterial blood-serum and of the cerebrospinal fluid is maintained in moderate disturbances of the acid-base balance, but that breakdown in this relationship may occur in severe nephritis. With Dr. G. Simon and Mr. J. Paterson Ross, Dr. Carmichael has made further observations on the effect of X-rays and radium on nerve-tissues, with special reference to the treatment of tumours of the brain by radiological methods. Dr. E. N. Allott, with Dr. J. A. Dauphinee of Toronto, has endeavoured to improve the methods for the determination of iodine in the blood. The method of Dr. W. H. Hurtley has been adapted, and the effect of small doses of iodides on the blood-iodine has been examined in normal subjects and in patients with toxic goitre. The excretion of iodine is smaller in these patients than in normal subjects. Determinations of the iodine in the blood of patients with toxic goitre have failed to confirm Lunde's finding that high values are found constantly in this disease.

Dr. E. P. Poulton, at Guy's Hospital, London, has again received a grant for expenses. He has continued the investigation of rheumatoid arthritis mentioned in previous reports. At the same place, Dr. A. C. Hampson and Dr. E. C. Warner have followed the effects of liver feeding on the metabolism of anaemic patients. They are also studying the calcium phosphate balance in encephalitis and other nervous diseases. The inquiry by Dr. Warner into the nutritional histories of rheumatic children is mentioned at p. 76.

With a personal grant made for the assistance of the Asthma Research Council, Dr. G. H. Oriel has continued at Guy's Hospital his study of allergic states. Working with Dr. F. A. Knott he has investigated a histamine-like substance isolated from sputum containing organisms of the Friedländer type. Further study has also been made of the occurrence of antigens in the urine in asthma,

urticaria, and some forms of eczema. Dr. H. W. Barber has again collaborated on the dermatological side of this inquiry.

At Guy's Hospital and at Queen Mary's Hospital, Stratford, Dr. A. A. Osman receives a personal grant and the assistance of Dr. H. G. Close. Further work has been done on the value of alkalies in the prevention and treatment of nephritis and of the renal complications of pregnancy. It has been found that throughout pregnancy the plasma bicarbonate is consistently lowered and the plasma chlorides and water content of the body are increased. Giving large doses of alkalies to patients with pre-eclamptic toxaemia promotes diuresis and aids in the control of albuminuria. The prophylactic use of alkalies throughout pregnancy in patients known to have suffered previously from albuminuria decreases the liability to a return of this complication. Studies of the water and electrolyte balance of the tissues in health and disease have been extended, with special reference to epilepsy and uraemic convulsions. Investigations of the acid-base balance in patients with bronchial asthma have shown that, while between the attacks a slight acidosis is usual, at the time of the attacks a condition of alkalosis is present and is probably due to hyper-ventilation. A statistical inquiry is being made into the incidence of the different types of renal disease in this country.

With a part-time grant, Mrs. P. M. T. Kerridge has continued her studies of nephritis in the Medical Unit at the London Hospital. She has investigated the occurrence of spontaneous outbursts of diuresis in patients with Bright's disease, and has described a simple method for estimating protein in the urine.

In the Medical Unit at St. Thomas's Hospital, London, Dr. W. J. Griffiths receives a part-time grant. He has isolated a pigment which is present in the blood in some types of jaundice, and is thought to be responsible for the 'direct' Van den Bergh reaction. Its chemical nature is being examined. Dr. Griffiths has also continued the studies of the mode of control of gastric secretion, in which he was associated with Professor H. Maclean: a report on this work is being prepared. Further studies have been made of the chloride and base distribution in the body in normal and pathological conditions, and particularly in Bright's disease.

At the same hospital, Mr. B. W. Williams has again received a grant. He is investigating, with Dr. A. M. Cook, the influence of the vagus nerve on gastric secretion.

At King's College Hospital, London, Dr. R. D. Lawrence has had a part-time grant for clinical and experimental work on diabetes; in this he is assisted by Dr. Kate Madders, also receiving a part-time grant. An unusual case of diabetes, in which an infection did not increase the insulin requirements, has been investigated, and a study of hereditary influence in diabetes is being made. With

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Dr. R. A. McCance (p. 77), further work has been done on the effects of different drugs upon the distribution of glycogen in the body.

The Council have again assisted work by Dr. J. C. Bramwell at Manchester. With Dr. Nora Regan, who receives a part-time grant, he has continued the investigation, mentioned last year, of the effects of pregnancy and labour on patients with heart disease. This has been done in the ante-natal clinic and wards of St. Mary's Hospital, Manchester. Mr. F. Braithwaite, working under the direction of Dr. Bramwell at the Royal Infirmary, has continued his studies of the graphic registration of the heart-sounds. At the same place, Dr. Sylvia Guthrie, with a part-time grant, is studying the clinical significance in heart disease of different types of cardiac impulse recorded graphically. Work by Dr. Bramwell and Dr. R. Ellis on the effects of dust inhalation in cotton operatives is mentioned separately below (p. 121).

Dr. J. F. Wilkinson, at the Royal Infirmary, Manchester, has again had the assistance of Dr. L. Klein provided by the Council. Further work has been done on the treatment of pernicious anaemia with gastric extracts. The value of hog's stomach in treatment has been confirmed, and attempts are being made to isolate in pure form the active substance concerned.

The expenses of work at Sheffield by Professor E. Mellanby and his co-workers have again been provided. Personal grants have been made to Dr. W. M. Roberts and Dr. H. N. Green: work by Mrs. Mellanby is mentioned at p. 85. Professor Mellanby has continued his study of the relations of particular deficiencies of diet to pathological changes in the central nervous system. The results throw light on the causation of convulsive ergotism and the changes in the nervous system found in pellagra and lathyrism. It appears that convulsive ergotism, which occasionally attacks rye-eating communities in epidemic form, is due to the toxic action of ergotized rye and the rye germ itself. It develops, however, only when the diet of the community is deficient in vitamin A or carotene. This agrees with and explains the phenomenon that this disease appears only among the poorer people and in times of famine and drought when dairy products and vegetables are almost unobtainable. Convulsive ergotism is thus not a simple form of deficiency disease; it appears when a toxic agent attacks the nervous system and only when this attack, in the absence of the protective vitamin, succeeds.

The nervous changes in pellagra are probably of similar origin. They do not occur when yellow maize is the cereal of the diet, but develop when white maize is substituted for it. Apparently the carotene that gives colour to the yellow maize, by the formation of vitamin A that follows its intake, similarly prevents the nervous

changes. Even ergot is without its harmful effect on the nervous system in the presence of yellow maize. It is of interest to note that in the Southern States of the U.S.A., where pellagra is common, white maize is the cereal mainly eaten.

Dr. Green has continued his experimental studies of the part played by diet, and especially by vitamin A and carotene, in resistance to bacterial infections. Professor Mellanby and Dr. Green, with the assistance of Dr. Doris Pindar and Mr. G. Davis, have completed an inquiry into the prophylactic action of vitamin A in puerperal sepsis. Five hundred and fifty women attending the ante-natal clinic of the Jessop Hospital and the Sheffield Municipal Clinic have been under observation. Alternate cases were given a preparation rich in vitamins A and D throughout the last month of pregnancy; the other cases were controls for comparison, and received the ordinary full diet without this supplement. It was found that in the group receiving added vitamins, only 1·1 per cent. developed pyrexia of the British Medical Association standard, while in the control group 4·7 per cent. of the women developed pyrexia. Other methods of comparison confirmed the protective action of the vitamin preparation. These results give new emphasis to the importance of suitable diet during pregnancy as a means of increasing the resistance to bacterial infection, and so lowering the maternal morbidity and mortality rates.

A further study has been made of the value of vitamin A in the treatment of puerperal septicaemia. Twenty-seven cases of septicaemia, bacteriologically diagnosed, have been treated with diets very rich in the vitamin, giving a mortality of seven cases. These include sixteen cases where *Streptococcus haemolyticus* was found in the blood, with five deaths. This mortality is well below that usually ascribed to this infection, but in the absence of sufficient control cases it is difficult to draw any definite conclusion as to the efficacy of the treatment.

Clinical studies of the effect of vitamin A and carotene on various nervous diseases are being made by Professor Mellanby and Dr. Roberts at the Royal Infirmary, Sheffield. The action of diets rich in these substances is being tested in cases of disseminated sclerosis, locomotor ataxia, and general paralysis of the insane. Dr. Roberts has also continued his investigation of the phosphatase content of the blood in various clinical conditions and is making a chemical study of the Van den Bergh reaction. His work on gastric secretion and motility has been published.

At the Welsh National School of Medicine, Cardiff, Dr. D. G. Leys has had an expenses grant. Studies have been made of the lactic acid content of capillary and venous blood under different conditions.

Part-time grants have again been made to workers in Professor

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D. Murray Lyon's department at Edinburgh. Dr. A. R. Gilchrist has studied the local fat atrophy that may follow repeated injections of insulin. It has been found that repeated injections of normal saline may produce a similar effect in the diabetic but not in the normal person. The subcutaneous fat of some diabetics is abnormally susceptible to injury. Regeneration of fat so destroyed may take as long as three years. Further studies have been made of the effect of different drugs on patients with disease of the coronary arteries and with heart block. At the Royal Maternity Hospital, Edinburgh, an investigation of the influence of pregnancy on heart disease has been completed, and the results published. With Professor Lyon and Dr. D. M. Dunlop, Dr. C. P. Stewart has continued his study of the treatment of chronic interstitial nephritis. He also has investigated the metabolic changes associated with obesity. With Professor S. Smith and Miss J. Robertson, he is studying the effects of alcohol and other narcotics on the rate of oxidation in brain tissue. Dr. Dunlop, Dr. Stewart, and Dr. R. Gaddie have completed their inquiry into fat metabolism in muscular exercise.

Dr. G. H. Percival has again received part-time and expenses grants for work on skin diseases at Edinburgh. He has continued his study of the treatment of chronic skin infections and is investigating the pathology of dermatitis. With Dr. C. P. Stewart, attempts are being made to confirm the finding of Barber and Oriel that a specific urinary 'proteose' is present in urticaria and other allergic conditions.

At Aberdeen, Professor L. S. P. Davidson has a grant for expenses. He is investigating, with Dr. J. Smith (p. 112), the treatment of broncho-pneumonia in children with a concentrated preparation of vitamin A. Work done on the serum treatment of lobar pneumonia is mentioned separately below. With Dr. A. M. Calder, receiving a part-time grant, Professor Davidson has continued his clinical and biochemical study of the diagnosis of cancer of the stomach. An investigation of atypical anaemias, simulating pernicious anaemia, has been completed.

At the James Mackenzie Institute for Clinical Research, St. Andrews, grants have again been made to Dr. A. Rowand. He has continued his inquiries, mentioned in previous Reports, into the health histories of children from birth. Records are also being kept of the subsequent histories of ailing children sent to the Institute for examination, with special reference to the relation between orthostatic albuminuria and subsequent nephritis, between vague abdominal pains and appendicitis, and between bronchial catarrh and pulmonary tuberculosis. An account of all this work is now being prepared for publication.

J. C. Armour, T. G. Brown, D. M. Dunlop, T. C. Mitchell, H. H. Searls, and C. P. Stewart—
'Studies on High Intestinal Obstruction: the Administration of Saline and other Substances by Enterostomy below the site of Obstruction.' *Brit. J. Surg.*, 1931, **18**, 467.

J. C. Bramwell—
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'Some Observations on the Circulatory Mechanism in Marathon Runners.' *Quart. J. Med.*, 1931, **24**, 329.

A. J. Clark, R. Gaddie, and C. P. Stewart—
'The Metabolism of the Isolated Heart of the Frog.' *J. Physiol.*, 1931, **72**, 443.

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'Insulin Phosphotungstate by Mouth.' *Lancet*, Lond., 24th Jan., 1931.
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R. D. Lawrence and R. A. McCance—
'Infections and Insulin Action; Observations on Unusual Case. *Brit. Med. J.*, 2nd May, 1931.
'The Effect of Starvation, Phloridzin, Thyroid, Adrenaline, Insulin, and Pituitrin on the Distribution of Glycogen in the Rat.' *Biochem. J.*, 1931, **25**, 570.

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'The Diabetic Acute Abdomen.' *Brit. Med. J.*, 19th Sept., 1931.

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'Keratoderma Blennorrhagicum.' *Lancet*, Lond., 21st Nov., 1931.

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'The Influence of Adrenaline on Carbohydrate Metabolism.' *J. Physiol.*, 1931, **71**, 275.

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'The Chlorides and Inorganic Constituents of the Serum and Cerebrospinal Fluid in Nephritis and Acidosis.' *Biochem. J.*, 1931, **25**, 1090.

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'The Elimination of Focal Sepsis in the Treatment of Parathyroid Tetany.' *Quart. J. Med.*, 1931, **24**, 469.

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'Diet and Health.' Hastings Lecture. *Brit. Med. J.*, 21st March, 1931.
'The Experimental Production and Prevention of Degeneration in the Spinal Cord.' *Brain*, 1931, **54**, 247.
'Maternal Mortality.' *Rep. Publ. Hlth. Congress*, Lond., 1930, p. 86.
'Diseases Produced and Prevented by Certain Food Constituents.' *J. Amer. Med. Ass.*, 1931, **96**, 325.

G. H. Oriel—
'Some Observations on the Pathogenesis of Eczema of Internal Origin and other Allergic Diseases.' *Proc. R. Soc. Med.*, 1931, **24**, 1171.

A. A. Osman—
'The Importance of Sugar in the Diet of the School Child.' *Proc. R. Soc. Med.*, 1931, **24**, 1103.

A. A. Osman and H. G. Close—
'The Diagnosis of Uraemia.' *Brit. Med. J.*, 20th June, 1931.
'Observations on the Plasma Bicarbonate and the Value of the Alkalies in the Treatment of some of the Renal Complications of Pregnancy.' *Proc. R. Soc. Med.*, 1931, **24**, 40.

G. H. Percival—
'Thallium Acetate in Treatment of Ringworm of the Scalp: Statistical Investigation of Subsequent Nutrition.' *Brit. Med. J.*, 4th April, 1931.
'Experimental Observations on Dermatitis due to Dyed Fur.' *Lancet*, Lond., 22nd Aug., 1931.
'A Study of the Skin Vessels in some Forms of Inflammation of the Skin.' *J. Pharmacol.*, 1931, **41**, 147.

G. H. Percival and H. J. Gibson—
'Observations on the Aetiology of Erythema Exudativum Multiforme.' *Brit. J. Derm.*, 1931, **43**, 329.

W. M. Roberts—
'The Effect of Oils on Gastric Secretion and Motility.' *Quart. J. Med.*, 1931, **24**, 133.

C. P. Stewart and R. M. Gray—
'The Detection and Estimation of Lactose in Urine.' *Edinb. Med. J.*, 1931, **38**, 109.

C. P. Stewart, R. Gaddie, and D. M. Dunlop—
'Fat Metabolism in Muscular Exercise.' *Biochem. J.*, 1931, **23**, 733.

J. F. Wilkinson—
'Treatment of Pernicious Anaemia with Hog's Stomach.' *Brit. Med. J.*, 17th Jan., 1931.
'Injection of Highly Purified Liver Preparations in Pernicious Anaemia.' *Lancet*, Lond., 10th Oct. 1931.

J. F. Wilkinson and T. H. Oliver—
'Some Clinical Conditions Associated with Achlorhydria.' *Lancet*, Lond., 10th Jan., 1931.

Clinical Trials of New Remedies

The Council have recently appointed a Therapeutic Trials Committee (p. 138) to arrange for clinical trials of new remedies which seem likely, on experimental grounds, to have value in the treatment of disease. Conditions have been the subject of discussion and agreement between the Council and the Association of British Chemical Manufacturers, under which manufacturers may submit applications to the Committee for clinical trials of their products. The Committee may invite suitable experts in particular branches of medicine or surgery to undertake the clinical tests of preparations submitted and approved, and the clinical reports on these will be published under the Committee's authority. The purposes of the scheme are more fully discussed at p. 22.

Serum Treatment of Pneumonia

Further trials of concentrated antipneumococcal serum in the treatment of lobar pneumonia have been made for the Council by Dr. R. R. Armstrong in London, Professor L. S. P. Davidson at Aberdeen, and Professor D. Murray Lyon at Edinburgh. Dr. Armstrong continues to receive a part-time grant, and the Council have made provision towards the cost of the serum used at these centres. Part-time and expenses grants have also been made to Dr. R. Cruickshank in respect of a similar investigation at Glasgow, where serum has been provided by the Scottish Branch of the British Red Cross Society.

So far, owing to the relatively small incidence of lobar pneumonia during the past winter, insufficient cases have been treated to establish definitely the value of serum in lowering the mortality from this disease, although clinical impressions indicate that, given early, it tends to accelerate crisis and to shorten the period of invalidism. The investigation is being continued.

R. R. Armstrong—
'A Simple Method for Deciding Pneumococcal "Type".' *Brit. Med. J.*, 7th Feb., 1931.
'Serum Treatment of Lobar Pneumonia: a Study in Immunology.' *Brit. J. Exp. Path.*, 1931, **12**, 279.

R. R. Armstrong and R. S. Johnson—
'Concentrated Antipneumococcal Serum in the Treatment of Lobar Pneumonia.' *Brit. Med. J.*, 25th April, 1931.
'Homologous Antipneumococcal Serums in the Treatment of Lobar Pneumonia.' *Ibid.*, 30th May, 1931.

SURGERY

The Council have continued to provide the expenses of an inquiry by Mr. W. B. Gabriel, at St. Mark's Hospital, London, into the after-histories of cases of rectal cancer treated by operation

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alone and with radium. A systematic record is now available of all those treated since 1910. Since 1927 cases of excision of the rectum have been grouped on a pathological basis by Dr. Cuthbert Dukes, pathologist to the hospital. It is hoped thus to obtain useful statistical data as to the prognosis in rectal cancer treated at different stages and by different methods.

At St. Bartholomew's Hospital, London, Mr. H. P. Nelson has had an expenses grant. He is investigating the prospects of treating malignant disease within the chest by means of radon seeds introduced through the trachea.

Mr. Lambert Rogers, at Cardiff, has again received part-time and expenses grants. Further work has been done on the vasomotor innervation of the peripheral blood-vessels, with special reference to surgical operations designed to improve local circulatory defects. Evidence has been obtained of a dual sympathetic innervation of some of the main arteries. With Professor C. M. West, developmental studies of the foramina of the human brain have been continued, in relation to the pathology of hydrocephalus.

Mr. J. W. Tudor Thomas, working with an expenses grant in Professor T. Graham Brown's department at Cardiff, has continued his experiments on the grafting of healthy corneal tissue on the eye to replace tissue that has become opaque through disease or accident. Study has been made of the conditions necessary to secure the growth of a graft that will unite and at the same time retain its transparency. Much work yet remains to be done, but the experiments—of which accounts have been published—give hope of a radical cure by surgical means of blindness due to opacity of the cornea.

In Professor D. P. D. Wilkie's department at Edinburgh, Mr. W. Ritchie Russell, with a part-time grant, is making a clinical study of head injuries. Two hundred cases have so far been examined. Records are being kept of the condition on admission, the stages of recovery, the changes in the cerebrospinal fluid, and the condition some months after discharge. The brain in fatal cases is also being examined. In the same department, a grant has recently been made to Mr. David Band for clinical and pathological work on tuberculosis of the urinary tract.

At Glasgow, Mr. W. A. Mackey receives part-time and expenses grants. He has continued his study of the mode of infection of the biliary passages and the formation of gall-stones. Microscopic studies have shown that the gall-bladder is able largely to recover from acute inflammatory attacks and that even in cases of empyema there may be complete regeneration of the lining epithelium. A further investigation has been made of innocent tumours of the kidney.

A grant has been made to Mr. L. R. Broster, at Charing Cross

Hospital, London, for expenses and assistance in work on the relation of tumours and other abnormalities of the suprarenal glands to secondary sex changes in women.

The Council have been glad to publish in their Series a report by Dr. O. A. Beadle, of New College, Oxford, on the anatomy and pathology of the intervertebral discs, in relation to spinal deformities. The data were collected by Dr. Beadle while working under Professor G. Schmorl, at Dresden, during the tenure of a Radcliffe Travelling Fellowship. His report includes a general survey of the researches on spinal deformities that have been carried out in Professor Schmorl's department since 1925. The Council believe that this material, thus fully presented in English, will be of practical value to general and orthopaedic surgeons.

O. A. Beadle—
'The Intervertebral Discs: Observations on their Normal and Morbid Anatomy in Relation to Certain Spinal Deformities.' *Sp. Rep. Ser. Med. Res. Coun.*, Lond., No. 161, 1931.

W. A. Mackey—
'Execretion Urography: An Experimental Investigation of the Properties of "Uro-selectan".' *Glasg. Med. J.*, 1931, **115**, 9.
'Cholelithiasis: some Pathological Observations.' *Ibid.*, 1931, **115**, 225.

H. P. Nelson—
'Experimental Coli-infection in the Urinary Tract of Rabbits.' *Trans. Med. Soc.*, Lond., 1930, **53**, 266.
'Irradiation of the Tracheo-Bronchial Lymphatic Glands in the Treatment of Carcinoma of the Lung.' *Lancet*, Lond., 22nd Nov., 1930.

W. Ritchie Russell—
'Hereditary Aspects of Leber's Optic Atrophy.' *Lancet*, Lond., 7th Nov., 1931.

L. Rogers—
'An unusually large Intrathecal Spinal Tumour.' *Brit. J. Surg.*, 1931, **18**, 669.
'The Time Factor during which Vascular Responses persist following Peri-arterial Sympathectomy.' *Ibid.*, 1931, **19**, 52.
'Laminectomy for Spinal Tumours.' *J. Coll. Surg. Australasia*, 1931, **3**, 311.

L. Rogers and C. M. West—
'The Foramen of Magendie.' *J. Anat.*, Lond., 1931, **65**, 457.

J. W. T. Thomas—
'Successful Grafting of the Cornea in Rabbits.' Hunterian Lecture. *Lancet*, Lond., 14th Feb. 1931.
'On the Return of Sensitiveness in Corneal Grafts in Rabbits.' *Proc. Roy. Soc.*, B, 1931, **108**, 301.

Obstetrics and Gynaecology

Disorders of Pregnancy

With a grant for expenses at University College, London, Dr. G. W. Theobald has investigated the parts played by mechanical and dietetic factors in causing the albuminuria of pregnancy. With Miss W. M. Wright (p. 104) he is also studying the calcium content

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of the tissues, particularly the liver, in women dying from pregnancy toxaemia.

At the Royal Maternity Hospital and the Simpson Memorial Hospital, Edinburgh, Dr. James Young has had a grant for assistance by Dr. Jessie C. B. Sym. A further study has been made of the after-histories of women who have suffered from the toxaemias of pregnancy. Special attention is being given to the problem of reducing, by dietetic and other measures, the risk of permanent disablement from these conditions.

Dr. Dugald Baird, at the Royal Maternity and Women's Hospital, Glasgow, has again received a part-time grant for work on infections of the urinary tract in pregnant women. The intravenous injection of substances opaque to X-rays has been used to study the physiology of the kidney and ureter: the method has been found specially suitable in pregnancy, since it gives a satisfactory picture without the passage of instruments. The after-histories of cases of pyelitis are being carefully followed, and intensive treatment is given, where necessary, to free the patient from infection before subsequent pregnancies.

Work at Guy's Hospital, London, on the albuminuria of pregnancy has been mentioned at p. 64. Studies at Manchester and Edinburgh of the effects of pregnancy and labour on patients with heart disease have also been noticed at pp. 65 and 67.

Work upon oestrin under the Sex Hormones Committee, and on tests for the diagnosis of pregnancy, is mentioned below at p. 105.

G. W. Theobald—
'The Albuminuria of Pregnancy.' *Lancet*, Lond., 31st Oct., 1931.

Puerperal Infections

In Professor F. J. Browne's Unit at University College Hospital, London, Mrs. J. Taylor has received a part-time grant. She has investigated a large series of obstetric cases, before and after delivery, to trace the sources of bacterial infection. Special attention has been given to the pathological significance of the anaerobic streptococci, and an attempt has been made at their classification.

Dr. Leonard Colebrook, of the Council's staff, has continued at St. Mary's Hospital and Queen Charlotte's Hospital, London, his studies of puerperal sepsis. This work has been greatly facilitated by the opening of the new Isolation Block and Research Laboratories of Queen Charlotte's Hospital, where a team of workers is now engaged under the scheme assisted by the generous benefaction of the Rockefeller Foundation, to which reference has already been made. With Dr. R. Hare, who receives a grant, Dr. Colebrook is investigating the therapeutic value of arsenical preparations in puerperal fever and the problem of bacteriotropic immunity to

streptococci. Further work has also been done on the biological characters of anaerobic streptococci and on the efficacy of antiseptics in midwifery. Dr. R. M. Fry and Miss E. Cooper are studying, at this hospital, the different factors predisposing to puerperal sepsis and the relative importance of haemolytic and anaerobic streptococci in its causation. With Mr. A. T. Fuller, Dr. Fry is also investigating the bacteriology and treatment of urinary tract infections in the puerperium.

Reference has already been made (p. 66) to work at Sheffield upon the value of dietetic measures for increasing resistance to puerperal infection. Dr. J. Smith of Aberdeen, whose other work is described at p. 112, has written the report mentioned below.

L. Colebrook—
'Puerperal Fever.' *J. Roy. Sanit. Inst.*, 1930, **51**, 161.
'The Anaerobic Actinomyces.' *A System of Bacteriology*, VIII, London, 1931.

R. Hare—
'Studies on Immunity to Haemolytic Streptococci. III. Observations on the Variations in Resistance to Phagocytosis Displayed by Broth Cultures of Strains of High and Low Virulence.' *Brit. J. Exp. Path.*, 1931, **12**, 261.

J. Smith—
'Causation and Source of Infection in Puerperal Fever.' *Reports of the Scientific Advisory Committee on Medical Administration and Investigation, Department of Health for Scotland*, 1931.

J. Taylor—
'Puerperal Infection.' *Univ. Coll. Hosp. Mag.*, 1931, **16**, 160, also *Post-Grad. Med. J.*, 1931, **6**, 184.

Physiology of Lactation

At the Royal Free Hospital, London, Miss Sybil Widdows and Miss Muriel Bond have again received part-time grants. Investigations of the composition of human milk during normal lactation have been extended to include a study of ante-natal milk and aberrant secretions of the mammary gland. The iron, chloride, and sodium contents of samples of milk are being determined, in addition to the protein, sugar, fat, and calcium. Special attention is being paid to the composition of milk samples obtained from mothers whose babies are not making satisfactory progress. Attempts are being made to correlate work on the iron content of milk with the observations of Dr. Helen Mackay (p. 75) on nutritional anaemia in breast-fed infants.

Pediatrics

The Council have continued to provide the expenses of work by Dr. G. B. Fleming and his colleagues at the Royal Hospital for Sick Children, Glasgow. Dr. Stanley Graham and Dr. Noah Morris, both receiving part-time grants, have investigated the biochemical changes produced by sodium salicylate. They have

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also studied the variations in the composition of the urine in newborn infants, and the effect of modifications of milk on the absorption and retention of minerals, fat, and nitrogen. Dr. Morris and Dr. F. J. Ford have continued their investigation of protein and mineral metabolism in rickets, tetany, and allied conditions. With Dr. Graham and Dr. J. B. Rennie, Dr. Morris is also studying the causative factors in infantile convulsions.

Dr. L. G. Parsons, at the Children's Hospital, Birmingham, has again received expenses and the assistance of Dr. E. M. Hickmans. Further studies have been made of nutritional anaemias, with special reference to the curative effects of iron, copper, and brewer's yeast. It has been found possible to cure experimental anaemia with iron-free yeast, although the addition of iron leads to a more rapid formation of haemoglobin. Observations on the biochemistry of coeliac disease have been continued, and a quantitative investigation is in progress of the absorption of vitamin A in this condition.

At the Queen's Hospital for Children, Hackney Road, London, Dr. Helen Mackay receives part-time and expenses grants. The Council have published her report on nutritional anaemia in infancy. With Mr. S. F. Rose, she has investigated, in relation to the work of Mrs. Mellanby (p. 85), the incidence of caries in the teeth of children known to have suffered from rickets. Studies are also being made of the effects on the health of infants and children in working-class households of an addition of vitamin A to the ordinary diet.

F. J. Ford—
'Calcium and Phosphorus Metabolism in Nephritis.' *Arch. Dis. Child.*, 1931, **6**, 209.

E. M. Hickmans and S. H. Edgar—
'The Blood Constituents in Acute Rheumatism before and after Salicylate Treatment.' *Arch. Dis. Child.*, 1930, **5**, 387.

H. M. M. Mackay—
'The Therapeutic Uses of Iron. The Effects of Iron Therapy on Artificially-fed Babies.' *Proc. R. Soc. Med.*, 1931, **24**, 552.

H. M. M. Mackay, assisted by L. Goodfellow: with a Statistical Appendix by A. B. Hill—
'Nutritional Anaemia in Infancy: with Special Reference to Iron Deficiency.' *Sp. Rep. Ser. Med. Res. Coun.*, Lond., No. 157, 1931.

H. M. M. Mackay and S. F. Rose—
'Vitamin D Deficiency, Dental Caries, and Tonsillar Enlargement. A Clinical Investigation of some late Effects of Rickets.' *Lancet*, Lond., 5th Dec. 1931.

O. Macrae and N. Morris—
'Metabolism Studies in Coeliac Disease.' *Arch. Dis. Child.*, 1931, **6**, 75.

N. Morris and S. Graham—
'Observations on the Chloride Metabolism in Congenital Pyloric Stenosis.' *Arch. Dis. Child.*, 1931, **6**, 27.
'The Value of Alkali in Salicylate Treatment.' *Ibid.*, 1931, **6**, 273.

N. Morris and S. Morris—
'On the Presence of a Volatile Organic Chlorine Compound in Blood.' *Biochem. J.*, 1930, **24**, 1716.
S. Morris, A. McL. Watson, and N. Morris—
'Metabolism Studies in Tetany.' *Biochem. J.*, 1931, **23**, 786.
L. G. Parsons—
'Coeliac Disease.' *Lancet*, Lond., 10th Jan. 1931.
'Observations on Fat Metabolism in Coeliac Disease.' *Trans. 2nd Internat. Pediatric Congress*, Stockholm, August 1930.
'The Anemias of Infancy and Early Childhood: Some Observations.' *J. Amer. Med. Ass.*, 1931, **97**, 973.

Rheumatic Fever in Children

At Bristol, Dr. Carey F. Coombs has had an expenses grant for a survey of the incidence of rheumatic heart disease in Gloucestershire, Somerset, and Wiltshire. The results of this investigation have been published. It has been found that rheumatic heart disease is particularly prevalent in the urban district of Bristol, and further work is contemplated to decide whether the same is true of other large cities.

Dr. E. C. Warner, at Guy's Hospital, London, has received expenses for an inquiry into the nutritional and family histories of children with rheumatic disease. In this he has had the co-operation of Dr. F. G. Winterton and of the Almoner's staff at the hospital. The results of this study are now being analysed.

At Great Ormond Street Hospital, London, a part-time grant has been made to Dr. R. Collis and a grant for assistance to Dr. W. W. Payne. Dr. Collis is investigating the relationship of haemolytic streptococci, isolated from the throat, to the lesions of acute rheumatic fever. With Dr. F. Griffith, of the Ministry of Health, a special study is being made of the response of rheumatic fever patients to the toxins of these organisms. Dr. Payne has investigated the changes in the urine associated with acute rheumatism, and with asthma, in children.

Grants have recently been made to Dr. D. Stewart and Dr. H. J. Gibson, in Professor T. J. Mackie's department at Edinburgh, for work on the bacteriology of acute rheumatism. They are in close touch with Dr. Collis and Dr. Griffith, and their investigation is being made on similar lines.

'Incidence of Rheumatic Heart Disease in Childhood (1927–30) in Gloucestershire, Somerset, and Wilts.' *Brit. Med. J.*, Suppl., 18th July, 1931.
W. R. F. Collis—
'Acute Rheumatism and Haemolytic Streptococci.' *Lancet*, Lond., 20th June, 1931.
E. C. Warner—
'Modern Views on Rheumatism in Childhood.' *Lancet*, Lond., 27th Sept., 1930.

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Studies in Growth

At University College, London, Dr. H. A. Harris has again received expenses and the assistance of Dr. A. E. Russell. Further studies have been made of the growth and ossification of the bones in health and disease. Special attention has been paid to the bone changes in the infants of mothers suffering from chronic infections and metabolic diseases.

With a personal grant, at Aberystwyth Miss R. M. Fleming has continued her work on growth in school children in relation to race and heredity. With the help of the Council's statistical staff, a full report is now being prepared for publication.

Studies of the physique and the physical and mental aptitudes of schoolboys have been continued at Manchester by Dr. A. A. Mumford, with a grant for expenses. Assistance in this work is being given by Dr. A. B. Hill, of the Council's statistical staff.

H. A. Harris—

'The Comparative Aspect of Growth in Children.' *Lancet*, Lond., 28th March, 1931.

'Lines of Arrested Growth in Long Bones of Diabetic Children.' *Brit. Med. J.*, 25th April, 1931.

'Cod-liver Oil and the Vitamins in Relation to Bone Growth and Rickets.' *Amer. J. Med. Sci.*, 1931, **181**, 453.

'The Anatomical and Physiological Characteristics and Development of Children between the Ages of 7+ and 11+.' *Memorandum to the Consultative Committee of the Board of Education. 'The Primary School'*, London (H.M. Stationery Office), 1931.

NUTRITION

Reference was made last year to the anthropometric and nutritional data kindly offered to the Council by Dr. G. E. Friend, Medical Officer of Christ's Hospital School, Horsham. Analyses of these data are being made for the Nutrition Committee (p. 136) by Miss M. L. Clark, receiving a grant; assistance in this work is being given by the Council's statistical staff.

At Glasgow, Professor E. P. Cathcart has again received expenses and the assistance of Mrs. A. M. T. Murray. Further analyses have been made of the ordinary diets of a series of typical houses in various towns. The data from St. Andrews were published by the Council last year, and those from Cardiff and Reading are now being prepared for publication.

Dr. R. A. McCance, at King's College Hospital, London, receives a part-time grant and the assistance of Mr. H. L. Shipp. He has nearly completed his studies of the chemical composition of the common cooked foods. Samples of many kinds of meat and fish have been analysed after cooking in various ways, and the relative losses in cooking determined. The results are being put together for full publication.

Work in Professor V. H. Mottram's department at King's College for Women, London, has again been assisted by an expenses grant. Miss W. M. Clifford has further investigated the effects of cooking on the digestibility of meats, and Dr. Gladys Hartwell has studied experimentally the nutritional values of cereals and other vegetables.

At St. Thomas's Hospital, London, Professor S. J. Cowell, with an expenses grant, has studied the relation of diet to experimental nephritis.

The Council have been glad to publish a report by Dr. J. B. Orr, Director of the Rowett Institute at Aberdeen, and Dr. J. L. Gilks, Director of Medical and Sanitary Services in Kenya Colony and Protectorate, on the physique and health of two African tribes, the Masai and the Akikuyu, with special reference to their diet. The investigation described was made for the Dietetics Committee of the Committee of Civil Research (now the Economic Advisory Council), and was financed by grants made by the Empire Marketing Board. Publication by the Medical Research Council was recommended by the Committee, in order that the report might be made available most effectively to those concerned. The information brought forward is of great interest in relation both to general scientific questions of nutrition and to particular problems presented by the native races inhabiting British colonies in the tropics.

E. P. Cathcart and A. M. T. Murray—
'The Validity of Family Coefficients.' *J. Nutrit.*, 1931, **3**, 483.

W. M. Clifford—
'The Effect of Cooking on the Digestibility of Meat.' *Biochem. J.*, 1930, **24**, 1728.

R. A. McCance and H. L. Shipp—
'The Colorimetric Determination of Sodium.' *Biochem. J.*, 1931, **25**, 449.
'The Micro-determination of Sodium in Biological Materials.' *Ibid.*, 1931, **25**, 1845.

J. B. Orr—
'The Development of the Science of Nutrition in Relation to Disease.' *Brit. Med. J.*, 23rd May, 1931.

J. B. Orr and J. L. Gilks—
'Studies of Nutrition. The Physique and Health of two African Tribes.' *Sp. Rep. Ser. Med. Res. Coun.*, Lond., No. 155, 1931.

J. B. Orr, J. J. R. Macleod, and T. J. Mackie—
'Studies on Nutrition in Relation to Immunity.' *Lancet*, Lond., 30th May, 1931.

Iodine in Foodstuffs

Reference was made last year to the inquiry by Dr. J. B. Orr of the Rowett Institute, Aberdeen, into the relationship of iodine in foodstuffs to the incidence of endemic goitre. An account of this work has been published by the Council. In view, however, of the

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difficulties of estimating minute quantities of iodine in organic combination, it has been thought desirable to re-examine the methods available, in the hope of improving and standardizing them. Assistance in this has been given by a special committee of chemists (p. 136), and the work is being done for the Council by Mr. C. O. Harvey of the Government Laboratory. The Council gratefully acknowledge the help they have received in this matter from the Government Chemist, Sir Robert Robertson.

J. B. Orr—
'Iodine Supply and the Incidence of Endemic Goitre.' *Sp. Rep. Ser. Med. Res. Coun.*, Lond., No. 154, 1931.

Vitamin Studies

Reference has already been made at p. 9 to theisolation and identification of artificially produced vitamin D at the National Institute for Medical Research.

Miss E. M. Hume, a member of the Council's staff working at the Lister Institute, has again had grants for assistance by Miss H. Henderson Smith and Miss M. M. Gaffikin. Oxycholesterol, prepared by Dr. Rosenheim (p. 28), was examined for vitamin A with negative results. The results did not agree with those reported by Seel. Studies have also been made of the influence of vitamins on the growth and fertility of animals, and of the dietetic factors in lactation.

Dr. L. J. Harris and Dr. T. Moore continue to give whole-time service to the Council, at the Dunn Nutritional Laboratory, Cambridge: a part-time grant has also been made to Mr. T. W. Birch. Dr. Harris has studied further the effects of overdosage with vitamin D. It has been shown that the abnormal calcification in bone and other tissues, produced in this way, is associated with a raised calcium and phosphorus content of the blood, due mainly to increased absorption from the food. The deposition of calcium in a particular body tissue, in these circumstances, may be determined by the presence of the enzyme 'phosphatase' in its cells. Dr. A. E. Barclay has co-operated on the radiological, and Mr. J. R. M. Innes on the histological, sides of this work.

An investigation is being made here of the relation of vitamin A to infections. The results confirm the suggestion that the function of this vitamin is to preserve the mucous membranes in a healthy state. In this way it may confer indirect protection against the invasion of pathogenic organisms. Analyses by Dr. Moore have shown that in human beings who have died from generalized infections the vitamin A content of the liver may be normal. Work by Dr. A. S. Griffith (p. 90) and Dr. Harris has not shown that deficiency of vitamins A or D in the diet of rats increases their liability to tuberculosis.

Further studies of vitamin A by Dr. Moore have led to the conclusion that its formation from carotene in the body probably occurs in the liver, which serves also as the body's store-house of the vitamin. With Mr. W. J. Dann, it has been shown that an animal's reserves of vitamin A are not appreciably depleted during deficiency of vitamin B. Mr. Dann has found that, in some solvents, vitamin A shows an unexpected resistance to oxidation.

Mr. Birch has studied the slowing of the heart, described by Drury and Harris, that may occur in vitamin B deficiency; confirmation has been got that the effective factor is in the vitamin 'B_1' and not in the 'B_2' fractions. With Dr. B. C. Guha, Mr. Birch has shown that vitamin B_1 has the properties of an organic base.

Dr. E. W. Fish (p. 84) and Dr. Harris have continued to study the influence of vitamin C on the teeth. In relation to this work, Miss I. Mills, voluntarily attached, has shown that fresh sheep's liver is a good source of this vitamin, whereas commercial 'chilled' liver is relatively deficient. With Sir John Russell, of the Rothamsted Experimental Station, an investigation is being made into the influence of soil treatments on the vitamin values of certain crops.

At Oxford, Dr. Vera Reader and Mr. H. W. Kinnersley have again received grants for work under the direction of Professor R. A. Peters, expenses being also provided. Studies of the different fractions of the vitamin B complex have been continued. Tests of Jansen and Donath's crystalline 'vitamin B' from rice polishings have shown it to be about 30 per cent. more active than the yeast B_1 obtained by Kinnersley and Peters: the product was found, however, to contain vitamin B_4 in addition. Jansen's 'activated clay' has been found to be a suitable standard for vitamin B_1 (see p. 53). Further attempts are being made to concentrate vitamin B_1 from yeast on a large scale. Observations of the heart block in rice-fed pigeons have been continued by Dr. C. W. Carter, who has obtained curative effects with whole wheat and yeast and is at present attempting to separate the effective substance. Further studies by Mr. Kinnersley upon the chemical changes in an avitaminous pigeon's brain show that the increased lactic acid does not come from glycogen, and Mr. R. B. Fisher has shown that vitamin B regulates the disappearance of lactic acid from the organs. Dr. Gavrilescu and Professor Peters find that, *in vitro*, the optic lobes especially show a lowering of oxygen uptake in glucose phosphate solutions, which is about half restored by addition of vitamin B_1 concentrates. This appears to be the first demonstration of the action of a vitamin outside the body.

During five months of last winter a highly concentrated preparation of vitamin A was used in a trial of its possible value in

increasing resistance to common infections among apprentices at the Royal Air Force Technical School, Halton. This was arranged in co-operation with the Air Ministry and with the consent of the parents of the boys. The comparative sickness figures for the boys receiving the preparation and those in the control groups showed a slight advantage in favour of the former, but the difference did not appear to be statistically significant. The fact that the general rate of sickness incidence during that winter was unusually low would no doubt tend to reduce the apparent effect of any real difference that may have been induced in the boys' resistance. The result, however, gives little evidence that the vitamin increases resistance to infections under the conditions of the experiment, with the dosage used and as an addition to a dietary of the good quality provided by Royal Air Force rations. Other trials are in progress elsewhere in which the effect of the vitamin will be tested when it is added to a poor diet and given in larger amounts. An experiment is also being made for the Council by Professor R. T. Leiper, London School of Hygiene and Tropical Medicine, of the value of vitamin A in increasing the resistance of chickens to worm infections.

At University College, London, Professor J. C. Drummond has again received a grant for expenses. With Professor Heilbron and Dr. R. A. Morton, of Liverpool, further studies have been made of the relations between the pigment carotene and vitamin A. It has been shown that carotene is the vitamin A equivalent in vegetable tissues, and the fact of the conversion of the pigment into the vitamin itself within the tissues of the animal body has been confirmed. No evidence has been obtained to support the view of Euler and Karrer that the vitamin A is a reduction product of carotene. On the contrary, the physical properties of the vitamin suggest strongly that it is an alcohol derived from the partial oxidation of a fragment of the carotene molecule. Experiments made with Dr. B. Ahmad indicate that only a small fraction of the carotene given to animals is actually converted into the vitamin. Preparations of reduced carotene (dihydrocarotene) showed a much inferior growth-promoting power to that of the parent pigment, and no support was obtained for the statement of Euler and Karrer that dihydrocarotene is three times more active than carotene itself in serving as a source of A for rats. With Dr. Muriel Bell it has been shown again that high proportions of cod-liver oil in the diet of rats may depress the rate of growth, and support has been found for the view of Hopkins, and that of Harris and Moore, that the cod-liver oil content of the diet must be balanced by enough vitamin B complex if normal growth is to proceed.

With Dr. F. L. Pyman, further work has been done here on the

isolation and chemical nature of vitamin B_1. The method described by Jansen and Donath has been explored in detail and a highly active crystalline product has been isolated. Evidence has been obtained, however, that this substance is not homogeneous, and work is now in progress to determine its exact relation to the vitamin. With Mr. M. White, a study has been made of the fractionation of vitamin B_2 from natural products. The best source examined so far has been an aqueous extract of liver.

The Council have again received a grant from the Empire Marketing Board for studies of the vitamin content of Empire foodstuffs, and the effects upon it of various modes of transport and preservation. This work is being done at the Lister Institute by Dr. S. S. Zilva, of the Council's staff, and he has had the assistance of Mrs. K. M. Balfour, Mr. F. E. Humphreys, Mr. S. W Johnson, Miss M. E. F. Crawford, Miss E. O. V. Perry, and Miss M. F. Bracewell.

An investigation of the relations of plant variety, environment, and maturity to the antiscorbutic activity of the orange and of the grape fruit has been completed. It was found that the factors studied do not notably affect the vitamin C activity. The results have been published.

The work on the influence of different physiological and cultural conditions on the vitamin C content of the apple has now established that apple tissue can be frozen and powdered at —20 C. and stored at this temperature for four months without losing antiscorbutic activity. This is being used to develop an improved method for the estimation of vitamin C in plant and animal tissues. The amount of vitamin C in the apple is found to increase as the skin is approached from the centre; it is more than six times as great in the peel as in the flesh near the core. A systematic study of the vitamins A, C, and D of the Indian mango is in progress. It has already been found that this fruit is a rich source of vitamin C, and that it also has an unexpectedly high vitamin A value.

The results of the investigation, during the past four years, into the vitamin contents of Empire butters are being prepared for publication.

Other work by Dr. Zilva has been directed to a study of the nature of vitamin C and to the improvement of methods for its estimation. With Dr. Bourdillon and Mr. Webster of the National Institute, he has studied a method for the assessment of the action of vitamin D. Tests have also been made of the activity of various stored antiscorbutic preparations provided for the British Arctic Air Route Expedition to Greenland.

At the Lister Institute, Dr. Harriette Chick and Dr. Margaret Fixsen have continued their work on the water-soluble B vitamins

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in relation to the 'biological values' of proteins. Deficiency of these vitamins in the diet of rats leads to immediate loss of appetite, and the apparent low biological values of the proteins, in these circumstances, are due to inadequate intake of carbohydrate and fat causing the proteins to be used for body fuel. The biological value of purified caseinogen is comparatively low; the values for the proteins of various cereals are now being redetermined by modern methods.

The different investigators in this field have done much work during the past year in preparation for the International Conference on Vitamin Standards, held in London in June under the auspices of the League of Nations: some account of this has already been given at p. 53. Reference has been made under other heads to work on vitamins by Professor E. Mellanby, at Sheffield (p. 65).

T. W. Birch and B. C. Guha—
'The Chemical Nature of Vitamin B_1 from Evidence Afforded by its Electrical Transference.' *Biochem. J.*, 1931, **25**, 1391.
M. F. Bracewell and S. S. Zilva—
'Vitamin C in the Orange and the Grape Fruit.' *Biochem. J.*, 1931, **25**, 1081.
M. F. Bracewell, F. Kidd, C. West, and S. S. Zilva—
'The Antiscorbutic Potency of Apples. II.' *Biochem. J.*, 1931, **25**, 138.
M. F. Bracewell, T. Wallace, and S. S. Zilva—
'The Antiscorbutic Potency of Apples, III.' *Biochem. J.*, 1931, **25**, 144.
C. W. Carter—
'Heart Block in Pigeons, Curative Factor.' *Biochem. J.*, 1930, **24**, 1811.
C. W. Carter, H. W. Kinnersley, and R. A. Peters—
'Maintenance Nutrition in the Adult Pigeon, and its Relation to Torulin (Vitamin B_1). I.' *Biochem. J.*, 1930, **24**, 1832. 'II.' *Ibid.*, 1930, **24**, 1844.
W. J. Dann and T. Moore—
'The Effect of Vitamin B Deficiency upon the Vitamin A Reserves of the Rat.' *Biochem. J.*, 1931, **25**, 914.
J. C. Drummond—
'Note on the Subcutaneous Administration of Vitamin D.' *Lancet*, Lond., 24th Oct. 1931.
M. A. B. Fixsen—
'The Biological Values of Proteins. II. The Biological Value of Purified Caseinogen and the Influence of Vitamin B_2 upon Biological Values, Determined by the Balance Sheet Method.' *Biochem. J.*, 1930, **24**, 1794.
N. Gavrilescu and R. A. Peters—
'Biochemical Lesions in Vitamin B Deficiency.' *Biochem. J.*, 1931, **25**, 1397.
L. J. Harris and J. R. M. Innes—
'The Mode of Action of Vitamin D. Studies on Hypervitaminosis D. The Influence of the Calcium-phosphate Intake.' *Biochem. J.*, 1931, **25**, 367.
E. M. Hume and H. H. Smith—
'Calcification of the Bones of Rats on a Diet low in Ergosterol.' *Biochem. J.*, 1931, **25**, 292.
'The Relation of a Fat-free Diet to the Scaly Tail condition in Rats described by Burr and Burr.' *Ibid.*, 1931, **25**, 300.
'The Value of Foodstuffs for Vitamin A.' *Lancet*, Lond., 20th Dec., 1930.

F. E. Humphreys and S. S. Zilva—
'Metabolism in Scurvy. III. The Absorption and Retention of Calcium and Phosphorus by Guinea-pigs.' *Biochem. J.*, 1931, **25**, 579.

B. C. P. Jansen, H. W. Kinnersley, R. A. Peters, and V. Reader—
'The Curative Activity of the Antineuritic Vitamin of Rice.' *Biochem. J.*, 1930, **24**, 1824.

H. W. Kinnersley and R. A. Peters—
'The Relation of Hydrogen Ion Concentration to the Precipitation of Purified Torulin (Yeast Vitamin B_1) by Phosphotungstic Acid.' *Biochem. J.*, 1930, **24**, 1856.

H. W. Kinnersley, R. A. Peters, and V. Reader—
'A Quantitative Comparison of the Curative Activity of Torulin (Vitamin B_1) upon the Adult Pigeon and the Adult White Rat.' *Biochem. J.*, 1930, **24**, 1820.

T. Moore—
'Vitamin A and Carotene. VII. The Distribution of Vitamin A and Carotene in the Body of the Rat.' *Biochem. J.*, 1931, **25**, 275.

V. Reader—
'The Assay of Vitamin B_4.' *Biochem. J.*, 1930, **24**, 1827.

H. Schütze and S. S. Zilva—
'Tuberculin Sensitivity in Rats.' *Brit. J. Exp. Path.*, 1930, **11**, 489.

S. S. Zilva—
'The Antiscorbutic Fraction of Lemon Juice. IX.' *Biochem. J.*, 1930, **24**, 1687.
'A Note on the Reprecipitation of the Antiscorbutic Factor from Decitrated Lemon Juice.' *Ibid.*, 1931, **25**, 594.

Dental Disease

The Committee (p. 136), of which Dr. H. C. T. Langdon acts as Secretary by arrangement with the Board of Education, continue to advise the Council on this subject. An important contribution towards the expenses of this work is made by the Dental Board of the United Kingdom.

Working under the direction of Dr. P. P. Laidlaw at the National Institute, Mr. G. E. S. Jeffery, with a personal grant, has investigated the permeability of dental enamel. This is important for an understanding of the means by which the nutrition of the teeth is maintained during life. It had previously been doubted whether the enamel was permeable. It has now been demonstrated by an electrical method that dyes and other substances can be made to pass rapidly through the enamel of teeth from young dogs. This permeability, however, decreases with advancing age. Similar results have been obtained with human teeth, though the process takes longer owing to their higher degree of calcification. Sections through the enamel show that the dyes are confined to the prism sheath.

Dr. E. W. Fish, receiving expenses at the Royal Dental Hospital, London, has completed his investigations of the age changes in enamel, and has continued his experiments on pulp reactions to injuries of the dentine. With Dr. Maclean, he has studied the viability in the dog of *Streptococcus mutans*, associated with human

caries. Work on the relation of vitamin C to the teeth has been continued, with Dr. L. J. Harris (p. 79) of the Dunn Nutritional Laboratory, Cambridge.

At Sheffield, Mrs. M. Mellanby has maintained her experimental studies of the relation of diet to periodontal disease, and is investigating, with Dr. C. Lee Pattison at the King Edward VII Hospital, the effects of a cereal-free diet rich in vitamin D on the progress of caries. In addition, with Dr. Langdon, she has continued to supervise the large-scale inquiry at Birmingham, already mentioned at p. 12, into the influence of diet on caries in children's teeth. Grants in respect of this investigation have again been made to Mr. A. Deverall and Miss M. Reynolds, and an interim report has been published by the Council.

Mr. E. Sheldon Friel, at Dublin, has continued the investigation of 'close-bite', for which he received expenses. The anthropometric measurements made in the past two years have been grouped according to age, and have been submitted to Dr. M. Young (p. 119) for statistical analysis. So far no consistent difference has emerged between the averages of the normal and 'close-bite' cases, but it is hoped that, with further analysis, some significant result may be obtained.

Dr. Matthew Young has also analysed the data collected for the Committee by Miss K. C. Smyth on the facial measurements of about 12,000 school-children with normal occlusion of the teeth. The object of this inquiry has been to establish standards of the various measurements of the face at different ages, and to determine the direction and normal rate of growth of the jaws in childhood as a basis for the study of the abnormal. A report will shortly be published by the Council, and an analysis of a corresponding series of measurements in children with abnormalities of the jaws is now being made.

'The Influence of Diet on Caries in Children's Teeth.' Interim Report by the Committee upon Dental Disease. *Sp. Rep. Ser. Med. Res. Coun.* Lond., No. 159, 1931.

E. W. Fish—

'The Pathology of the Dentine.' *Proc. 7th Aust. Dent. Congr.*, Brisbane, July 1930, p. 72.

'The Clinical Application of some Recent Research Work on the Dentine.' *Birmingham Med. Rev.*, 1930, 5, 164.

'A Résumé of Recent Research Work on the Dentine.' *Tijdschr. tandheelk.*, 1930, **37**, 178.

'Age Changes in the Permeability of Dog's Enamel.' *J. Physiol.*, 1931, **72**, 321.

Neurology.

In Sir Charles Sherrington's Department at Oxford, Dr. J. C. Eccles receives a part-time grant and has continued his studies of reflex action. Work during the year has thrown new light upon

some of the events in a motor neurone before and during the setting up of a reflex discharge. This has led to an investigation, with Mr. H. E. Hoff, of the rhythmic responses of motor neurones, and a mathematical study of the conditions underlying rhythmic discharge has been undertaken. An attempt is also being made to determine whether the behaviour of the rhythmic centre of the heart conforms with that of a motor neurone. Preliminary accounts of these studies have been published.

At the National Hospital, Queen Square, London, Dr. D. E. Denny Brown has perfected the torsion myograph for which he received expenses. It is hoped shortly by this means to investigate the neuro-muscular mechanisms in disease. At the same hospital Dr. Macdonald Critchley has an expenses grant and has continued his clinical and pathological studies of senile changes in the nervous system. In the pathological investigations he has again had the co-operation of Dr. J. G. Greenfield. He is also making a microscopic study of the basal arteries and choroid plexus of the brain at different ages: this work is being done at King's College Hospital with Dr. A. Gilpin and Dr. D. J. C. Earl.

Dr. Ruby Stern, at the National Hospital, has continued with a part-time grant her work on syphilis of the nervous system. Attention has been directed this year to the pathology of the rarer forms of cerebral syphilis and its relation to clinical symptoms. With Dr. E. A. Carmichael (p. 63), Miss Stern has studied the pathology of five cases of alcoholic neuritis with Korsakow's syndrome. The lipoid content of the brain-cells was found to resemble that in pellagra, and the suggestion has been made that this syndrome may result from lack of a factor essential to lipoid metabolism. A grant for assistance has recently been made to Dr. Carmichael, at this hospital, for studies of the effects of diet in epilepsy.

A part-time grant has been made to Dr. R. G. R. West, at St. Bartholomew's Hospital, London, for experimental work on tetany. With Professor H. Hartridge, it has been shown that minute doses of curare may abolish parathyroid tetany without causing paralysis. Work is in progress to test the action of curare in different nervous diseases in man.

At the London Hospital, Dr. Dorothy S. Russell receives a personal grant for the study of tumours of the brain. With Mr. Hugh Cairns, an investigation has been made of the gliomata, with reference to their metastases in the brain and spinal cord. Several cases of tumours arising in the retina of the eye have been examined.

Miss E. C. Eaves at Sheffield has again had part-time and expenses grants and the assistance of Miss M. M. Croll. Further observations have been made on the pathology of chronic epidemic

encephalitis. It has been found that even in cases of long duration there is little wasting of the brain and little loss of phosphorus compounds. This is in contrast to what is found in degenerative nervous diseases such as general paralysis of the insane and Huntingdon's chorea. On the other hand, an increase of calcium salts in the brain is relatively common in encephalitis. The changes in the cells of the cortex and mid-brain in chronic encephalitis have been investigated, and a study has been made of the resulting tract degenerations in the spinal cord in this disease. Microscopic studies of the posterior lobe of the normal human pituitary have also been continued, with special reference to the nerve-supply of the gland-tissue.

Further work on tumours of the brain has been done by Dr. F. E. Reynolds with grants at the Scottish Asylums Research Laboratory in the University of Edinburgh. A study of bacterial infections of the nervous system has been published with Mr. A. Logan Turner. Under the direction of Dr. Reynolds, work is in progress at this laboratory on the role of the microglia in destructive lesions of the brain, and on the lymphatic channels of the peripheral nerves.

Other work at Edinburgh, dealing with injuries to the head, has already been mentioned at p. 71.

The Council have again provided the expenses of work at Edinburgh by Sir E. Sharpey Schafer and his colleagues. Further studies have been made of the effects on the thyroid and pituitary glands, and on metabolism, of joining the phrenic nerve to the cervical sympathetic. Mrs. M. Cameron has continued here her observations on the regeneration of the cardiac fibres of the vagus nerve after injury.

With a part-time grant, at Liverpool, Dr. Tudor Jones has extended his observations on the nerve-supply of small blood-vessels and on the comparative anatomy of the conducting mechanisms of the heart.

In Professor Winifred Cullis's Department, at the Royal Free Hospital, London, Dr. Evelyn Hewer receives a grant. With Professor M. F. Lucas Keene, further studies have been made of the development of the nervous system in the human foetus.

Dr. R. S. Allison, of Ruthin Castle, Wales, has published the results of an inquiry into the incidence of disseminated sclerosis in North Wales. His expenses were provided by the Council.

For part of the year under review the Council continued their part-time grant to Miss K. Chevassut, working at the Westminster Hospital in the endeavour to confirm her published evidence for a filter-passing organism in disseminated sclerosis. In view of the use that had been made of her work in practising a vaccine therapy of the disease, the Council had arranged, as they explained

in their last Report, for an independent investigation at the National Institute by Dr. Carmichael, in association with other experienced observers, of the evidence she had put forward. His results failed to confirm Miss Chevassut's work, and she was not able herself either to find additional evidence or to account for the discrepancies between her work and that of others. The Council, with the assistance of the medical and pathological staff at the National Hospital, Queen Square, proposed a simple crucial test for the validity of her fundamental observations. After a preliminary test of this kind had given a negative result, she refused to take part in another, and the Council, at the end of 1930, terminated her grant and withdrew the other forms of assistance they had given.

R. S. Allison—
'Disseminated Schlerosis in North Wales. An Inquiry into its Incidence, Frequency, Distribution, and other Aetiological Factors.' *Brain*, 1931, **53**, 391.
E. A. Carmichael—
'A Study of a Human Mid-brain Preparation.' *J. Neurol. Psychopath.*, 1930, **10**, 324.
'The Aetiology of Disseminate Sclerosis: some Criticisms of recent Work, especially with regard to the "spherula insularis".' *Proc. R. Soc. Med.*, 1931, **24**, 25.
E. A. Carmichael and R. O. Stern—
'Korsakoff's Syndrome: its Histopathology.' *Brain*, 1931, **54**, 189.
M. Critchley—
'The Neurology of Old Age.' Goulstonian Lectures. *Lancet*, Lond., 23rd May, 6th and 20th June 1931.
E. C. Eaves—
'Some observations on Calcium and Phosphorus in the Brain in Different Conditions.' *Brit. J. Exp. Path.*, 1931, **12**, 113.
J. C. Eccles—
'Studies on the Flexor Reflex. III. The Central Effects Produced by an Antidromic Volley.' *Proc. Roy. Soc.*, B, 1931, **107**, 557.
J. C. Eccles and H. E. Hoff—
'Rhythmic Responses of Motoneurones.' (Preliminary communication.) *Proc. Physiol. Soc., J. Physiol.*, 1931, **71**, xxi.
'Stimulation of the Pace-maker of the Mammalian Heart.' *Ibid.*, 1931, **72**, Proc. 31.
J. C. Eccles and C. Sherrington—
'Studies on the Flexor Reflex. I. Latent Period.' *Proc. Roy. Soc.*, B, 1931, **107**, 511. 'II. The Reflex Response Evoked by Two Centripetal Volleys.' *Ibid.*, 1931, **107**, 535. 'IV. After Discharge.' *Ibid.*, 1931, **107**, 586. 'V. General Conclusions.' *Ibid.*, 1931, **107**, 597. 'VI. Inhibition.' *Ibid.*, 1931, **109**, 91
H. Hartridge and R. West—
'Parathyroid Tetany in Dogs, and its Abolition by Curare.' *Brain*, 1931, **54**, 312.
F. E. Reynolds and J. K. Slater—
'Ueber die Pathologie der Gliome.' *Virchows Arch.*, 1931, **282**, 772.
E. Sharpey-Schafer—
'The Nomenclature of the Autonomic Nervous System.' *J. Physiol.*, 1931, **71**, 362.
C. S. Sherrington—
'Quantitative Management of Contraction in Lowest Level Co-ordination.' Hughlings Jackson Lecture. *Brain*, 1931, **54**, 1.

A. L. Turner and F. E. Reynolds—
Intracranial Pyogenic Diseases. Edinburgh (Oliver & Boyd), 1931.
R. West—
'Pituitary Cyst. An account of a Case with Tonic Fits resembling Tetany.' *Lancet*, Lond., 11th July 1931.

Psychology and Psychiatry

A part-time grant has been made to Miss M. Ekenberg, at the Children's Clinic, London, for a study of psycho-neuroses in childhood. Special attention is being paid to the investigation and treatment of nocturnal enuresis by psychological methods.

At the Maudsley Hospital, London, Mrs. M. A. B. Brazier receives a personal grant for work under the direction of Dr. F. L. Golla. She is studying, by means of specially designed apparatus, the electrical capacity and resistance of the human body in normal and abnormal psychical states.

An inquiry into the aetiology of mental deficiency is being made by Dr. L. S. Penrose at the Royal Eastern Counties Institution, Colchester. This is supported jointly by the Council, the Darwin Trust, and the Institution. About 200 cases have been examined from the physical, mental, and genetic points of view, and attempts are being made to find the parts played in causation by heredity and other factors.

Dr. F. A. Pickworth, at the Hollymore Mental Hospital, Birmingham, has received expenses. Further study has been made of the relation of nasopharyngeal sepsis to infection within the cranial cavity and to symptoms of mental disorder.

At the Cardiff City Mental Hospital a grant has again been made for investigations under the general direction of Dr. P. K. McCowan, the Medical Superintendent, and Dr. J. H. Quastel has been provided with assistance in his biochemical work by Mr. A. M. H. Wheatley and Mr. D. R. Davies. Studies have been made of the blood-sugar level in cases of mental disorder, and these have given evidence of a close relationship between the sustainment of hyperglycaemia and the emotional tension of the subject. The use of the 'hyperglycaemic index' has proved of value in following the course of treatment of patients in the manic-depressive group. Dr. Quastel and Mrs. Penrose have continued their work on the relation between the oxidative activity of a cell and its structure, a point which has an important bearing on the chemical activity of the brain: it is shown that any modification of the brain-cells, by toxins for instance, is likely to be reflected first in a decrease or cessation of the normal processes of oxidation. This has been followed up by a study of the types of substances which inhibit oxidation in the brain cortex and other tissues. Another investigation has dealt with the action of dye-stuffs on the catalytic activity of various tissues.

Reference has been made under the preceding head to work by Dr. F. E. Reynolds in the Scottish Asylums Laboratory at Edinburgh. Investigations in industrial psychology are mentioned at p. 123 below.

P. K. McCowan and J. H. Quastel—
'Blood Sugar Studies in Abnormal Mental States.' *J. Ment. Sci.*, July 1931, and *Lancet*, Lond., 3rd Oct. 1931.

L. S. Penrose—
'The Creases on the Minimal Digit in Mongolism.' *Lancet*, Lond., 12th Sept. 1931.

J. H. Quastel—
'A Colour Test for O-Dihydroxy Phenols.' *Analyst*, 1931, **56**, 311.
'The Action of Dyestuffs on Enzymes. II. Fumarase.' *Biochem. J.*, 1931, **23**, 898.
'Trypanocidal Action and Toxicity to Enzymes.' *Ibid.*, 1931, **25**, 1121.

J. H. Quastel and A. H. M. Wheatley—
'Biological Oxidations in the Succinic Acid Series.' *Biochem. J.*, 1931, **25**, 117.
'The Action of Dyestuffs on Enzymes. I. Dyestuffs and Oxidations.' *Ibid.*, 1931, **25**, 629.

Tuberculosis

Two committees (p. 137), of which Dr. A. S. MacNalty acts as Secretary by arrangement with the Ministry of Health, continue to supervise work in this subject. Reference to the Dorothy Temple Cross Fellowships in Tuberculosis is made at p. 127.

In the whole-time service of the Council, at the Field Laboratories, Cambridge, Dr. A. Stanley Griffith has continued his studies of the incidence of bovine tuberculosis in man. He has confirmed his previous observations that this type of infection is rarely met in the lungs, but is commonly the cause of bone and joint disease. Of the cases of tuberculous meningitis so far examined, 30 per cent. have yielded bacilli of the bovine type. He has continued his work with Professor J. B. Buxton upon methods of immunizing cattle against tuberculosis. This has included studies of the value of immunization by B.C.G. vaccine in comparison with that of other methods. Material equipment in buildings for this work was provided by a grant from the Empire Marketing Board. The success already attained in immunizing calves against tuberculous infection has justified the Council in providing the cost of experiments on a larger scale which are now in progress. Further studies have been made with Dr. L. J. Harris (p. 79) of the influence of vitamin deficiency upon resistance to tuberculosis, and of the value of irradiated ergosterol in promoting calcification in tuberculous lesions.

Professor S. L. Cummins, of the Welsh National Memorial Association, Cardiff, has had grants for expenses and for assistance by Dr. Cicely Weatherall and Dr. Enid Williams. With Dr. Weatherall, studies have been made of the effects of different

chemical compounds on cultures of the tubercle bacillus, with a view to the chemotherapy of tuberculosis. Attempts have also been made to grow tubercle bacilli from the blood of patients with various clinical forms of the disease.

Work with Dr. A. F. S. Sladden on the pathology of 'coal-miner's lung' is mentioned separately below (p. 121). In relation to this, Professor Cummins and Dr. Weatherall are investigating the adsorbent action of coal dust on the active principle of tuberculin. They have found experimentally that anthracite dust renders tuberculin inert, and the suggestion is made that herein lies a possible explanation of the relative immunity of coal-miners to tuberculosis. A clinical and pathological study of the lungs of retired coal-miners has been made by Dr. Enid Williams.

At Oxford Dr. R. L. Vollum receives a part-time grant for work under the general direction of Professor G. Dreyer. He has studied further the effect of cultural conditions in increasing the virulence of 'B.C.G.', and has investigated the conditions under which *B. tuberculosis* may circulate in the blood. Evidence has been obtained that tubercle bacilli may be present in visceral lesions, or in the blood, in a 'chromophobic' state, in which they may be small in size, non-acid fast, and unstainable by the usual methods. They may, however, be seen in simple wet preparations from young cultures, stained with methylene blue.

Dr. W. M. Cumming, of Grassington Sanatorium, Yorkshire, has a grant for the expenses of an inquiry into the different strains of tubercle bacilli that may be present in the sputum in phthisis. Special attention has been given to cases with a previous history of glandular tuberculosis.

With part-time and expenses grants Dr. S. Roodhouse Gloyne, at the City of London Hospital for Diseases of the Chest, has continued his study of improved cultural methods for the detection of tubercule bacilli in milk.

Further work on the chemistry of the tubercle bacillus has been done by Mr. E. T. Waters, receiving grants for assistance to Dr. W. H. Tytler at the Central Tuberculosis Laboratory of the Welsh National Memorial Association, Cardiff. Studies of the specific polysaccharide have been extended, and efforts have been made to isolate from the protein the nucleic acid fraction which is held to be responsible for the allergic reaction.

At Glasgow, Dr. Mary A. Griffin is investigating the effect of chemical and physical agents on the antigenic properties of the tubercle bacillus.

An expenses grant has been made to Mr. E. G. Bowen, of Aberystwyth, for field studies of the incidence of tuberculosis in Wales, in relation to racial type and social environment. In consultation with Professor S. L. Cummins and Professor H. J. Fleure,

a survey has been made of central Wales, and the work is being extended to include Breconshire and Carnarvonshire.

The Council have published a report by Dr. P. M. D'Arcy Hart, of University College Hospital, London, on the diagnostic use of tuberculin in the human subject.

Reference has already been made at p. 40 to work at the National Institute on the chemistry of the tubercle bacillus.

J. B. Buxton and A. S. Griffith—
'The Use of B.C.G. in the Vaccination of Calves against Tuberculosis. Interim Report.' *Lancet*, Lond., 21st Feb. 1931.

W. M. Cumming, S. J. Hartfall, and J. G. Thomson—
'Latent and Occult Tuberculous Infection of Bronchial Glands.' *J. Path. Bact.*, 1931, **34**, 157.

S. L. Cummins—
'Metal Therapy in Tuberculosis.' *Bull. Hyg.*, 1931, **6**, 455.

S. L. Cummins and S. B. H. Walker—
'Investigation and Assessment of One Hundred Cases of Pulmonary Tuberculosis.' *Tubercle*, Lond., 1931, **12**, 155.

S. L. Cummins and C. Weatherall—
'The Retardation of Lytic Processes by Colloidal Silica Solution.' *Brit. J. Exp. Path.*, 1931, **12**, 239.
'Effects of Colloidal Silica upon the Growth of Tubercle Bacilli in Blood.' *Ibid.*, 1931, **12**, 245.

S. L. Cummins, C. Weatherall, and E. T. Waters—
'Adsorption of Tuberculin by Coal Dust.' *J. Hyg.*, Camb., 1931, **31**, 464.

P. D'Arcy Hart—
'The Value of Tuberculin Tests in Man, with special reference to the Intracutaneous Test.' *Sp. Rep. Ser. Med. Res. Coun.*, Lond., No. 164, 1932.

G. Dreyer and R. L. Vollum—
'Mutation and Pathogenicity Experiments with B.C.G.' *Lancet*, Lond., 3rd Jan. 1931.
'Bacillaemia in Experimental Tuberculosis together with Experiments on Mutation and Pathogenicity of a Human Strain of *B. tuberculosis*.' *Ibid.*, 9th May 1931.

A. S. Griffith—
'Studies of Protection against Tuberculosis. Results with B.C.G. Vaccine in Monkeys.' *Sp. Rep. Ser. Med. Res. Coun.*, Lond., No. 152, 1931.
'Chronic Infection of the Udder of a Goat with Avian Tubercle Bacilli.' *J. Comp. Path.*, 1931, **44**, 144.

Bovine Tuberculosis in Scotland

Support has again been given to an inquiry into the incidence of tuberculosis among herds in Scotland, with special reference to the hygiene of the milk supply. Particulars of this investigation were given in the Annual Report for 1928–29. Bacteriological studies are being made to determine in what proportion of cows reacting to the tuberculin test the milk is infected.

In a selected part of Ayrshire, where eradication is being attempted, 50 per cent. of the herds have now been freed from the disease. The total percentage of tuberculin-reactors in the area shows a steady decrease, especially in the case of young animals.

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The demand from farmers outside the area to be allowed to come under the scheme is increasing, and much advice has been given upon the disinfection of farm premises and the isolation and feeding of stock. The work is being done by Mr. L. Jordan, M.R.C.V.S., from the Hannah Dairy Research Institute. Dr. A. Stanley Griffith, of Cambridge, continues to co-operate in the bacteriological work.

A. B. Fowler and N. C. Wright—
'Reactors in Tuberculin-Tested (Licensed) Herds.' *Hannah Dairy Research Institute, Bulletin No.* 2, 1931.

L. Jordan—
'Eradication of Bovine Tuberculosis.' *Official Handbook of the Council of Milk Recording Societies,* 1931, p. 70.

Cell and Tissue Growth

The work supported by the Council under this head is almost wholly centred at the Strangeways Laboratory, Cambridge, where the Council have provided a large part of the general upkeep from the beginning. They provide the personal grants here to Dr. F. G. Spear, Dr. Janet S. F. Niven, and Mr. W. H. Love. Dr. H. B. Fell has continued her investigation, by tissue culture methods, of the ossification of the bones in the chick. Micro-dissections have also been made of cells growing *in vitro*. In confirmation of previous work, it has been shown that the cell is killed by puncture of the nucleus, although it can recover from injury to the cytoplasm. In cells with two nuclei, degenerative changes appear around the injured nucleus, but recovery of the cell is possible. Actively dividing cells are particularly susceptible to injury.

The Council have been pleased to learn that the Royal Society have now appointed Dr. Fell to a whole-time research Fellowship for a period of five years, in recognition of the value of her work and of the supervision she is giving to the important group of researches in this laboratory.

Mr. C. H. Waddington has extended his studies of the development of bird embryos artificially cultivated. During part of the year he worked under Professor Goldschmidt at Berlin, while holding a Rockefeller Medical Fellowship awarded by the Council. Dr. P. D. F. Murray has studied by tissue culture methods the differentiation of the red-blood cells in the chick. An inquiry by Dr. Janet Niven into the repair of embryonic long bones has been completed. She is also investigating the proliferative capacity of cartilage cells at different stages of development. Miss K. Tansley (p. 99) is studying in artificial culture the regeneration of the visual purple of the eye.

Further work on the effect of X-rays on tissue cultures of normal and malignant cells has been done by Miss S. F. Cox. In relation

to this, Mr. Love is investigating the effects of homogeneous X-radiation on Jensen's rat sarcoma. Dr. Spear has continued his work on the delayed lethal effects of gamma rays on tissues artificially grown. Studies have been made of the effects of spaced radiation on the mitosis of cells, and it has been found that repeated short exposures have a more powerful effect than continuous irradiation of the same total duration. This inquiry has already been practically useful in the guidance of the treatment of cancer by particular radiological methods.

Working in the biochemistry department, Cambridge, and at the Strangeways Laboratory, Mrs. B. E. Holmes and Miss E. Watchorn have again received personal grants. They have completed their study of the effects of different carbohydrates on the nitrogen metabolism of embryo kidney, and have begun an investigation of the influence of gamma rays on the metabolism of cells in culture.

R. Chambers and H. B. Fell—
'Micro-operations on Cells in Tissue Cultures.' *Proc. Roy. Soc.*, B, 1931, **109**, 380.

S. F. Cox—
'Tissue Culture and its Applications to Radiological Problems—Time and Intensity Factors in Dosage.' *Brit. J. Radiol.*, 1931, **4**, 111.
'Sensitivity to X-rays of Cells *in vitro*.' *Arch. exp. Zellforsch.*, 1931, **11**, 121.

H. B. Fell—
'Osteogenesis *in vitro*.' *Arch. exp. Zellforsch.*, 1931, **11**, 245.

H. B. Fell and R. Robison—
'The Development and Phosphatase Activity *in vivo* and *in vitro* of the Mandibular Skeletal Tissue of the Embryonic Fowl.' *Biochem. J.*, 1930, **24**, 1905.

H. B. Fell and E. N. Wilmer—
'The Structure, Behaviour, and Physiological Characteristics of Vertebrate Cells cultivated *in vitro*.' *Trans. Faraday Soc.*, 1930, **26**, 772.

W. H. Love—
'The Occurrence of Mitosis in Tissue Cultures.' *Arch. exp. Zellforsch.*, 1931, **10**, 442.
'Some Effects of X-Radiation on Dividing Cells in Tissue Cultures. Part I.' *Ibid.*, 1931, **11**, 435.

J. S. F. Niven—
'The Repair *in vitro* of Embryonic Skeletal Rudiments after Experimental Injury.' *J. Path. Bact.*, 1931, **34**, 307.

F. G. Spear—
'The Delayed Lethal Effect of Radium on Tissue Cultures *in vitro*—Comparison of Continuous and Spaced Radiation.' *Proc. Roy. Soc.*, B, 1931, **108**, 190.
'Immediate and Delayed Effects of Radium (Gamma Rays) on Tissue Cultures *in vitro*.' *Brit. J. Radiol.*, 1931, **4**, 146.

E. Watchorn and B. E. Holmes—
'Studies in the Metabolism of Tissues Growing *in vitro*. IV. Effect of Fructose, Galactose, and Xylose upon the Ammonia and Urea Production of Embryo Kidney Tissue.' *Biochem. J.*, 1931, **25**, 843.

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Malignant Disease

Cancer research in Great Britain has long received much support from various private funds derived from voluntary contributions in gifts or legacies. The Imperial Cancer Research Fund and the younger British Empire Cancer Campaign are two chief agencies for the promotion of this kind of work, and at various special Hospitals work is supported in the same field. It has always been the policy of the Council to co-operate as closely as may be possible with these several interests and so to expend their own funds as to get the best co-ordination and economy in common effort.

Work closely related to problems of cancer is described under the last heading, and also under that of the National Institute at p. 34 above. Other investigations into cancer are noticed in the clinical and biochemical sections (pp. 67, 70, 107). Studies of the treatment of malignant disease by radium and X-rays are mentioned separately below in the next section. The following studies of the conditions governing tumour growth have also been assisted by the Council.

Dr. Helen Chambers, at the Middlesex Hospital, has again received a whole-time grant. Work has been continued on the experimental production of immunity to tumours. It has been found that during the degenerative changes which follow when malignant cells are deprived of their normal blood-supply, a stage is reached at which the cells acquire a fleeting property of being able to produce immunity to themselves. Inoculated with living tumour cells, an animal thus immunized fails to produce a growth, although the transmission of this particular tumour is readily obtained in untreated controls. These results may have a possible application to the treatment of some forms of human cancer, and it is proposed to begin clinical experiments on these lines at the Marie Curie Hospital.

Further work on immunity to tumours has been done by Mr. W. E. M. Wardill at the College of Medicine, Newcastle-on-Tyne. The Council have provided expenses.

In Professor Crew's Department at Edinburgh, Dr. Esmé Gilroy has again received grants. She has continued her studies of the effects of arginine and of thyroxine on mice with transplantable tumours. She has at the same time studied the vitamin B content of commercial liver extracts: evidence has been obtained that these could be used with advantage where it is desired to give large doses of the B vitamins.

At the Middlesex Hospital, Dr. F. Dickens, a member of the Council's staff, has continued his work with Dr. F. Šimer on the respiration of normal and tumour tissues. They have confirmed the defective oxidation of carbohydrate in tumour cells, and are

investigating further the nature of the defect. Other work by Dr. Dickens is mentioned at p. 107.

With a part-time grant, at Cambridge, Mrs. A. Pirie has co-operated with Mrs. B. E. Holmes (see p. 94) in biochemical studies of the Rous sarcoma, with special reference to the inactivation of filtrates and the properties of the tumour-producing agent. An account of this work has been published.

At the request of the Council last summer, Dr. F. Campbell Smith, Dr. E. R. Holiday, and Dr. J. R. Marrack undertook at the London Hospital an investigation of the Bendien spectrophotometric test for cancer. The results, which have been published, were unfavourable to the claims that had been made for the value of this test as a method of diagnosis.

F. Dickens—
'Cancer as a Problem in Tissue Metabolism.' *Cancer Rev.*, 1931, **6**, 57.

F. Dickens and D. H. Patey—
'Observations on Metabolism of Human Mammary Carcinoma.' *Lancet*, Lond., 6th Dec. 1930.

F. Dickens and F. Šimer—
'The Metabolism of Normal and Tumour Tissue. III. A Method for the Measurement of Respiratory Quotient in Serum.' *Biochem. J.*, 1931, **25**, 973. 'IV. The Respiratory Quotient in Bicarbonate-Media.' *Ibid.* 1931, **25**, 985.

E. Gilroy—
'Further Observations upon the Correlation between the Arginine and Vitamin B content of Diets, and the Effect of Thyroxine upon Tumour Growth.' *Biochem. J.*, 1930, **24**, 1659.
'The Effect of Arginine upon the Body Weight of Mice Injected with Thyroxine, and Bearing the Tumour M 63.' *Ibid.*, 1931, **25**, 414.
'The Vitamin B Content of Commercial Liver Extracts and Stomach Preparations.' *Lancet*, Lond., 14th Nov. 1931.

B. Holmes—
Cancer and Scientific Research. London (Sheldon Press), 1931.

A. Pirie and B. E. Holmes—
'The Cause of Inactivation of the Rous Sarcoma Filtrate during Incubation.' *Brit. J. Exp. Path.*, 1931, **12**, 127.

F. C. Smith, E. R. Holiday, and J. Marrack—
'An Investigation of the Spectrophotometric Aspects of the Bendien Test.' *Lancet*, Lond., 29th Aug. 1931.

Radiology and Radium Therapy

Researches into the medical uses of radium, particularly in the treatment of cancer, is directed for the Council by the Radiology Committee (p. 138), who also serve the interests of the British Empire Cancer Campaign in radiology.

The stock of radium held by the Council on behalf of H.M. Government has been supplemented by a further quantity provided by the British Empire Cancer Campaign and, more recently, by a loan of one gramme from the National Radium Commission. The British Empire Cancer Campaign continues to defray the

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current expenses of the radon centre at the Middlesex Hospital, where an important fraction of the Council's radium is kept in solution as a source of emanation. The following centres have again taken part in a co-ordinated scheme of research work into the treatment of cancer: The Middlesex Hospital, London; St. Bartholomew's Hospital, London; University College Hospital, London; St. Peter's Hospital, London; St. Mark's Hospital, London; The Marie Curie Hospital, London; The General Hospital, Birmingham; The Royal Infirmary, Manchester; The Royal Infirmary, Cardiff; The Royal Infirmary, Aberdeen; and the Irish Radium Committee, Dublin.

A few other institutions share in the facilities for the supply of radon, and a supply of radium is lent for experimental purposes to Dr. J. C. Mottram, at the Radium Institute, London. Grants are made by the Council for assistance in the research work at the Middlesex Hospital, and to Dr. J. Gray (p. 110) at Aberdeen, who is co-operating with the Radium Officer there in the pathological examination of tumours before and after irradiation.

With the additional radium lent by the National Radium Commission, the Council have been able to assist clinical work on the treatment of cancer at the Royal Free Hospital, London, and by the Scottish Eastern Branch of the Medical Women's Federation, Edinburgh. Fractions of this radium have also been allocated for experimental work at the Lister Institute, London, the Strangeways Research Laboratory, Cambridge, and Professor D. P. D. Wilkie's department at Edinburgh.

A summary of the reports received from the clinical centres upon the work done in 1930 has been published.

'Medical Uses of Radium: Summary of Reports from Research Centres for 1930.' *Sp. Rep. Ser. Med. Res. Coun.*, Lond., No. 160, 1931.

M. Donaldson—

Treatment of Lymphatic Glands in Carcinoma of the Cervix Uteri.' *Brit. Med. J.*, 20th Dec. 1930.

'After-Effects of Irradiation of Uterus.' *Ibid.*, 1st August 1931.

A. Eidinow and J. C. Mottram—

'Divided Dosage in Radium Therapy.' *Lancet*, Lond., 6th June 1931.

J. C. Mottram—

'Interpretation of Blood Counts in Radium and X-ray Workers.' *Lancet*, Lond., 3rd Jan. 1931.

'Effect of Radiation on Macrophages.' *Ibid.*, 31st Jan. 1931.

'On the Disappearance of Lymphocytes from the Blood Following Exposures to X-rays and Radium.' *J. Path. Bact.*, 1931, **34**, 800.

'Secondary Radiation from Bone.' *Proc. R. Soc. Med.*, 1931, **24**, 1491.

'Experiments on the Susceptibility of Tumours and Tumour Cells to Radiation.' *Acta radiol.*, 1931, **12**, 1.

R. S. Pilcher—

'Radium and Pain. An Investigation of Certain Results of Radiotherapy in Cases Treated at University College Hospital.' *Lancet*, Lond., 28th Nov. 1931.

Biological effects of Radiation

Work done in this subject at the Strangeways Laboratory, Cambridge, has already been noticed (p. 93).

At the Middlesex Hospital, Dr. H. A. Colwell has again received a part-time grant. He has investigated the action of radium upon different chemical substances, and has continued his work on the effects of X-rays on chick embryos. Further clinical studies have been made of the use of fluorescein in conjunction with X-rays in the treatment of cancer.

Dr. Sylvia B. Wigoder, at the Royal Infirmary, Bristol, has had an expenses grant for work on the effect of X-rays on plant and animal tissues.

Vision and Hearing

At the Galton Laboratory, London, Dr. Julia Bell has again received a personal grant for work under the general direction of Professor Karl Pearson. Further studies have been made of hereditary diseases and anomalies of the eye, and other problems of inheritance. Special attention has been given to the aetiology of hereditary glaucoma in relation to the size of the eyeball.

With a part-time grant at St. Mary's Hospital, London, Miss Ida Mann has completed her work on the comparative morphology of the iris. An investigation has also been made of the development of the cornea in man and lower animals. Facilities for the comparative studies have been generously provided by the Zoological Society.

J. Bell—

'Hereditary Optic Atrophy (Leber's Disease).' *The Treasury of Human Inheritance, II. Anomalies and Diseases of the Eye. Nettleship Memorial Volume, Part IV*, 1931.

'Some New Pedigrees of Hereditary Disease. A. Polydactylism and Syndactylism. B. Blue Sclerotics and Fragility of Bone.' *Ann. Eugenics*, 1930, **4**, 41.

'Three Further Cases of Hereditary Digital Anomaly seen in the Outpatient Department of Great Ormond Street Hospital for Sick Children.' *Ibid.*, 1931, **4**, 233.

I. Mann—

'The Reptilian Iris.' *Trans. Ophthal. Soc. U.K.*, 1930, **50**, 310.

'Iris Patterns in Vertebrates.' *Trans. Zool. Soc. Lond.*, 1931, **21**, 355.

Physiology of Vision

The Committee shown at p. 139 have continued to supervise work on this subject, both in general and in its relation to particular problems of the Defence Services and of industries.

Under the general direction of Professor F. C. Bartlett at Cambridge, Miss M. D. Vernon, with a personal grant, has completed a general study of the physiological and psychological factors in reading. She has also investigated the effects and

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limitations of the simultaneous visual perception of form and movement, in particular the suggestion that the response to movement presented peripherally may inhibit the recognition of form or position simultaneously presented to direct vision. Mr. G. C. Grindley, with a part-time grant, has studied problems of peripheral and central perception; these have special reference to a constant illusion of position in the peripheral vision by which objects near the edge of the field are referred to a place nearer the centre of fixation than they actually occupy. A report has been published. An investigation of the visual effects of glare has revealed a distinction between the so-called 'disability' glare, which appears to have a harmful effect on vision, and 'discomfort' glare; the latter, while uncomfortable for the observer, seems to be accompanied by no diminution of visual efficiency. Preliminary experiments on a method for more accurate study of 'discomfort' glare have been carried out by Mr. A. H. O. Tozer.

With a part-time grant at Glasgow, Mr. R. W. Pickford is completing his study of the psychological processes involved in reading.

At University College, London, grants have again been made to Mr. W. S. Duke-Elder and Mrs. P. M. Duke-Elder for work on the physiology and pathology of intra-ocular pressure, with special reference to glaucoma. Studies have been made of the vascular responses of the eye, and the physical chemistry of the vitreous body is being further examined. Dr. E. B. Robertson, with a personal grant, has assisted in this work.

At the same place, Dr. R. J. Lythgoe receives a part-time grant and the assistance of Mrs. W. H. Corkill. He has continued his work on the relation of the adaptation of the eye to visual perception under different conditions. A detailed investigation has been made of the relation of pupil diameter to acuteness of vision.

At University College, also, Mrs. M. C. Bourne has had a part-time grant for work on the chemical changes of the optic lens associated with cataract, and a personal grant has been continued to Dr. W. A. Gray for a study of the pathology of infections after penetrating injuries of the eye.

Miss K. Tansley, with a grant for expenses, has completed a stage of her work upon visual purple and its relation to dark adaptation and to night blindness. A report has been published. She is now studying the regeneration of visual purple, by tissue culture methods, at the Strangeways Research Laboratory, Cambridge (p. 93).

At the Imperial College of Science, London, part-time grants for assistance to Professor L. C. Martin have been made to Mr. F. W. Warburton and Mr. W. J. Morgan. Further work has been done in colour vision, with special reference to the sensitivity of the eye to colour saturation.

Work at Cardiff by Mr. J. W. Tudor Thomas, on the replacement of opaque corneal tissue by grafting, has already been mentioned in the surgical section (p. 71).

The following investigations have been made for the Defence Services.

Surgeon-Commander M. B. Macleod, R.N., has completed his inquiry at the Naval Gunnery Schools into the factors making for proficiency in gunnery. A similar investigation into the factors involved in proficient signalling has also been concluded by Major R. M. Dickson, R.A.M.C., at the Royal Corps of Signals School, Catterick. Co-operation on the psychological side of these inquiries was given by Mr. E. Farmer and Mr. E. G. Chambers, of the staff of the Industrial Health Research Board. In these investigations, estimation of the relative importance of visual and of psychological factors was found to be affected by the fact that both the naval and military groups were already highly selected for visual efficiency.

Dr. H. Bannister, receiving a part-time grant at Cambridge, has made progress with his investigations into the visual factors in good marksmanship. With the co-operation of the War Office, facilities for these have been obtained at Aldershot, Shorncliffe, Colchester, and Dover. It is hoped that the information gained will throw light on the relations between eye dominance, shooting ability, and general soldierly efficiency. Dr. Bannister is at present collecting data from recruits on whom visual tests have been made in the past, in the hope of finding other physical factors which correlate with marksmanship.

J. Colle, P. M. Duke-Elder, and W. S. Duke-Elder—
'Studies on the Intra-Ocular Pressure. I. The Action of Drugs on the Vascular and Muscular Factors Controlling the Intra-Ocular Pressure.' *J. Physiol.*, 1931, **71**, 1.

W. S. Duke-Elder—
'An Investigation into the Effect upon the Eyes of Occupations involving Close Work.' *Brit. J. Ophth.*, 1930, **14**, 609.
'The Drainage of the Intra-Ocular Fluids.' *Ibid.*, 1930, **14**, 620.
'The Nature of the Vitreous Body.' *Ibid.*, 1930, Monograph Suppl. 4.
'New Observations on the Physiology of the Extra-ocular Muscles.' *Trans. Ophthal. Soc. U.K.*, 1930, **50**, 181.
'The Intra-ocular Pressure and the Drainage of the Aqueous Humour.' *Brit. J. Exp. Path.*, 1930, **11**, 438.
'The Metabolism of the Eye. I. Physiologic Aspects.' *Arch. Ophth.*, 1931, **6**, 1. 'II. Clinical Applications.' *Ibid.*, 1931, **6**, 158.

W. S. Duke-Elder and P. M. Duke-Elder—
'The Contraction of the Extrinsic Muscles of the Eye by Choline and Nicotine.' *Proc. Roy. Soc.*, B, 1930, **107**, 332.
'The Vascular Responses of the Eye.' *Ibid.*, 1931, **109**, 19.
'Studies on the Intra-ocular Pressure. II. The Physico-chemical Factors Controlling the Intra-ocular Pressure.' *J. Physiol.*, 1931, **71**, 268.

W. S. Duke-Elder, P. M. Duke-Elder, and J. C. Colle—
'Ophthalmo-Manometry.' *Brit. J. Ophthal.*, 1931, **15**, 575.

G. C. Grindley—
'Reports of the Committee upon the Physiology of Vision, IX.

Psychological Factors in Peripheral Vision.' *Sp. Rep. Ser. Med. Res. Coun.*, Lond., No. 163, 1931.

K. Tansley—
'The Regeneration of Visual Purple: Its Relation to Dark Adaptation and Night Blindness.' *J. Physiol.*, 1931, **71**, 442.

M. D. Vernon—
The Experimental Study of Reading. Cambridge (University Press), 1931.

The Physiology of Hearing

Work on fundamental auditory problems and on their practical implications continues to be directed by the Committee shown at p. 139.

At Cambridge, under Professor F. C. Bartlett, further experiments have been made on the effects of continuous auditory stimulation. The results so far give no evidence of auditory fatigue, but show some persistent after-effects that may probably be explained in terms of 'adaptation'. Miss K. G. Pollock has continued her inquiries into the psychological effects of noise and vibration on the performance of selected tasks. An interim report has been made, in which it is concluded that, while no experimental evidence is available to show that automatic performance is adversely affected by noise or vibration, the presence of noise must be regarded as an adverse condition which is met by an unconscious increase of effort. Although in some kinds of work a continuous noisy background often appears to have an initial stimulating effect, in constructive work involving mental effort a consistent slight deterioration has been observed. Discontinuous noise was found to be more subjectively disturbing than continuous noise, and 'meaningful' noise to be more or less disturbing than 'unmeaning' noise according to whether it was interesting or familiar.

At the request of the War Office, the Committee have continued their investigation into the qualities required by anti-aircraft listeners, and into the methods of training for this work. At Cardiff, Dr. J. H. Shaxby, with a grant for expenses and the assistance of Mr. F. H. Gage, has extended his observations on the phenomena of binaural stimulation with pure tones of varying intensity and frequency. His work has been chiefly concerned with the effects of time and intensity differences on accurate localization of sound reaching the two ears. Dr. H. E. O. James at Manchester, with a part-time grant, has also been working at problems of binaural stimulation. A report on the subject of sound localization is being published by the Council.

The Committee are supervising an investigation by Dr. G. P. Crowden, at the London School of Hygiene, of hearing standards and tests; this work is being done in co-operation with a medical sub-committee of the National Institute for the Deaf.

General Physiological Researches

At University College, London, Mr. J. B. Bateman has had a part-time grant for work under the direction of Professor A. V. Hill. Studies have been made of the osmotic behaviour of isolated tissue and body fluids and of simple living organisms under natural conditions. Part of this work has been done under Dr. E. J. Allen at the Marine Biological Laboratory, Plymouth. An expenses grant has been made to Miss Mary Hetherington, at Bedford College, London, for studies of the osmotic interchanges in mammalian tissues.

With a part-time grant at University College, London, Dr. H. P. Gilding has continued his work on the physiology of the cardiovascular system. Work has been done on the distribution and function of the vaso-constrictor nerves. With Dr. W. H. Newton, studies are being made of the action of histamine on the heart and pulmonary circulation.

Research on the physiology of the heart, by Professor J. A. MacWilliam, at Aberdeen, has again been assisted by a small grant for expenses.

The Council are providing the expenses of work on gastric function by Professor M. J. Stewart (p. 121) at Leeds. With Dr. L. A. Rowden, serial X-ray photographs have been taken from a number of healthy students, after the administration of opaque meals. The object is to define the normal limits of gastric motility, for the guidance of clinical work in medicine and surgery.

At the Royal College of Surgeons, London, Dr. G. Scott Williamson has again received expenses and the assistance of Dr. Innes H. Pearse. Further work has been done on the functions of the thyroid and thymus glands and on the relations that exist between them.

Part-time and expenses grants have been made to Dr. A. W. Spence, at St. Bartholomew's Hospital, London. He has studied the effects of dietetic deficiency on the structure and functions of the thyroid gland, and has confirmed McCarrison's finding that it is possible to produce lymphadenoid goitre by a diet deficient in vitamins.

At Newcastle-on-Tyne Professor D. Burns received a grant for expenses. Observations of parathyroid tetany have been continued, with special reference to the significance of guanidine poisons in the blood. Mrs. C. M. Burns has investigated the utilization of mineral salts in tetany.

J. B. Bateman—
'A Note on the Heat Production of Blood.' *Proc. Physiol. Soc., J. Physiol.*, 1931, **71**, xviii.

H. P. Gilding—
'The Relation of the Nervous System to a Patchy Ischaemia (Bier's Spots) in Animals. *Brit. J. Exp. Path.*, 1931, **12**, 66.
M. Hetherington—
'The State of Water in Mammalian Tissues.' *J. Physiol.*, 1931, **73**, 184.
J. A. MacWilliam—
'Alternation of the Mammalian Heart-Beat and of the Arterial Pulse.' *Quart. J. Exp. Physiol.*, 1930, **20**, 333.
G. S. Williamson—
'Thyrotoxicosis.' *Practitioner*, 1930, **125**, 684.

Metabolic Studies

At Aberdeen, Professor J. J. R. Macleod and Dr. J. M. Peterson have continued, with a grant for expenses, their work on carbohydrate metabolism. Studies have been made of the balance between the absorption of carbohydrate and its use and storage in the body. It has been shown that a quantitative relationship exists between the concentrations of lactic acid and of carbon dioxide in the blood. Investigation of the role of the nervous system in carbohydrate metabolism is in progress. Dr. W. L. Lamb has received a part-time grant for work at the Rowett Institute, Aberdeen, under the general direction of Professor Macleod. He is studying experimentally the effects of different diets and of thyroid feeding on the action of insulin.

Dr. G. A. Clark, at Sheffield, has again had an expenses grant. An investigation has been made of the part played by the vagus nerves in the secretion of insulin. Further work has been done on the action of adrenaline on the skin vessels.

A part-time grant has been made to Dr. M. W. Goldblatt at St. Thomas's Hospital, London. He has studied the influence of different hormones on carbohydrate and fat metabolism, with special reference to the combined effects of insulin and adrenaline and of thyroid and pituitary extracts. Observations on the changes in metabolism following adrenalectomy are also being made.

At Liverpool, Professor J. H. Dible has received a grant for part-time assistance by Dr. J. Libman. Work has been done on the factors influencing the utilization of fat in the body under normal and abnormal conditions.

I. A. Anderson, R. A. Cleghorn, J. J. R. Macleod, and J. M. Peterson—
'The Effect of Evisceration on the Respiratory Metabolism of the Decerebrate Preparation.' *J. Physiol.*, 1931, **71**, 391.
G. A. Clark—
'The Influence of the Vagus Nerves on the Secretion of Insulin.' *J. Physiol.*, 1931, **73**, 297.
G. A. Clark and H. E. Holling—
'The Protein Content and Osmotic Pressure in Serum of Young Animals.' *J. Physiol.*, 1931, **73**, 305.
M. W. Goldblatt and R. W. B. Ellis—
'The Effect of Insulin on Growth, Nitrogen Excretion, and Respiratory Metabolism.' *Biochem. J.*, 1931, **25**, 221.

The Physiology of Muscle

With grants at Edinburgh, Mr. and Mrs. P. Eggleton have continued their work on the chemical analysis of muscle. Studies have been made of the non-protein nitrogen compounds in voluntary muscle. With Professor A. J. Clark, an investigation is in progress of the phosphorus compounds in heart-muscle under different conditions, with special reference to the changes produced by lack of oxygen.

At Sheffield, Dr. C. G. Imrie has again had the assistance of Dr. Marion Brown. Further observations have been made on the effects of creatine, given by mouth, on the output of phosphates in the urine, and on the creatine and phosphorus content of voluntary muscles. It has been found that creatine feeding is followed by a temporary reduction in the excretion of phosphates by the kidney and by an increase of creatine in the muscles. There is evidence that the total acid-soluble phosphorus in muscles is also increased. In view of the influence of parathyroid hormone on the metabolism of phosphorus, and the occurrence of creatinuria after removal of the parathyroid glands, experiments are being made to test the effects of parathyroid extract on this reaction between creatine and phosphorus.

Mr. A. D. Ritchie, at Manchester, has had a grant for assistance by Mr. C. A. Mawson. Work on the chemistry of muscle has been continued with a view to determining the parts played by lactic acid production and the breakdown of phosphagen in muscular contraction.

At University College, London, Miss W.. M. Wright receives a part-time grant for work under the direction of Professor E. B. Verney. Further studies have been made of the toxic action of quarternary ammonium salts on muscle-nerve preparations.

M. Brown and C. G. Imrie—
'On the Creatine and Phosphorus Content of Muscle.' *J. Physiol.*, 1931, **71**, 214.
'The Influence of Creatine on the Excretion of Phosphates by the Kidney.' *Ibid.*, 1931, **71**, 222.

A. J. Clark, M. G. Eggleton, and P. Eggleton—
'Phosphagen and Cardiac Function.' *J. Physiol.*, 1931, **72**, Proc. 25.

H. R. Ing and W. M. Wright—
'The Curariform Action of Quarternary Ammonium Salts.' *Proc. Roy. Soc.*, B, **109**, 337.

A. Klisiecki, M. Pickford, P. Rothschild, and E. B. Verney—
'Functional Division of the Splanchnic Nerve under Local Anaesthesia in the Dog, and the Secretion of Urine.' *J. Physiol.*, 1931, **72**, Proc. 26.

Haemoglobin

A Committee (p. 139) directs work on this subject. The expenses of several workers under Professor J. Barcroft at Cambridge have again been provided. Dr. F. J. W. Roughton has continued

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his studies of the heat of the reaction between oxygen and haemoglobin. This was found to be the same inside the red blood-corpuscle as in solutions of haemoglobin. Under the supervision of Dr. Roughton, Mr. G. E. Millikan has extended his measurements of rapid biochemical reactions by photo-electric methods. He has investigated the rate of combination of haemocyanin with oxygen and the rate of dissociation of oxyhaemocyanin.

J. Barcroft and R. Margaria—
'Some Effects of Carbonic Acid on the Character of Human Respiration.' *J. Physiol.*, 1931, **72**, 175.
W. H. Forbes and F. J. W. Roughton—
'The Equilibrium between Oxygen and Haemoglobin. I. The Oxygen Dissociation Curve of Dilute Blood Solutions.' *J. Physiol.*, 1931, **71**, 229.

Intracellular Respiratory Pigment

At the Molteno Institute, Cambridge, Dr. D. Keilin has again received grants. In extension of his work on intracellular respiration he has investigated further the composition of the respiratory pigment cytochrome and its chemical relation to haemoglobin. It has been shown that ordinary haemoglobin can be derived from one of the components of cytochrome extracted from bakers' yeast. Other work by Dr. Keilin is mentioned at pp. 112 and 116.

M. Dixon, R. Hill, and D. Keilin—
'The Absorption Spectrum of the Component *c* of Cytochrome.' *Proc. Roy. Soc.*, B, 1931, **109**, 29.
R. Hill and D. Keilin—
'The Porphyrin of Component *c* of Cytochrome and its Relationship to other Porphyrins.' *Proc. Roy. Soc.*, B, 1930, **107**, 286.

Sex Hormones

Work in this subject is directed by a Committee (p. 137) of which Dr. F. H. A. Marshall is Chairman.

At University College, London, Dr. A. S. Parkes has been provided with the assistance of Miss M. Hill. Tests have been made of ovary-stimulating extracts, prepared under the supervision of Dr. G. F. Marrian, with a view to detecting any separation of the hormones responsible for the different phases of ovarian activity. Dr. Marrian has a grant for expenses.

By arrangement with the British Drug Houses, Ltd., it is hoped soon to obtain enough crystalline oestrin to allow controlled clinical tests to be made under the joint supervision of the Sex Hormones Committee and the Therapeutic Trials Committee (p. 138).

An expenses grant has recently been made to Dr. S. Zuckerman for comparative studies of the reproductive cycle. This work is being done at University College, London, and at the gardens of the Zoological Society.

In the Department of Animal Genetics, at Edinburgh, Dr. B. P. Wiesner receives an expenses grant. Further studies of the Aschheim-Zondek test for pregnancy have been made at the Pregnancy Diagnosis Station, and the method of the test has been improved. Observations of the relation of anterior pituitary hormones to sex function have been continued, with special reference to their effects in senility.

Professor E. C. Dodds, at the Middlesex Hospital, London, has had a grant for assistance by Mr. E. J. Gallimore. Investigation is being made of the chemistry of testicular hormone and its isolation from the urine.

At the Lister Institute, London, a personal grant has again been made to Professor V. Korenchevsky, and he has had the assistance of Mrs. M. Dennison. Work on the preparation of testicular extracts has been extended. The effect of these extracts in increasing metabolism has been confirmed, and further evidence has been got that the substance responsible for this action is derived from the seminiferous tissue. Studies are being made of the relation of vitamin A and vitamin B_1 to sex function.

E. C. Dodds, A. Greenwood, H. Allen, and E. J. Gallimore—
'Properties of the Comb-Growth-Promoting Substance Obtained from Testes and Urine.' *Biochem. J.*, 1930, **24**, 1031.

M. Hill and A. S. Parkes—
'On the Relation between the Anterior Pituitary Body and the Gonads. 'III. Fractionation and Dilution of Ovary-Stimulating Extracts.' *Proc. Roy. Soc.*, B, 1931, **107**, 455.
'Studies on Ovulation. IV. Induction of Ovulation in the Hypophysectomized Rabbit by Administration of Anterior Lobe Extracts.' *J. Physiol.*, 1931, **71**, 36. 'V. The Action of the Ovulation-producing Substance of Urine of Pregnancy on the Hypophysectomized Rabbit.' *Ibid.*, 1931, **71**, 40.
'Effect of Untreated Urine of Pregnancy on the Hypophysectomized Rabbit.' *J. Physiol.*, 1931, **72**, Proc. 15.

A. S. Parkes and S. Zuckerman—
'The Menstrual Cycle of the Primates. II. Some Effects of Oestrin on Baboons and Macaques.' *J. Anat.*, Lond., 1931, **65**, 272.

B. P. Wiesner—
'Pregnancy Diagnosis Station: Report on Second Year's Working.' *Brit. Med. J.*, 16th May 1931.

B. P. Wiesner and P. G. Marshall—
'The Gonadotropic Hormones (ρ-Factors). I. The Preparation and Properties of Extracts of Anterior Lobe, Placenta, and Pregnancy Urine.' *Quart. J. Exp. Physiol.*, 1931, **21**, 147.

General Biochemical Researches

At Cambridge, Miss E. Watchorn (p. 94) has shown that the concentration of magnesium in the cerebrospinal fluid is usually higher than that in the serum, and is unaffected by wide variations in the serum values. Studies of tuberculous meningitis have shown that, while in this disease the estimated magnesium of the cerebrospinal fluid is much lower than normal, it does not

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necessarily correspond with the serum figures. In other forms of meningitis the magnesium content of the cerebrospinal fluid is generally normal. Dr. R. A. McCance (p. 77), of King's College Hospital, London, has co-operated in this inquiry. Further work has been done by Miss Watchorn on the experimental production of urinary calculi by alterations of diet.

Dr. G. A. Harrison, at St. Bartholomew's Hospital, London, has again received an expenses grant. The study of spermine in human tissues, to which reference was made last year, has been extended. It has been shown that the prostate gland contains more than ten times as much spermine as any other organ. Attempts are being made to find the physiological significance of this widespread substance.

At Cardiff, Mr. J. Pryde has grants for expenses, and the assistance of Mr. R. T. Williams. He has continued his studies of the chemical structure of carbohydrates and their derivatives. Further observations have been made of the composition of adenosine from plant nucleic acid, and of the nature of the sugar in animal nucleic acid.

Dr. Frank Dickens (p. 95), a member of the Council's staff, has worked during part of the year as the guest of Professor Otto Warburg at Berlin. He has investigated the catalytic oxidation of carbohydrate derivatives. This work is being continued at the Middlesex Hospital.

A part-time grant has again been made to Dr. W. Robson, at King's College, London. Further experiments have been done on the synthesis of amino-acids and their derivatives, with special reference to tryptophan. With Mr. W. Boyd, a biochemical study of the extract of parathyroid claimed by Thompson to inhibit the growth of Jensen's rat sarcoma has been begun. An attempt is being made to isolate the active constituent.

With grants at Addenbrooke's Hospital, Cambridge, Dr. C. G. L. Wolf has continued his work on serological tests for the diagnosis of cancer and on the metabolism of persons of advanced age. He has had the assistance of Miss B. H. E. Cadness, provided by the Council.

B. H. E. Cadness and C. G. L. Wolf—
'Weiterer Beitrag zur Fuchsschen Reaktion der Serodiagnostik des Carcinoms. II.' *Biochem. Z.*, 1931, **238**, 287.
'Harnproteasen. I.' *Fermentforschung*, 1931, **13**, 1.

R. W. Humphreys, J. Pryde, and E. T. Waters—
'Constitutional Studies in the Mono-Carboxylic Acids derived from Sugars. Part V. Hexonic and Pentonic Acid Amides. The Action of Sodium Hypochlorite on the Isomeric Trimethyl Arabonamides.' *J. Chem. Soc.*, May 1931, p. 1298.

J. Lamb and W. Robson—
'The Erlenmeyer Synthesis of Amino-Acids.' *Biochem. J.*, 1931, **25**, 1231.

R. A. McCance and E. Watchorn—
'Inorganic Constituents of Cerebrospinal Fluid. I. Calcium and Magnesium.' *Quart. J. Med.*, 1931, **24**, 371.

J. Pryde and R. T. Williams—
'The Pyranoid Structure of Glycuronic Acid and of Theophylline Arabinoside.' (Letter.) *Nature*, Lond., 1st August 1931.

Bacterial Chemistry and Immunity Reactions

Research in bacterial chemistry at the National Institute has already been mentioned (p. 38).

In the whole-time service of the Council, at Cambridge, Miss M. Stephenson has continued her work on the chemistry of gas-forming bacteria. A hitherto undescribed enzyme has been found to play an important part in the bacterial production of methane gas. Besides occurring in anaerobic organisms, this enzyme exists in many common members of the *coli-typhosus* group. Accounts of its properties have been published. At the same place, Miss Una Wallace has concluded her work on the action of dyes upon diphtheria toxin, for which she received a grant.

At Leeds, Professor J. W. McLeod (p. 112) has investigated the electric potentials developed in bacterial cultures in relation to the phenomena of bacterial oxidation and reduction. Work has also been done on the cultural characteristics and virulence of different forms of the diphtheria bacillus. Dr. J. Gordon, with a part-time grant, has studied here the action of dyes on the haemolysins of *Streptococcus haemolyticus* and *B. welchii*. Congo Red inactivates these haemolysins and the inactivation is reversible, resembling the effect of this dye on complement. With Dr. K. E. Cooper, Dr. Gordon has continued his study of the combinations in which phosphorus may occur in bacterial cultures.

Dr. F. C. Happold, also working at Leeds, has had part-time and expenses grants for studies of the 'X' antigens of the food-poisoning group. They have been found to be identical in 'rough' and in 'smooth' cultures. With Mr. A. Taylor, further work has been done on the lipolytic activity of tubercular tissues.

At the London Hospital, Dr. P. Fildes receives part-time and expenses grants, and the Council provide him with the assistance of Mr. B. C. J. G. Knight. Further studies have been made of the oxidation-reduction potentials of anaerobic cultures. With Dr. J. A. Campbell, of the National Institute, Dr. Fildes has re-investigated, by a different method, the effects of varying oxygen tensions on the germination of tetanus spores in living tissues.

J. S. Anderson, F. C. Happold, J. W. McLeod, and J. G. Thomson—
'On the Existence of two forms of Diphtheria Bacillus—*B. diphtheriae gravis* and *B. diphtheriae mitis*—and a new Medium for their Differentiation and for the Bacteriological Diagnosis of Diphtheria.' *J. Path. Bact.*, 1931, **34**, 667.

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J. Cooper and K. E. Cooper—
'A Study of the Phosphorus Distribution in Bacterial Cultures. II.' *Brit. J. Exp. Path.*, 1931, **12**, 234.

J. Gordon—
'The Action of Congo Red on Streptococcal Haemolysin and on *B. welchii* Haemolysin.' *J. Path. Bact.*, 1931, **34**, 439.

J. Gordon and P. G. Marshall—
'The Recognition of the Cleavage of Fats and Lipins.' *A System of Bacteriology*, IX, London, 1931.
'Bacterial Pigments.' *Ibid.*

F. C. Happold—
'The Correlation of the Oxidation of certain Phenols and of Dimethyl-p-Phenylenediamine by Bacterial Suspensions.' *Biochem. J.*, 1930, **24**, 1737.

F. C. Happold and A. Taylor—
'The Lipolytic Activity of Tubercular Guinea-pigs' Tissues. III. Variation of Activity with the Spread of the Disease.' *Brit. J. Exp. Path.*, 1931, **12**, 272.

B. C. J. G. Knight—
'Surface Films of Batyl, Chimyl, and Selachyl Alcohols.' *Biochem. J.*, 1930, **24**, 257.

J. W. McLeod—
'Variations in the Periods of Exposure to Air and Oxygen necessary to kill Anaerobic Bacteria.' *Acta Path. Microbiol. Scand.*, 1930, Suppl. 3, 255. (*Commun. Inst. sérothér. Copenh.*, Vol. 20.)

M. Stephenson and L. H. Stickland—
'Hydrogenase: A Bacterial Enzyme Activating Molecular Hydrogen. I. The Properties of the Enzyme.' *Biochem. J.*, 1931, **25**, 205. 'II. The Reduction of Sulphate to Sulphide by Molecular Hydrogen.' *Ibid.*, 1931, **25**, 215.

General Pathological Researches

In Professor H. R. Dean's department, at Cambridge, Dr. R. A. Webb and Dr. H. W. Florey receive part-time grants. Microscopical investigations have been made of the mucus-secreting cells of the alimentary tract at different stages of their activity. With Dr. H. M. Carleton, Dr. Florey has studied the effects of irritation on the mucous membrane of the trachea and bronchi. An inquiry into the chemical action of lysozyme on bacteria is being made with Miss M. Stephenson (p. 108). Dr. Webb has continued his work on the origin of the blood monocytes and their relation to the epithelioid cells of tuberculosis.

In the same department, Dr. A. N. Drury gives whole-time service to the Council. Further investigation has been made of the physiological action of nucleic acid derivatives, especially the adenine group. Several of these substances have been shown to have definite depressor activity, in addition to their effect in dilating the coronary arteries of the heart. It has further been found that some of them, including muscle adenylic acid, have the power of producing local and general leucocytosis. It is suggested that their liberation in the body may play a part in the hyperaemic

and infiltration stages of inflammation, and further work is in progress to decide whether this is so. Dr. Drury is also studying the action of nucleic acid products upon the strength of the heart beat, in order to determine whether the improvement in systole, which they produce experimentally, is due to coronary dilatation or to a specific effect on the heart muscle. With Dr. L. J. Harris (p. 79), and Miss C. Maudsley, of Melbourne, Australia, further work has been done on the effects of a deficiency of B vitamins on the heart.

With grants at Glasgow, Dr. D. F. Cappell has continued his studies of the reticulo-endothelial system and its part in resistance to infection. He has also investigated the effects of different chemotherapeutic agents on *Bartonella* infection in mice. At the same place, Dr. W. B. Kyles has recently had an expenses grant for experimental work on diseases of the liver. The Council have been glad to learn of Dr. Cappell's appointment during the year to the Chair of Pathology at Dundee.

Working as a member of the Council's staff at St. Bartholomew's Hospital, London, Dr. M. H. Gordon has again directed the combined clinical and pathological investigation of lymphadenoma, made under the Rose Bequest. Recent work has indicated the presence in this disease of a pathogenic agent hitherto unrecognized, and attempts are being made to find its nature. Dr. Gordon has also co-operated in new studies of antimeningococcal sera, in relation to the recent epidemic of cerebrospinal fever. This work was undertaken at the request of the Ministry of Health, since it had been found that the sera, prepared from old strains, that were available at the beginning of the epidemic, were inactive in treatment. By use of material collected during the past epidemic, assistance has been given to the manufacturers who are preparing a supply of new sera for future years.

Further observations on the pathology of nephritis have been made by Dr. J. Gray with part-time and expenses grants at Aberdeen. A report has been prepared. Other work by Dr. Gray has been noticed at p. 97.

At Manchester, Professor J. Shaw Dunn has continued his experimental studies of nephritis. With Dr. H. L. Sheehan he has investigated the effects of different colloids and lipoid substances on the glomeruli of the kidney. The Council have provided expenses.

At Addenbrooke's Hospital, Cambridge, Dr. J. F. Gaskell has again received grants. The action of alcohol in lowering resistance to pneumonia has been further investigated. Evidence has been obtained that the high death-rate from pneumonia in alcoholics is due to their inability to deal with the temporary septicaemia which occurs in the early stages of the disease. A survey of the incidence

of the different pneumococcal 'types' in pneumonia at Cambridge during the past seven years is being prepared for publication.

Dr. Janet M. Vaughan, at the Royal Northern Hospital, London, has had an expenses grant for work on acholuric jaundice. Estimations of the blood-cholesterol in this disease have been made before and after splenectomy, and the results have been correlated with changes in the blood picture and red-cell fragility.

An expenses grant has been made to Dr. R. Hallam and Dr. J. W. Edington at Sheffield for an investigation of the pathology of *Erythema multiforme.*

Under an arrangement with the British Red Cross Society, part-time and expenses grants have recently been made to Dr. H. F. Brewer, medical officer to the London Blood Transfusion Service, for work at St. Bartholomew's Hospital on haematological and other problems of blood-transfusion.

D. W. Bennet and A. N. Drury—
'Further observations Relating to the Physiological Activity of Adenine Compounds. *J. Physiol.*, 1931, **72**, 288.

A. N. Drury, L. J. Harris, and C. Maudsley—
'Vitamin B Deficiency in the Rat. Bradycardia as a Distinctive Feature.' *Biochem. J.*, 1930, **24**, 1632.

H. Florey—
'The Mechanism of Goblet-cell Secretion in the Mammal; the Effects of Cyanide.' *Brit. J. Exp. Path.*, 1931, **12**, 301.

H. Florey and R. A. Webb—
'Mucus Secretion in Acute Experimental Inflammation of the Colon, and other Mucous Membranes of the Cat; Histological Changes.' *Brit. J. Exp. Path.*, 1931, **12**, 286.

H. L. Sheehan—
'The Deposition of Dyes in the Mammalian Kidney.' *J. Physiol.*, 1931, **72**, 201.

J. M. Vaughan, G. L. Muller, and L. Zetzel—
'The Response of Grain-fed Pigeons to Substances Effective in Pernicious Anaemia.' *Brit. J. Exp. Path.*, 1930, **11**, 456.

Bacteriology, Protozoology, and Mycology

Studies of the bacteriology of puerperal infections have been noticed at p. 73, and of tuberculosis at p. 90.

At St. Bartholomew's Hospital, London, Sir Frederick Andrewes has again had a grant for assistance by Mrs. E. M. Christie. Further work has been done on the serological classification of the haemolytic streptococci. At the same place, Dr. L. P. Garrod, with part-time and expenses grants, has investigated the sensitivity of *Streptococcus pyogenes* to germicides, with the object of comparing the efficacy of different antiseptics used in midwifery. Attempts are also being made to find a selective medium for the growth of *S. pyogenes.*

With a part-time grant at the Middlesex Hospital, Dr. L. E. H. Whitby has continued his studies of the bacteriology of chole-

cystitis. Observations have also been made on the value of 'bacteriophage' in the treatment of infections of the urinary tract.

A grant has been made to Dr. A. B. Rosher, at Charing Cross Hospital, London, for assistance by Mr. D. Cator in studies of influenza bacilli.

At Oxford, Dr. A. D. Gardner (p. 56) has been provided with the assistance of Mr. P. H. Leslie. Work on the bacteriological diagnosis of whooping-cough has been extended, and it has been shown that the Danish 'cough-droplet' method is reliable. Further investigation has been made of the antigenic changes undergone by *B. pertussis* in culture, in relation to the preparation of protective vaccines.

Studies of the bacteriology of the common cold have been continued by Professor J. W. McLeod, at Leeds, with a grant for assistance by Dr. L. Hoyle. Attention has been directed to the bacteria most frequently isolated from patients with acute coryza, and experiments have been made to determine the best method of preparing 'anti-catarrh' vaccines. Other work by Professor McLeod is mentioned at p. 108.

In Professor T. J. Mackie's department at Edinburgh, Dr. J. M. Alston and Dr. M. H. Finkelstein have received part-time and expenses grants. With Dr. D. Stewart, Dr. Alston has made a further study of the immunological changes in the blood of patients with lobar pneumonia before and after serum treatment. This work has been done in relation to the clinical trials of concentrated antipneumococcal serum made for the Council at Edinburgh (see p. 70). Dr. Finkelstein has investigated experimentally the effect of diet on resistance to infection.

Dr. J. Smith (pp. 67, 74) has again received a grant at the City Hospital Laboratory, Aberdeen. He has continued his inquiry into the prevalence of undulant fever in the north-east of Scotland, and has investigated the incidence of *Brucella abortus* in the milk supply. A number of different strains of this organism have been examined as to their cultural, biochemical, and serological characters.

With an expenses grant, at St. Thomas's Hospital, London, Dr. T. E. Osmond has studied experimentally the infectivity of secretions in primary and secondary syphilis.

At Glasgow, Dr. J. A. W. McCluskie has had part-time and expenses grants. Experimental work on spirochaetes has been continued, with special reference to the transmission and virulence of different strains of *Treponema pallidum*.

Under the direction of Dr. D. Keilin, at the Molteno Institute, Cambridge, Miss M. Vincent and Dr. P. Tate have done further work on parasitic protozoa and the life-histories of insects. Research on chemotherapy by these workers is mentioned at p. 116 below.

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J. M. Alston—
'An Analysis of Bacterial Antigens on the Basis of Chemistry and Function.' *Edinb. Med. J.*, 1931, n.s. **38**, 522.

J. M. Alston and H. J. Gibson—
'A note on the Experimental Transmission of "Louping-ill" to Mice.' *Brit. J. Exp. Path.*, 1931, **12**, 82.

J. M. Alston and D. Stewart—
'Some observations on Passive Immunity in the Normal Subject Produced by Anti-pneumococcic Sera.' *Brit. J. Exp. Path.*, 1930, **12**, 49.

L. P. Garrod—
'The Efficiency of Antiseptics used in Midwifery.' *Brit. Med. J.*, 4th April 1931.

P. H. Leslie and A. D. Gardner—
'The Phases of *Haemophilus pertussis*.' *J. Hyg.*, Camb., 1931, **31**, 423.

J. W. Lobban and J. Smith—
'The Vernes Resorcin Test in the Diagnosis and Prognosis of Tuberculosis.' *Brit. J. Tuberc.*, 1931, **25**, 11.

Virus Diseases

Work on this subject at the National Institute has already been described (pp. 14 and 29).

At University College, Dundee, Dr. J. Craigie has received a whole-time grant. Under the direction of Professor W. J. Tulloch, he has continued his studies of the vaccinia-variola flocculation reaction for the diagnosis of small pox. A further report has been published by the Council.

A grant has again been made to Dr. F. W. Twort at the Brown Institution, London. Observations are being made of the properties of the transmissible bacteriolytic agents and on the general characters of vaccinia and other viruses.

J. Craigie—
'A Method of Drying Complement from the Frozen State.' *Brit. J. Exp. Path.*, 1931, **12**, 75.

J. Craigie and W. J. Tulloch—
'Further Investigations on the Variola-vaccinia Flocculation Reaction.' *Sp. Rep. Ser. Med. Res. Coun.*, Lond., No. 156, 1931.

Canine Distemper

At the Farm Laboratories of the National Institute, Dr. P. P. Laidlaw and Mr. G. W. Dunkin are engaged in the final stages of the work on this subject for which expenses are provided by the *Field* Distemper Council from the fund administered under the advice of the Distemper Research Committee (p. 137).

The highly successful issue of these investigations will now make it possible to bring the research work to an end in the near future. The vaccine-virus method for the immunization of dogs against distemper is firmly established, and its value has been amply demonstrated. As stated last year, some difficulties were met when the preparations were first issued on a commercial scale, and results

much less satisfactory than those obtained with the experimental product were for a time reported. These difficulties have now been overcome by various improvements in methods. These include the use of a dried preparation of virus which can be stored or transported without serious loss of potency, and the introduction of a test for standardizing the strength of the vaccine. The Wellcome Laboratories have by these means been enabled to resume the commercial issue of the preparations, which are now being widely used with good effect. Satisfactory results are also reported from America.

Longer experience is obviously required to determine fully the durability of the immunity produced, but useful evidence on this point has been secured from an examination of the after-histories of foxhounds immunized in 1928 and 1929 with products issued by the investigators. Questionnaire forms were issued in the autumn of 1930 to thirty-nine Masters of foxhounds throughout the country, and replies were received from thirty-five of them. In two cases no figures were available, and in many others a proportion of the hounds could not be accounted for owing to their having been drafted elsewhere. The age of the hounds at the time of this inquiry was from one-and-a-half to three years.

As regards twenty-three different packs, the Masters reported that there had been subsequent exposure, sometimes repeated exposure, to infection. The number of hounds inoculated had been 750, and the subsequent histories of 650 of these were known. Of the 650, all had been intimately exposed to infection; only nine had contracted distemper, with death in two cases; twenty-six others had had illnesses of doubtful nature, but twenty of these were in one pack and the veterinary surgeon was of opinion that the condition was not distemper.

In the other twelve packs, the Masters could not definitely say that there had been exposure to infection. In these packs 340 hounds had been inoculated, and the subsequent histories of 214 were known; none, in fact, had had distemper. Some credit for the unusual freedom from distemper in these kennels may be taken for the method.

Taking the cases in which exposure to infection was certain, the incidence of distemper among 650 hounds belonging to twenty-three packs is only 1·4 per cent, and the death-rate from this cause 0·3 per cent. Without inoculation, the incidence of distemper among young foxhounds in this country is nearly 100 per cent., and the death-rate is frequently 50 per cent. and may exceed 75 per cent.

Meanwhile, Dr. Laidlaw and Mr. Dunkin have been chiefly occupied, as has already been mentioned at p. 34, in developing a second method of immunization, based upon the use of an anti-

distemper serum prepared by the hyper-immunization of a dog that has either recovered from an attack of distemper or been made immune with vaccine and virus by the earlier method. Although the principle is fundamentally different, the serum resembles the vaccine in that it induces a temporary state of resistance which can be converted into a lasting immunity by an inoculation of fresh virus. There is the important practical advantage, however, that the virus can be inoculated simultaneously with the serum, although at a different site, instead of after an interval of a week or more. Secondly, there is the important further gain that the serum—in this case administered alone—can be used to protect dogs already exposed to infection and in the incubation period of the disease, and that it is also of value as a form of treatment in declared cases of distemper.

This anti-serum, giving an alternative means of prevention and also a useful method of treatment, is already being issued commercially by the Wellcome Laboratories. Only greater experience of its use and some technical improvement in its production are required before the matter may safely be regarded as having passed wholly from the research stage to that of accepted practice.

G. W. Dunkin and P. P. Laidlaw—
'Some further observations on Dog Distemper.' *J. Amer. Vet. Med. Ass.*, 1931, **78**, 545.
P. P. Laidlaw and G. W. Dunkin—
'Studies in Dog Distemper. VI. Dog Distemper Anti-Serum.' *J. Comp. Path.*, 1931, **44**, 1.
'Dog Distemper Anti-serum.' *Vet. Rec.*, 1931, **11**, 359.

Chemotherapy and Tropical Diseases

The Chemotherapy Committee (p. 138) have continued to supervise work upon new chemical compounds of probable therapeutic value. Their relations with the Therapeutic Trials Committee have been mentioned at p. 22. The members of the Committee representative of chemistry are appointed by the Department of Scientific and Industrial Research, work on the chemical side being supported by the Department and that on the biological side by the Council. As in previous years attention has chiefly been directed to the search for new agents against infections with trypanosomes, spirochaetes, and malarial parasites.

New compounds for testing have been submitted by Professor G. Barger, Professor Clemo, Professor J. B. Cohen, Professor Gibson, Dr. W. O. Kermack, Dr. F. L. Pyman, Professor R. Robinson, and Dr. Turner, and also from Dr. H. King and Dr. A. Cohen of the National Institute, and from Professor G. T. Morgan, with his assistants, Dr. J. G. Mitchell, Dr. E. Walton, and Dr. Jessie Stewart, at the Chemical Laboratory, Teddington.

Work on chemotherapy at the National Institute has been noticed at p. 47.

New compounds made at Leeds by Professor Cohen and his assistants, Dr. Ashley and Mr. K. Cooper, have been tested at Glasgow by Professor C. H. Browning and Miss R. Gulbransen; the latter receives a whole-time grant. The anil quinoline compounds have been found to be active against experimental streptococcal infections. The styryl compound '314' has been tested on trypanosomiasis in man and animals in Tanganyika Territory, in South Africa, and in the Sudan. It appears, however, that the trypanocidal action of this substance is not sufficiently high in relation to its toxicity to enable it to be used with safety as a curative agent.

At the Liverpool School of Tropical Medicine, Professor Warrington Yorke has again had grants for assistance by Dr. F. Murgatroyd and Dr. F. Hawking. Work on potential trypanocides has been continued. Experiments are being made with a series of amides containing arsenic which have been prepared by Professor Morgan. When the laboratory results are complete, the most promising of these substances will be therapeutically tested.

The anti-malarial and amoebicidal properties of various synthetic drugs have been tested at Cambridge, under the direction of Dr. D. Keilin, by Dr. P. Tate and Miss M. Vincent, both receiving personal grants. Further studies have been made of the effects of quinine and plasmochin on bird malaria. New compounds prepared by Professor Robinson have also been examined. Trials in man of Professor Robinson's anti-malarial compound 'R 36' have also been made for the Committee by Lieut.-Col. James of the Ministry of Health.

C. H. Browning—
'Antiseptic Dyes: Selective Antiseptics.' *A System of Bacteriology*, I, London, 1930.
'Chemotherapy.' *Ibid.*, VI, London, 1931.
C. H. Browning, J. B. Cohen, S. Ellingworth, and R. Gulbransen—
'The Antiseptic and Trypanocidal Action of certain Styryl and Anil Benzthiazole Derivatives.' *Proc. Roy. Soc.*, B, 1931, **108**, 119.
'Therapeutic Interference Caused by Isomerides of Trypanocidal Styryl Quinoline Derivatives.' *Proc. Roy. Soc.*, B, 1931, **109**, 51.
'The Chemotherapy of Experimental Streptococcus Infections.' *J. Path. Bact.*, 1931, **34**, 592.
J. B. Cohen, K. E. Cooper, and P. G. Marshall—
'Some Aliphatic and Aromatic Amino Derivatives of α-Quinoline Methiodide.' *Proc. Roy. Soc.*, B, 1931, **108**, 130.
W. Yorke, F. Murgatroyd, and F. Hawking—
'Studies in Chemotherapy. IV. The Action *in vivo* of Certain Arsenical and Antimonial Compounds and of Bayer 205 on *T. rhodesiense* and on Atoxyl- and Acriflavine-resistant Strains of this Parasite.' *Ann. Trop. Med. Parasit.*, 1931, **25**, 313. 'V. Preliminary Contribution on the Nature of Drug Resistance.' *Ibid.*, 1931, **25**, 351.

By arrangement with the Nigerian Government a grant is made from the Council's special fund for research in tropical diseases to

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Dr. R. F. M. Burnie, working at Kano, Northern Nigeria. Dr. Burnie has completed his studies of tropical ulcer, mentioned last year, and is studying problems of relapsing fever. Special attention has been paid to the degrees of protection against this disease conferred by injections of blood taken from patients during an attack or in a remission; the former method has been found to give definite evidence of immunity.

Experimental Epidemiology and Vital Statistics

Professor W. W. C. Topley and Professor M. Greenwood have continued their studies in experimental epidemiology at the London School of Hygiene, the Council providing the heavy expenses of the work and the assistance of Mrs. J. Wilson.

Three experiments on the effect of prophylactic vaccination against mouse-typhoid have now been completed, and the results analysed. It has been found that the vaccinated mice have an expectation of life which is significantly greater than that of unvaccinated controls submitted to the same epidemic risks. The immunity of the vaccinated mice is, however, only relative, and it does not suffice to suppress an epidemic prevalence, even when all immigrants to an infected herd are vaccinated before admission to the cage. Under conditions in which exposure to risk was slight or temporary, the vaccinated mice might well escape the disease, but when the contact with infection is continuous, they tend ultimately to succumb.

The recent description by Miss Marchal (p. 30) of 'infectious ectromelia' in mice has provided an opportunity to study a contagious virus disease in epidemic form. In the two epidemics so far studied, the life-tables have differed essentially from those recorded in bacterial diseases such as mouse-typhoid and *Pasteurella* infection. It appears that many of the mice contract a non-fatal infection with ectromelia, which gives an immunity sufficient to protect them against continuous subsequent exposure to the disease.

The results of these experiments indicate that the processes of herd immunization in bacterial and virus infections may be fundamentally different, although further work with other diseases is needed to decide whether this applies generally. In the case of mouse-typhoid, immunization will, from the herd point of view, confer this advantage, that a group so protected will withstand a period of acute exposure to risk better than untreated animals. But provided conditions of severe exposure to risk are maintained, the general effect on the herd will be relatively trivial. On the other hand, in the case of a virus disease, it is probable that if admission to a herd in which the disease had gained a footing were

restricted to immunized animals, the herd mortality might be completely arrested.

No opportunity has yet occurred of studying a mouse disease in which the type of immunity involved is anti-toxic rather than anti-bacterial. Experience with human diseases such as diphtheria and scarlet fever suggests that infections of this type would approximate in their behaviour to the virus diseases rather than to such bacterial infections as mouse-typhoid.

A series of experiments have been made to find the effect of different diets on the epidemic spread of mouse-typhoid. No evidence was obtained that any of the diets tested reduced the herd mortality from this infection.

M. Greenwood—
'Factors Determining the Difference Between an Epidemic of One Disease and That of Another.' *Brit. Med. J.*, 8th Aug. 1931.
'On the Statistical Measure of Infectiousness.' *J. Hyg.*, Camb., 1931, **31**, 336.

M. Greenwood, W. W. C. Topley, and J. Wilson—
'The Mortality of a Herd of Mice under "Normal" Conditions.' *J. Hyg.*, Camb., 1931, **31**, 403.
'Contributions to the Experimental Study of Epidemiology. The Effect of Vaccination on Herd Mortality.' *Ibid.*, 1931, **31**, 257, and 484.

W. W. C. Topley, M. Greenwood, and J. Wilson—
'The Effect of Diet in Epidemic Infections in Mice.' *J. Path. Bact.*, 1931, **34**, 163.
'A Strain of *Bact. aertrycke* with unusual Epidemic Characters. *Ibid.*, 1931, **34**, 523.

Statistics

The Council's statistical work is under the direction of the Committee (p. 140) of which Professor M. Greenwood is Chairman. A staff provided by the Council works for the Committee in Professor Greenwood's department at the London School of Hygiene and Tropical Medicine. The Committee continue to serve the Ministry of Health in the field of medical statistics and there is close collaboration between the Committee's staff and that of the School. The vacancy on the staff of the Committee created by the death of Mr. H. E. Soper has been filled by Dr. J. O. Irwin.

As in previous years, the Statistical Committee have given much expert assistance to the work of the Nutrition Committee, the School Epidemics Committee, and the Industrial Health Research Board. An account of their work under the last heading will be found below. Advice and assistance on statistical matters have also been given to many individual workers.

Although it is not a primary function of the staff of the Committee to undertake research in statistical theory, it happens in all applied scientific research that novel questions of pure method arise. In a paper published during the year under review Dr. L. Isserlis has made an important contribution to statistical methods,

while work by Dr. Irwin has included a mathematical treatment of the problem of general intelligence and specific abilities.

Mr. W. T. Russell is continuing his statistical studies of cancer mortality, and Mr. W. J. Martin, also of the Committee's staff, is collaborating with Miss R. M. Fleming (p. 77) in her anthropometrical study of children.

Dr. Matthew Young, in the whole-time service of the Council, has again worked at University College, London, in the department directed by Professor G. Elliott Smith. He has completed the analysis of the data collected by the Status Lymphaticus Committee, to whose published report reference has already been made at p. 19. He has also analysed the data on facial measurements collected for the Dental Committee by Miss K. C. Smyth and mentioned in more detail at p. 85 above.

Further work has been done by Dr. Young on the structure of the brain cortex at different ages, special attention being given to the areas concerned with the function of speech. At the Hospital for Sick Children, Great Ormond Street, London, he has collected anthropometric data from a series of children with asthma and rheumatism, in order to determine whether any special relationship exists between type of bodily build and predisposition to these diseases. In this inquiry, he has had the assistance of Dr. A. Bonnard, provided by the Council.

G. C. Campion and M. Young—
'The Relative Positions of the Cartilaginous and Osseous Transmeatal Axes in the Head.' *J. Anat.*, Lond., 1931, **65**, 328.

P. G. Edge—
'The Scope and Uses of Vital Records in the Tropics.' *Proc. R. Soc. Med.*, 1931, **24**, 1269.
'Documentos Demográficos de España, Anteriores al Censo.' *Bol. Tecn. Direc. Gen. Sanidad,* June 1931.

L. Isserlis—
'On the Moment Distributions of Moments in the Case of Samples Drawn from a Limited Universe.' *Proc. Roy. Soc.*, A, 1931, **132**, 586.

W. J. Martin—
'A Biometric Study of the Weights of Infants during First Days of Life.' *Ann. Eugen.*, 1931, **4**, 327.

W. T. Russell—
'A Review of the Cancer Statistics in England and Wales and in Scotland between 1891 and 1927.' *J. Hyg.*, Camb., 1931, **31**, 406.
'Mortality from Cancer According to Site in the Counties of Scotland, 1923–8.' *Ibid.*, 1931, **31**, 563.

H. M. Woods and W. T. Russell—
An Introduction to Medical Statistics. London (P. S. King), 1931.

M. Young and H. M. Turnbull—
'An Analysis of the Data collected by the Status Lymphaticus Investigation Committee.' *J. Path. Bact.*, 1931, **34**, 213.

School Epidemics

The Committee (p. 140) under the chairmanship of Sir George Newman have continued their inquiry into the incidence and

spread of epidemics in residential schools. Twenty-nine schools are co-operating, in addition to the Royal Hospital School, Greenwich, and the Royal Naval College, Dartmouth. The total population at risk is about 14,000.

These pupils include both boys and girls, and for all of them careful records of health are being kept for the Committee. Reports showing every case of illness are sent each week during the school term, so that the particulars may be incorporated in the central card-index. Over a period of years statistical data are thus being accumulated which should, on final analysis, yield valuable information for the guidance of measures for the better control of epidemic diseases. Already, indeed, many points of much interest have emerged. It has been found also that the arrangements with the schools have enabled the Committee to make intensive study of particular outbreaks of special kinds.

The influenza epidemic which affected most of the schools during the Lent Term, 1931, gave an opportunity for studying the spread of this disease and its complications. The bacteriological work done for the Committee by Dr. F. Griffith, of the Ministry of Health, was much increased owing to an unusual prevalence of tonsillitis and other infections due to haemolytic streptococci. The thanks of the Council must again be given to Dr. Griffith and to the staffs and medical officers of the schools for their indispensable assistance in this inquiry.

J. A. Glover and J. Wilson—
'An Extensive Epidemic of Catarrhal Jaundice.' *Lancet,* Lond., 28th March 1931.

VI. INDUSTRIAL HEALTH

Researches into Industrial Diseases

Industrial Pulmonary Disease

Reference was made last year to the appointment of a Committee (p. 140) to advise the Council on new lines of inquiry and to supervise work on this subject. The Committee have had under consideration the dust hazards in various industries, including haematite and anthracite mining, and asbestos manufacture, and have explored the subject of standardization of radiographical technique for pulmonary disease. They have drawn up a scheme for investigating the physical state and chemical composition of atmospheric dusts as they occur in industry, and an arrangement has now been effected between the Council and the War Office by which these investigations will be made in co-operation with the staff of the Chemical Defence Research Experimental Station, Porton, the Council providing the expenses of the work.

Experimental work on the effects of dust inhalation has been continued by Mr. F. Haynes at St. Bartholomew's Hospital, London, under the direction of Dr. J. S. Haldane, the Council defraying the expenses. At the same place, Professor E. H. Kettle, with grants for expenses and the assistance of Dr. H. E. Archer, has investigated the tissue reactions brought about by various irritants and their influence on the development of tuberculosis. Many of the important dusts encountered in industries have been examined in this respect. With Dr. R. Hilton (p. 63), Professor Kettle has made further observations on experimental silicosis and its relation to tuberculosis. Dr. Archer has analysed a number of tissues and body fluids to establish a satisfactory method for the estimation of their silica content.

At Cardiff and Swansea, Professor S. L. Cummins (p. 90) and Dr. A. F. S. Sladden have continued, with a grant for expenses, their pathological studies of 'coal-miner's lung'. With Dr. Cicely Weatherall, Professor Cummins has also investigated the effects of colloidal silica on bacteria and on cellular exudates. A clinical study of the lung conditions in retired coal-miners has been made, under Professor Cummins's direction, by Dr. Enid Williams.

With grants for expenses, at Leeds, Professor M. J. Stewart (p. 102) and Professor B. A. McSwiney have done further work on asbestosis. With Dr. E. S. Fowweather, Professor Stewart is making comparative histological and biochemical studies of the lungs of town and country dwellers and of persons who have been engaged in different industries.

At Manchester, Dr. J. C. Bramwell (p. 65) and Dr. R. Ellis

have completed their inquiry into cardio-respiratory symptoms in cotton operatives. Evidence was obtained that the asthmatic dyspnoea occurring in many of these workers was attributable to the inhalation of cotton dust, but their condition, clinically and radiologically, could not be distinguished from emphysema produced in other ways. The parts played by sensitization and allergy in causing these symptoms are being investigated on behalf of the Committee by Professor H. B. Maitland, who has had the assistance of Dr. A. Brown.

S. L. Cummins—
'Anthracosis, Silicosis, and Tuberculosis in Coal-miners.' *Lancet*, Lond., 31st Jan. 1931.

J. S. Haldane—
'Silicosis and Coal Mining.' *Trans. Inst. Mining Eng.*, 1931, **53**, 415.

F. Haynes—
'Experimental Dust Inhalation in Guinea-pigs.' *J. Hyg.*, Camb., 1931, **31**, 96.

F. E. Tylecote and J. S. Dunn—
'Case of Asbestos-like Bodies in the Lungs of a Coal-miner who had never worked in Asbestos.' *Lancet*, Lond., 19th Sept. 1931.

Miners' Nystagmus

The Committee named at p. 140 direct investigations on this subject.

Further studies have been made of the relation of defective and variable illumination to nystagmus, and a memorandum on the amount and quality of illumination which, in the opinion of the Committee, should be constantly received by workers at the coal-face, is being prepared. Dr. T. L. Llewellyn is continuing his experiments with some electric hand and cap lamps which appear by their use to have produced improvement in the condition of men already suffering from nystagmus. A study of the loss of candle power in lamps used during a whole shift has been made at a large colliery by Mr. S. Adams of the staff of the Industrial Health Research Board.

An inquiry into the psychological aspects of miners' nystagmus and allied conditions is being made for the Committee by Professor M. Culpin (p. 123).

The Industrial Health Research Board

For a more detailed account of the work of the Board than is given here, reference may be made to their Eleventh Annual Report, published separately last July; it includes an analysis of the work published by them during the years 1926–30.

Eleventh Annual Report of the Industrial Health Research Board, London (H.M. Stationery Office), 1931.

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Statistical Studies

The Statistical Committee, in addition to their work already mentioned (p. 117), have continued to advise the Board and have directed the investigations described below.

Dr. A. B. Hill, of the Committee's staff, has made a preliminary inquiry into the possibility of obtaining statistical evidence of the effects of anthracite dust on the lungs of coal-miners. This work has been undertaken at the request of the Mines Department and on behalf of the Committee on Industrial Pulmonary Disease. It has been difficult to obtain a sufficient number of surface workers, available for medical examination, who have been exposed only to anthracite dust, and to find a statistically adequate control group. Much help has, however, been given by officials of the Mines Department and by the representatives of employers and employed, and the data provided by the preliminary survey are now under consideration.

Dr. May Smith, in continuation of her study of the variations in the sickness absenteeism of employees in different occupations, has compiled in tabular form the sickness rates experienced by a number of establishments differing from each other in the security of tenure contract and pension conditions offered to employees. A tendency, which is apparent from these figures, for the more secure groups to experience a higher sickness rate than the less secure, is being examined more closely.

The Physiology of Muscular Work

Mr. D. E. R. Hughes and Mr. J. Chalmers, working under the direction of Professor E. P. Cathcart with personal and expenses grants, are completing their survey of the physique of men in different industrial and other occupations.

At the London School of Hygiene Dr. G. P. Crowden is continuing his study of the influence of vibration on the human body. The Council have provided his expenses.

Industrial Psychology

A noteworthy advance during the year has been the appointment of Dr. Millais Culpin to a new Chair of Industrial Medical Psychology in the University of London. This Chair has been instituted at the London School of Hygiene. Professor Culpin continues to give part-time service to the Council and he will have the assistance of Dr. May Smith and Mr. E. Farmer, both of the Board's staff, as honorary lecturers in the School.

Professor Culpin and Dr. Smith have continued their study of occupational psychoneuroses. On behalf of the Deep Diving Com-

mittee of the Admiralty Professor Culpin has made an investigation of the psychological factors underlying symptoms felt by some divers in deep water. The results of this inquiry, which have an important bearing on selection of men for work of this type, have been reported to the Admiralty.

Under the direction of Professor F. C. Bartlett at Cambridge, Mr. J. M. Blackburn and Mrs. M. Drury Smith have again received part-time grants for a study of 'learning curves'.

At Manchester, under Professor T. H. Pear, Miss R. Goldthorpe and Miss M. G. Potter have concluded their investigation into the relative effects of concentrated and distributed practice on proficiency. In the same laboratory, Mrs. E. M. Henshaw has completed a report on the transference of acquired skill from one technical operation to another. This study was made with Mr. J. N. Langdon, of the Board's staff, and Miss P. G. Holman, who receives a personal grant.

At St. Andrews University, Dr. C. A. Mace has a grant for expenses; he is directing inquiries into the influence of incentives on mental and physical efficiency. This work, which was begun by Mr. H. Ferguson and Mr. A. Swinton, is being continued by Mr. J. M. Milne, Mr. J. F. Taylor, and Mr. A. S. Robertson. A similar investigation is being made here by Miss Holman, with special reference to the performance of workers of subnormal ability.

Mr. E. Farmer, Mr. E. G. Chambers, and Mr. F. J. Kirk, all of the Board's staff, have continued their inquiries into the value of psychological tests in vocational selection as indicated by subsequent proficiency and accident proneness. Their field of work has been chiefly in the Government Services. With Major R. M. Dickson, R.A.M.C., further studies have been made for the Royal Corps of Signals, while an inquiry into the special requirements in naval gunnery has been continued with Surgeon-Commander M. B. Macleod, R.N. An investigation into the capacities required in recruits for the Royal Tank Corps has also been made.

Another group of Air Force apprentices has been tested with the special object of developing group methods of testing, and other specialized branches of the Defence Services are being included in the survey so that the conclusions ultimately to be drawn may be based on extensive data. The Council are indebted to the Admiralty, the War Office, and the Air Ministry for their help in promoting all these Service inquiries.

Mr. S. Wyatt, Mr. J. A. Fraser, and Mr. J. N. Langdon, assisted by Mr. F. G. L. Stock and Mr. L. Frost, have continued their study of various aspects of repetitive work. An inquiry into the special abilities required for the operations of examining or inspection in manufacture has been completed.

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M. Culpin—
'The Conception of "Nervous Disorder".' *Lancet*, Lond., 27th Dec. 1930.
'Some Cases of "Traumatic Neurasthenia".' *Ibid.*, Lond., 1st August 1931.

Industrial Investigations

The following work has also been done by the staff of the Board.

Heating and Ventilation. Dr. H. M. Vernon, assisted by Mr. C. G. Warner, has investigated problems of radiant heat measurement from the point of view of the physiological adequacy of various radiant heating systems. A report has been submitted to the joint Committee on Heating and Ventilation problems, appointed by the Council and the Department of Scientific and Industrial Research.

The same two observers have studied the influence of air temperature and humidity on working capacity.

Coal Mining. Dr. Vernon, Dr. T. Bedford, and Mr. Warner have completed their studies of absenteeism in coal-miners, in relation to short time and other conditions, and of the variations in absenteeism due to sickness in different districts. A report has been published.

Ultra-Violet Radiation. Mr. H. C. Weston, assisted by Mr. S. Adams, has recorded throughout a year the penetration of natural ultra-violet radiation into a factory with windows glazed with special glass, transparent to ultra-violet rays. It was found that, speaking generally, the operatives received less ultra-violet radiation during a whole day in the factory than during a short walk to and from their work.

Noise. Mr. Weston and Mr. Adams have examined the effects of the adoption of 'ear defenders' on the output of workers in a Lancashire weaving-shed.

At the request of the Treasury, Dr. May Smith is investigating, in one of the Government departments, the output and health records of two groups of typists—the one using noiseless, and the other ordinary typewriters.

Lighting. Mr. Weston and Mr. Adams are making experiments on the effects of different types of illumination on the efficiency of persons doing rough work.

H. M. Vernon, T. Bedford, and C. G. Warner—
'Two Studies of Absenteeism in Coal Mines. I. The Absenteeism of Miners in Relation to Short Time and other Conditions. II. A Study of Absenteeism at certain Scottish Collieries.' *Rep. Indust. Hlth. Res. Bd.*, No. 62, 1931.

VII. TRAVELLING FELLOWSHIPS

The Rockefeller Medical Fellowships

The arrangement continues by which the Rockefeller Foundation of New York generously entrust the Council with the award in Great Britain of medical Fellowships endowed by the Foundation. These are tenable in the United States, or, in special cases, in other countries, by workers who have had suitable training in the medical sciences, and who intend subsequently to devote themselves to a career of higher teaching or research in the British Isles.

All the Fellows of the eighth annual group (1930–31) have now returned to this country. Mr. R. C. Brock studied problems of thoracic surgery under Dr. E. A. Graham, at St. Louis; Dr. F. B. Byrom worked at metabolic problems under Dr. Russell Wilder and Dr. Baird Hastings, at Chicago; Dr. Desmond Curran studied psychiatry under Dr. Adolf Meyer at Baltimore, and Dr. C. C. Ungley problems of anaemia, under Dr. Minot, at Boston. Dr. A. S. Paterson worked for six months at Baltimore under Dr. Adolf Meyer, and for the rest of the year on nervous pathology under Professor W. Spielmeyer, at Munich. Dr. A. A. Moncrieff studied pulmonary diseases under Professor Brauer and Professor Kleinschmidt at Hamburg.

For the academic year 1931–32, Fellowships have been awarded to the following: Dr. E. T. Conybeare, Demonstrator of Physiology, Guy's Hospital, London; Mr. G. M. Dean, Department of Surgery, Aberdeen University; Dr. M. H. Finkelstein, Department of Bacteriology, Edinburgh University; Dr. O. S. Gibbs, late Professor of Pharmacology, Dalhousie University, Canada; Dr. E. M. Lourie, Assistant Lecturer in Protozoology, Liverpool School of Tropical Medicine; Dr. A. W. Spence, Demonstrator of Pathology, St. Bartholomew's Hospital, London; Mr. C. H. Waddington, Strangeways Research Laboratory, Cambridge; Mr. K. H. Watkins, Assistant Resident Surgical Officer, Royal Infirmary, Manchester.

Mr. Waddington received a special short-term Fellowship for work on embryology and tissue culture under Professor Goldschmidt at Berlin; he has already returned to this country. Dr. Conybeare holds his Fellowship on modified terms while receiving emoluments from another source.

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The Dorothy Temple Cross Research Fellowships in Tuberculosis

The Council have made a second series of awards of these Research Fellowships in Tuberculosis, established under the generous endowment by Mrs. Odo Cross, to which full reference was made last year. These Fellowships are open to suitably qualified British subjects intending 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. In the award of Fellowships, preference is to be given to candidates who wish to make their studies or inquiries outside the borders of Great Britain.

Of the Fellows of the first annual group, Dr. A. I. G. McLaughlin has now returned to this country. He studied clinical problems of tuberculosis, for the first six months at the New York State Hospital for Incipient Tuberculosis, Ray Brook, N.Y., and afterwards at the Laennec Hospital, Paris. Dr. R. J. Matthews has completed a study of tuberculosis among the native population in Zanzibar. Lieut. S. M. Burrows, R.A.M.C., is shortly returning from the Sudan for a period of work in Europe, and the tenure of the Fellowship awarded to him last year is being extended.

For the academic year 1931–32, Fellowships have been awarded to Dr. C. A. Birch, Senior Medical Registrar and Tutor at the Royal Infirmary, Liverpool, and to Dr. R. L. Vollum, Demonstrator in Pathology at Oxford University. Dr. Birch is studying problems of tuberculosis at industrial centres in the United States and Dr. Vollum will visit Germany and Austria to study some recent developments there.

VIII. CONCLUSION

In accordance with the statutory rules for retirement, the two senior members, Professor T. R. Elliott and Professor J. B. Leathes, left the Council at the close of the year now reviewed, and their places were taken respectively by Lord Dawson of Penn, President of the Royal College of Physicians and Physician to the London Hospital, and Dr. Edward Mellanby, F.R.S., Professor of Pharmacology in the University of Sheffield.

The programme of work, of which a summary account has now been presented, has overtaxed the ordinary financial resources of the Council, and for reasons wholly independent of the results of the national financial crisis of last autumn. For the past four years there has been no increase in the grant-in-aid voted by Parliament for the work of the Council. In a service relatively so young as this, there must always be a rising expenditure as men in scientific or subordinate positions gain in normal increments of pay, and as permanent material equipments are being gradually built up. At the same time, many fresh and urgent demands have been made upon the Council's funds for work in some of the new and rapidly developing fields of medicine, while additional calls have been made upon them by other Government Departments for investigations of immediate practical relevance to the public service or the public health.

The Council referred last year to the heavy new responsibilities that have come to them in the work of determining and applying new standards of measurement for biological substances useful either as remedies or as foods. An international conference upon biological standards held in London last June under the League of Nations, to which detailed reference has been made at p. 51, made special calls upon the Council for preparatory work.

These various demands, though each of them may be taken as gratifying evidence of progress in well-founded work, have combined to overburden the ordinary resources of the Council. They thought it undesirable a year ago to ask for larger provision from Parliament to meet some of these additional burdens, and they met the adverse balance of their budget by making a special call upon money generously given them by private hands. Besides this emergency contribution to their work, the Council have received, as in many recent years, substantial contributions from public bodies and other voluntary sources to particular parts of their work that would otherwise have been quite beyond their reach within the limits of their Parliamentary grant.

With these circumstances in view it was naturally gratifying to

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the Council that the Committee on National Expenditure appointed last March found in their report of July no occasion to recommend any reduction in the expenditure of the Council or any change in their present responsibilities.

In consequence of the crises in national finance during the autumn, however, the Council have made increasing effort to diminish the total cost of their programme while preserving in every possible way its best value and utility. They proceeded at once to this task, and as one part of it they have called upon the whole of the workers in their service to submit, for the duration of the present emergency, to sacrifices in remuneration corresponding as nearly as possible with those inflicted in similar administrative and research services under the Crown.

During the past year the Council have received inquiry whether they are prepared to accept smaller donations to their funds, in augmentation of the capital sums given or bequeathed to them that have been mentioned from time to time in these Annual Reports. The inquirer was informed that the Council have in fact gratefully received donations on several occasions, either for the general purposes of their work or for the assistance of special lines of investigation. He was informed, also, that money received from private sources is never regarded as relieving in any way the expenditure from public funds, and is applied immediately to the support of research work without deduction of any kind for administrative expenses. He has since made a generous donation to the funds of the Council, and has expressed the intention of repeating it as an annual subscription. For this assistance to their work, the Council wish here to record their sincere thanks.

The Council must again, in conclusion, record their strong sense of indebtedness to the numerous distinguished workers in various fields of science and clinical medicine who have given voluntary advisory service to the Council as members of special Committees for supervising investigations. Their names are set out upon other pages below. For this generous aid, often given at heavy expense of time and trouble, the Council would here once more repeat the expression of their gratitude.

D'ABERNON,
Chairman of the
Medical Research Council.

WALTER M. FLETCHER,
Secretary of the Council.

38 Old Queen Street,
Westminster, S.W. 1.

22nd January, 1932.

APPENDIX A

(*See page 27*).

MEMORANDUM BY THE MEDICAL RESEARCH COUNCIL ON THE PATENT LAW IN RELATION TO MEDICAL RESEARCH

(*Submitted to the President of the Board of Trade for consideration by the Departmental Committee on the Patents and Designs Acts and Practice of the Patent Office,* 1929–1931.)

This subject has been receiving the careful consideration of the Medical Research Council during the past few years. They have become increasingly aware of certain difficulties and anomalies in the present position, and some of these have been brought into prominence by recent events.

(2) As the body charged by H.M. Government with the duty of directly promoting medical research, the Council are naturally concerned also in facilitating the stages by which the results of medical discovery are brought into practical application. This general concern is shared of course by other Departments which are charged with the care of the public health or with the administration of special medical services. The Council have necessarily a special interest in the effects, direct or indirect, which the operation of the Patent Law may have upon the prosecution and success of research work itself. In this are involved some questions of high national importance which, in the Council's view, call for serious consideration at the present time.

Special Relations of Patent Law to Discovery in the Medical Field.

(3) The operation of the Patent Law offers problems which seem to be peculiar to this field of work. This is well recognized by the legislature already. The law as amended in 1919 gives special treatment to patents covering medicine and foods. In the public interest special limitations are already placed both upon applicants for patents in these substances, restricting the nature of the subject matter permitted, and upon the holders of any rights in these substances, depriving them of power to exercise a monopoly.

(4) It is the fact that in practice little use of the Patent Law is, as a rule, made by medical research workers. There is a strong professional tradition against patenting, which arises from ethical objections taken to any monopoly in the fruits of medical discovery or to private profit being derived from them. Even where it may be admitted that patenting for purely defensive purposes, or with a view to gaining some useful control in the public interest, is unobjectionable, there is an absence of the usual inducement to take out a patent in the case of a medical worker who considers himself debarred from making pecuniary gain himself. In the Council's view, importance must be attached to this attitude of the medical profession, and it will be noted that its effect is to make the law operate in the medical field capriciously in favour of the few who take advantage of it and find themselves unobstructed by rival claims. It cannot be said that the Patent Law has had any significant effect, in this country and in the medical field, of stimulating the work of discovery.

(5) A consequence which the Council regard as of the first importance arises from this fact that medical workers do not generally resort to patenting. Medical research work is at present conducted under conditions of great freedom of intercourse and of the interchange of information and ideas. This free intercourse between research workers is of great advantage for the advancement of the subject, and any impediment to it should be avoided or removed. If medical research workers in general are driven to defensive patenting by the action of a few, the conditions of research must

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become changed for the worse by the introduction of secrecy in respect of incomplete or unpublished work. Under present conditions, moreover, the Patent Law gives opportunities to the unscrupulous for abusing the customary openness and confidence of others.

(6) Medical research lies chiefly in the biological field. Here knowledge is less exact, and in general less complete, than in the sciences dealing with inorganic phenomena. As a result, biological discoveries tend to be vague at first, and patents drawn for them, if they are to be effective, must attempt to cover a wide range of possibilities. These claims, if allowed, must tend definitely to discourage further developments, because research workers will naturally be reluctant to explore fields which appear to be already covered by proprietary rights.

The Operation of the Existing Law.

(7) The problem which the Medical Research Council have had to consider is thus twofold. On the one hand they have had to consider the course of action that seems most appropriate under the conditions created by the existing law, and on the other hand they have considered whether amendment of the law itself should be sought.

(8) Under the first heading, the Council have agreed that in the present state of the law it may be advisable that a medical discovery should be patented, with a view either to controlling its application or to protecting it against improper exploitation. They consider, however, that this is desirable only where the control is exercised in the public interest, where no pecuniary gain is derived from the rights, and where the action taken does not seem likely to hamper the freedom of research or to discourage further investigation.

(9) The Council have themselves made very sparing use of the Patent Law. They accepted, some years ago, the British patent rights—offered to them by the Canadian University to which the discoverers had transferred them—in the method of preparing 'insulin', the active principle of the pancreas which is valuable in the treatment of diabetes. The chief reason which led the Council to take this step was the fact that at that time there was in this country no legal provision for controlling the strength and quality of therapeutic preparations which could not be tested by direct chemical means. By use of the patent rights, under which the Council granted manufacturing licences without royalty, it was possible to secure for the British public and for others a regular supply of insulin of proper quality and standard strength, and to exclude inferior preparations from the market. Since that date, however, the Therapeutic Substances Act, 1925, has provided for Government control over the quality and potency of these substances, which was obviously required but previously lacking. The Council have thus had no further occasion to exercise their patent rights in the case of insulin, and another instance of the same kind is not now likely to recur.

(10) In other cases which have come to their notice, the Council have refused to countenance patenting, or have declined existing patent rights which have been offered to them, because they have considered the patenting to be unnecessary or even undesirable. They still consider, however, that cases may arise in which, under the present conditions, patenting may be necessary, but merely as a defensive measure against patenting by others.

(11) In the past year the Council watched with anxiety the effect of the Patent Law upon the commercial development of an important discovery made in their own laboratories, namely, the production of vitamin D in highly potent form by the ultra-violet irradiation of ergosterol. This discovery came at an advanced stage in a long series of researches by many workers to which large financial support had been given from public moneys. As is the usual practice in the medical field, this discovery was made free to the world by publication, and manufacturing firms were thus given the opportunity of bringing its benefits to the public. This action by manufacturers has, however, been hampered by the claims made under a

British patent (No. 236197) which had been granted to a foreign worker, Professor Steenbock of Wisconsin, U.S.A., some years earlier. This patent for a process of imparting anti-rachitic properties to foodstuffs by artificial ultra-violet irradiation, was drawn in wide terms which are now claimed as covering not only work of more recent date and greater importance, but also the valuable practical applications which the latest discovery has made possible and easy. In effect, therefore, the application of results obtained with the support of public funds and given freely to the world is now actually subject to royalties payable by members of the public to the representatives of a foreign worker who obtained a patent at a stage when knowledge of the subject was quite imperfect. The effect of this patent is the greater in that there are no other patents in the field covering either the preceding or the subsequent stages of the work. The only defence against the recurrence of unfortunate situations of this kind would appear, in the present state of the Law, to be a general recourse to patenting by medical workers. This would bring a drastic and deleterious change in the present conditions of medical research work which the Council must feel it their duty strongly to resist in the interest of the progress of medical knowledge.

(12) The Steenbock patent, in its relation to the subsequent discovery here by Rosenheim and Webster, seems to provide a valuable illustration of the dangers of the present situation in general. It may therefore be useful to offer the following more detailed observations upon it:

(*a*) What Professor Steenbock did in effect patent was a law of nature—i.e. that the natural product, vitamin D, is formed by the action of ultra-violet light upon certain natural substances: so far as is known, this is the only way in which this vitamin is formed in nature, whether in the body or in various foodstuffs and other organic materials. What he did in form patent was a process for artificially inducing this action to take place. But the process in itself contained nothing novel and required no ingenuity to devise, for with a knowledge of the natural law the application was ready to hand.

(*b*) The Steenbock patent was based upon very imperfect knowledge of its subject matter: it covered the production of a substance of undetermined composition from an unknown constituent of certain complex materials by an action not then understood. The patent was nevertheless drawn in wide general terms so that it is now claimed as covering all the applications of the more definite discoveries of subsequent date.

(*c*) The Steenbock process was of doubtful commercial value, yielding products no more potent than those already known in nature. The parent substance of the vitamin—the constituent of the various materials capable of activation—has since been found to be a substance called ergosterol. By using this substance pure, a product can be obtained having thousands of times the potency of any previously known. The new discovery, besides greatly advancing theoretical knowledge, has given a process which is of immediate medical and commercial importance.

(*d*) Professor Steenbock may have priority of publication as regards the irradiation of foodstuffs as such, but this was founded on the earlier and unpatented discoveries of various workers, and notably of workers of British nationality. It was already well known that vitamin D existed in many natural substances, and that ultra-violet irradiation of the body gave a result similar to that of feeding with the vitamin. It was believed that the action of ultra-violet light on the body was due to the formation therein of the vitamin, and it was at least suspected that the vitamin could be similarly produced outside the body. At the time of Professor Steenbock's discovery other workers had already made progress in following this obvious clue. Without denying him credit for the particular step he took, it would seem wholly unreasonable that he should acquire the power to control the results of so much previous and so much subsequent work.

(*e*) It should be noted, also, that the discovery of ergosterol as the 'provitamin' was not derived from Professor Steenbock's work, but from the still earlier work on the irradiation of the body: it was the fact that sterols are found in the skin that gave the clue. The new discovery was therefore not logically a development of Steenbock's, but scientifically independent of it. It is only the wide terms of his patent which enable him now to claim control over the application of knowledge which is of more recent date and of independent origin.

(*f*) It may also be noted that Professor Steenbock made early disavowal of any intention to derive personal profit from his patent, a fact which no doubt influenced other workers who might otherwise have protected their subsequent discoveries, even if these would rank, legally, only as developments of his. He transferred his patent rights to his University of Wisconsin, and the University, whether with or without his acquiescence, is proposing to derive profit from them.

Universities and Patent Rights.

(13) Professor Steenbock is not the only worker in the medical field who has thought that the known objections to patenting in the medical field are related solely to the question of personal pecuniary profit by the discoverer. There are signs that, on the American Continent in particular, the practice of taking out a patent for such a discovery, and assigning it to a Committee acting on behalf of the discoverer's University, is likely to spread. Experience has shown that such Committees are apt to use their patent rights so as to exercise scientific control over the testing of products coming within their wide range. This is not only hampering to the freedom of research, but threatens in certain instances to produce a clash between our own national control, under the Therapeutic Substances Act, and that exercised by unofficial foreign Committees.

(14) Experience has further shown that such a holding Committee may be ready to regard their patent as a means of raising money for the endowment of further research, in the University which they represent. Such a system is likely to be regarded in this country as detrimental to the University spirit; with the result that there is a real danger that our people may be effectively taxed for the support of research in foreign Universities. If the practice grows of looking to royalties under patent rights as a normal source of support to research work in Universities, it can hardly fail to have an undesirable influence upon the spirit in which inquiry should be undertaken. It would be deplorable if in effect research workers in a University felt that their efforts might be measured and even their promotion affected by the potential patent value of results they might produce.

Discovery and Invention.

(15) The dangers and difficulties which have just been illustrated in recent experience appear to the Council to have arisen from the unsuitability of the operations of the Patent Law to the field of biology and medicine, as distinct from that of the physical sciences and their practical applications. For discussion of this subject distinction may be drawn between the work of scientific discovery on the one hand, by which new phenomena of nature are observed and their laws ascertained, and, on the other hand, the work of practical invention, by which natural phenomena are turned by appropriate devices into direct use. The prime object of the Patent Law is to stimulate invention. It is intended to secure that a proper share of the commercial reward, if realizable, shall go to the inventor himself. The law is not aimed at stimulating the work of discovery; it would be impossible to frame a law that could assign reward here with justice, even if money reward could be supposed, as is not the case, to be an effective means of stimulus. Faraday's discovery of the primary electro-magnetic phenomena could not have been stimulated by any patent law, and could not have

been patented. Thousands of inventors have subsequently secured patent rights and patent profits in particular applications to human affairs of his basal discovery.

Summary.

(16) The objections to the operation of the Patent Law in the field of biology and medicine may be summed up as follows:

(*a*) The discovery of new facts of nature in the medical field, concerned as they are with the body of man himself and the factors affecting it, may lead obviously and at once, without any intervening steps of ingenious invention, to valuable practical uses. There is not the same possibility of clear distinction between the discoverer on the one hand and the inventor on the other as there is in the inorganic field, where fundamental knowledge is far more complete and where much individual ingenuity is required to devise new practical applications. Those who seek to use the Patent Law in the medical field for personal or localized profit will be apt (as experience already proves) to claim proprietary rights in some particular use of a new discovery that follows it almost automatically, and may not in itself, considered as a practical invention, be particularly meritorious in the sense of deserving pecuniary reward.

(*b*) Biological discoveries in their first phases are necessarily in the form of vague knowledge, and patents which may be sought by persons making useful application of them are likely to be drawn (as again experience has shown) in wide terms that really go beyond the knowledge of the moment. In the inorganic field patented inventions have to be, because they can be, more exactly defined, and do not necessarily stake out claims by which further research by others in the same field may be discouraged or hampered.

(*c*) Although resort to the Patent Law is open to every one, it is in fact little used in the medical field, for reasons to which importance must be attached: in effect, therefore, the law works capriciously in favour of the few who break the tradition. Medical research is in general organized on a basis of free intercourse between workers: it is important that this should be preserved, but the introduction of rivalry in obtaining patents—even if only in defence against those who break the general tradition—would make this obviously difficult or impossible.

Conclusions.

(17) The conclusion to be drawn from these observations seems to the Medical Research Council to be almost irresistible. It is that the law should be amended to extend still further the special treatment already given by it to medical discoveries and, as in some other countries, to abolish altogether the right of patenting these. It appears to them that in the medical field the Patent Law does not achieve its purpose of stimulating discovery, because it is in fact relatively little used and the incentives to research are other than pecuniary; that in practice the Patent Law here works mischievously, because of the undue advantage obtainable by the few, mainly foreigners, who resort to it; and that this situation, if not remedied, is likely to have a very harmful effect upon medical research work.

(18) The Council are aware that the definition of a 'medical' discovery, for the purposes of such amending legislation, must present certain difficulties. For example, there are some synthetic chemicals, originally prepared and protected by patents with a view to their use for other purposes, such as dyeing, which have been found to have their chief value as therapeutic agents. Similarly, the process for preparing a particular substance, found to be medically useful, may involve a master-patent covering a wide range, and having its chief importance in relation to the preparation of substances for other uses. Any amendment of the law would have to take account of this possibility, that medical discovery may give commercial value to

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patents granted for other purposes. The Council have no reason to believe, however, that such problems would present greater difficulties in this country than in others, where the suggested exclusion has already long been in force.

(19) The Council also realize that there may be valid objection from the commercial point of view to the abolition of medical patents without international agreement. They believe, however, that there are possible alternative courses which would be free from objection on this ground but would yet be nearly equivalent to total abolition for the purposes to which the Council attach importance. The Council are aware, for instance, that a proposal is being made that there should be compulsory dedication of medical patents to some public official, body, or department acting in this matter as a national trustee. They believe that this proposal may be well worthy of consideration, but it appears to them that, if it be adopted, great care must be taken in framing provisions in detail so as to ensure that the grounds of objection to the present system are in fact removed. In particular, they would suggest that it would be in the highest degree undesirable that a national trustee should be charged with any duty with regard to obtaining, holding, or exploiting medical patents in other countries.

(20) The Medical Research Council would therefore urge that the most serious consideration should now be given to the question of seeking changes in the existing law which would secure either the total abolition of the right of patenting in the medical field or some nearly equivalent restriction of that right.

London,
29th November, 1929.

APPENDIX B

INVESTIGATION COMMITTEES FOR SPECIAL SUBJECTS

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Professor Edward Mellanby, M.D., F.R.C.P., F.R.S.
J. B. Orr, D.S.O., M.C., D.Sc., M.D.
G. P. Crowden, M.Sc., M.R.C.S. (*Secretary*).

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(*Jointly with the Lister Institute of Preveniive Medicine.*)
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Miss Harriette Chick, C.B.E., D.Sc. (*Secretary*).
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O. Rosenheim, D.Sc., F.R.S.
S. S. Zilva, D.Sc.

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Sex Hormones.

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Tuberculosis.

Tuberculin.

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