THE THOMAS BAKER, ALICE BAKER, AND ELEANOR SHAW MEDICAL RESEARCH INSTITUTE

ALFRED HOSPITAL, PRAHRAN
VICTORIA, AUSTRALIA

Twenty-Third Annual Report

1949

and

A Retrospect

1926 — 1950

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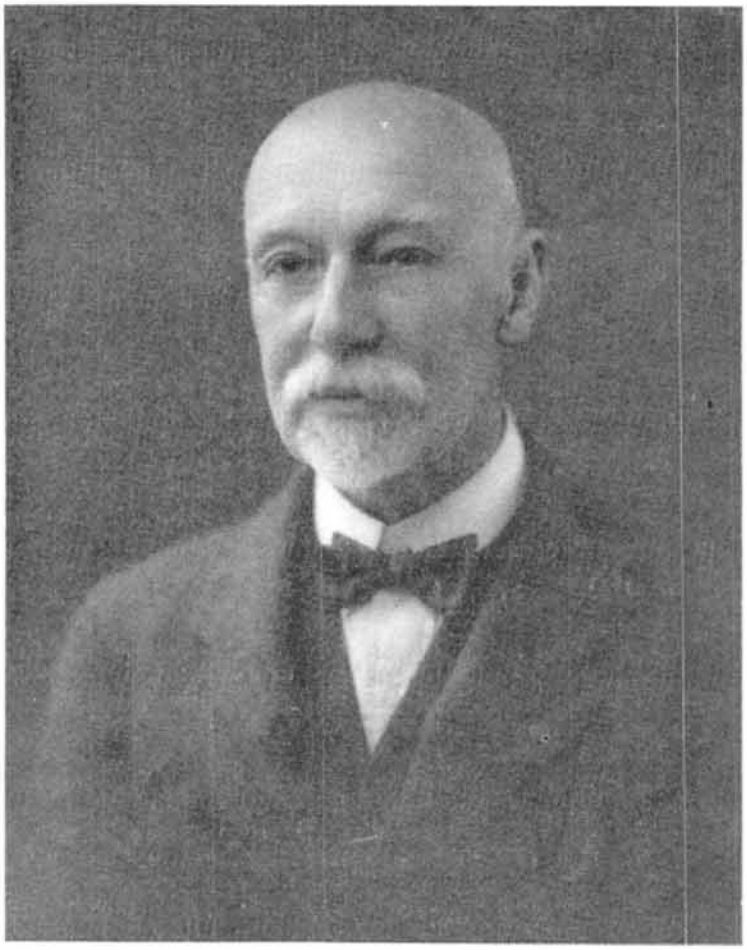
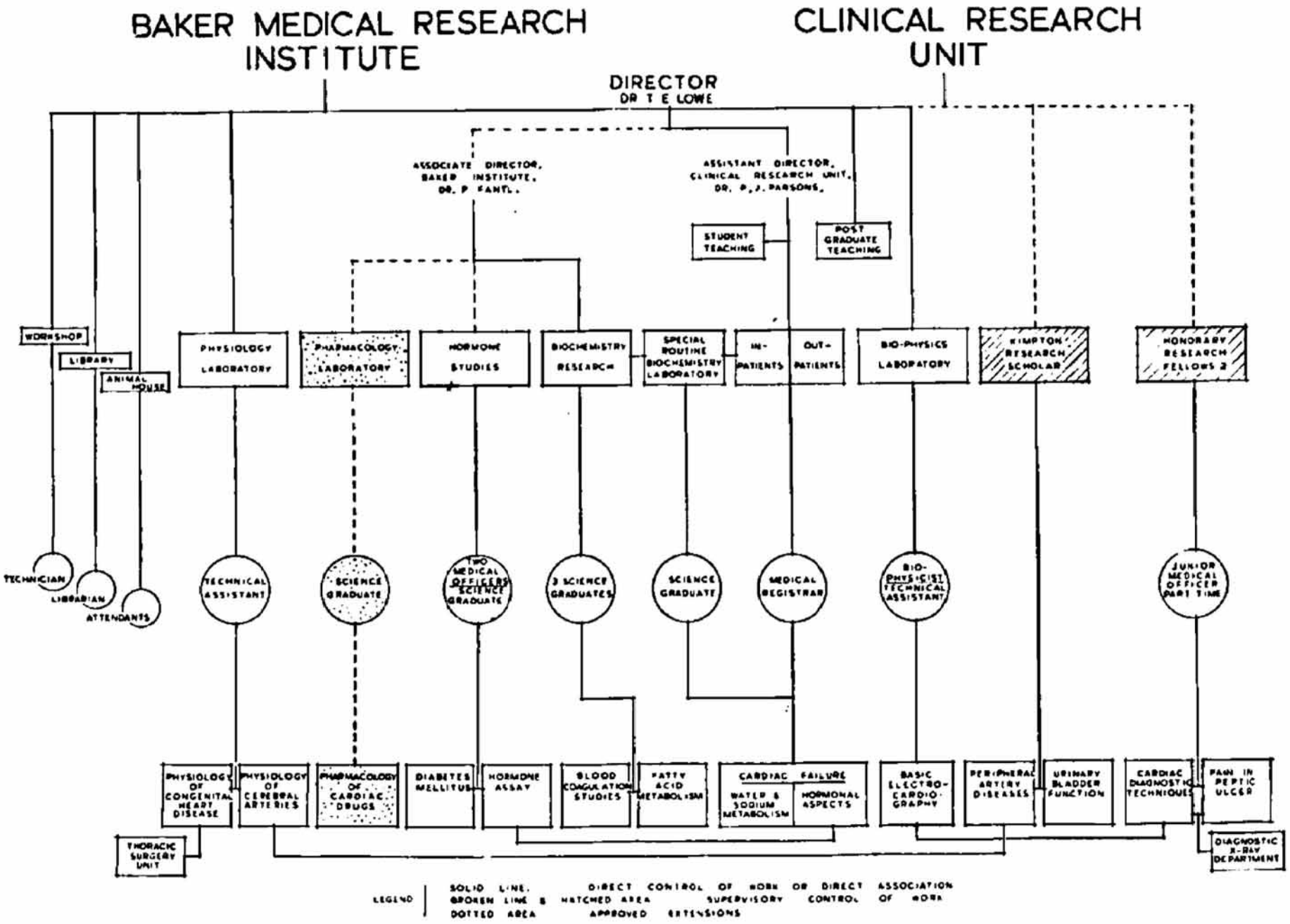
*Supported by grants from National Health and Medical Research Council.

†Partially supported by grant from National Health and Medical Research Council.



Late Thomas Baker, Esq.

RESEARCH ORGANISATION



DIRECTOR'S REPORT TO THE TRUSTEES.

Gentlemen,

Before reviewing the activities of the Institute for 1949, I wish to place on record my appreciation of the work of Dr. P. Fantl, Associate Director, who, owing to the illness of Dr. A. B. Corkill, carried out the duties of Acting Director until my appointment on May 1st. Not only did he carry this burden to the satisfaction of all concerned, but he has been a loyal and devoted associate to me in the difficult period following my appointment to the directorship.

In his report for 1948 it was mentioned that the Board of Management of the Hospital had decided to establish a Clinical Research Unit. This unit came into being in March, 1949, and represents a development of vital importance to the Institute. The Institute has as its object the conduct of research in various fields of medical science, and, as it has developed over the past quarter century, its personnel and equipment have been largely devoted to basic problems rather than towards the clinical application of research. Thus, to make any basic discoveries available for treatment of patients, the co-operation of members of the Hospital Honorary Staff was sought from time to time. This co-operation has always been readily given to the Institute Staff, but the time which busy honoraries can devote to such research is limited. The creation of the Clinical Research Unit with its team of full-time workers will diminish the demands made by the Institute on the Honorary Staff in this regard. It is apparent, therefore, that the Clinical Research Unit greatly enhances the facilities available to the Institute. Conversely, a Clinical Research Unit cannot develop to the full without the backing of workers in the basic medical sciences. The Institute and the Clinical Research Unit should in a short time become indispensable to each other, and the very close association implied is assured as they have the same Director. Further, to make the utmost use of the facilities of both, it is desirable that there should be a core of research in a field common to both. To provide this core it has been planned to carry on studies in cardio-vascular diseases as a common line of research. Within the Baker Institute the basic work in this field comprises studies of blood coagulation, endocrine glands and cardio-vascular physiology, all of which is in progress, and arrangements have been made to commence in 1950 a study of the pharmacological action of cardiac drugs. The other fields of activity of the Institute are indicated in the following pages and will be continued.

During the year, previously planned changes have taken place and the routine biochemistry, media making and electro-cardiographic sections have been transferred to the Hospital administration. Dr. Fantl has also been appointed Consultant Biochemist to the Hospital. This re-organisation has released a considerable amount of space within the Institute building, much of which has been made available for basic research projects and the projected pharmacology laboratory.

Drs. R. R. Andrew and H. B. Kay, who have in the past worked in the Baker Institute, have been appointed Honorary Research Fellows of the Clinical Research Unit as their research projects are essentially clinical in type.

Considerable improvements to the buildings of the Institute have been carried out this year. The main building has been repainted throughout, several old outbuildings have been renovated and converted, some into store-rooms, one for inflammable materials, and one into an animal boarding house. Arrangements have also been made to instal steam heating in the animal breeding house.

During the year a working arrangement was made with the Library of Alfred Hospital so that a satisfactory exchange of journals between the two libraries has become possible. This has avoided much unnecessary duplication of subscriptions and has to some extent offset the rising cost of periodical journals.

Grateful acknowledgment is made of gifts to the library from the following:—Abbott Laboratories; Bayer Products Ltd.; Bausch & Lomb Optical Co.; Hospitals and Charities Commission; Commonwealth Scientific & Industrial Research Organisation; Felton, Grimwade & Duerdins Ltd.; Imperial Chemical Industries of Australia and New Zealand Ltd.; International Anesthesia Research Society; L'Institute Bunge; Mayo Clinic; Medical Research Council, London; Middlesex Hospital Medical School; Munitions Supply Dept.; National Health & Medical Research Council, Canberra; New York State Department of Health; Parke, Davis & Co.; Queensland Institute of Medical Research; Rockefeller Institute for Medical Research; Royal College of Physicians, Edinburgh; South African Institute for Medical Research; Mr. A. J. Trinca, F.R.C.S.; Walter & Eliza Hall Institute.

Our thanks are also due to various libraries that have lent many journals to us, and particularly to the librarians, whose assistance is greatly valued.

As in previous years much assistance, both professional and in materials, has been given to us by other organisations and grateful acknowledgment for such is expressed to the following and their associates:—

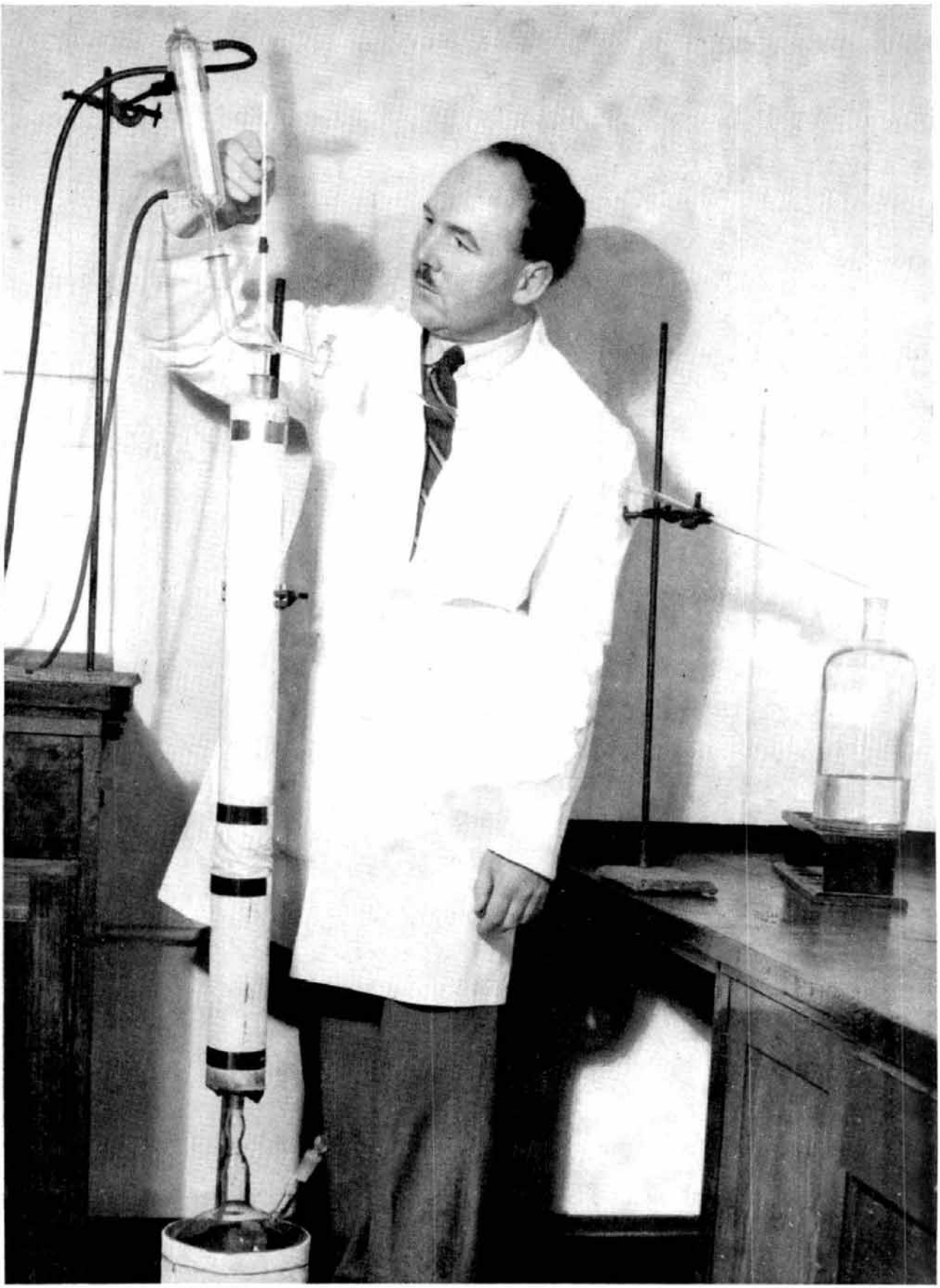
National Health and Medical Research Council.
Professor V. M. Trikojus (Biochemistry Department, University of Melbourne).
Dr. F. G. Morgan (Director, Commonwealth Serum Laboratories).
Dr. A. W. Turner (C.S.I.R.O.).
Members of the Honorary Medical Staff, Alfred Hospital.
The Red Cross Blood Transfusion Service.
Staff of Kodak A'asia. Pty. Ltd.

It is a pleasure for me to thank the Trustees for their wholehearted support of plans I have put forward for the development of the Institute.

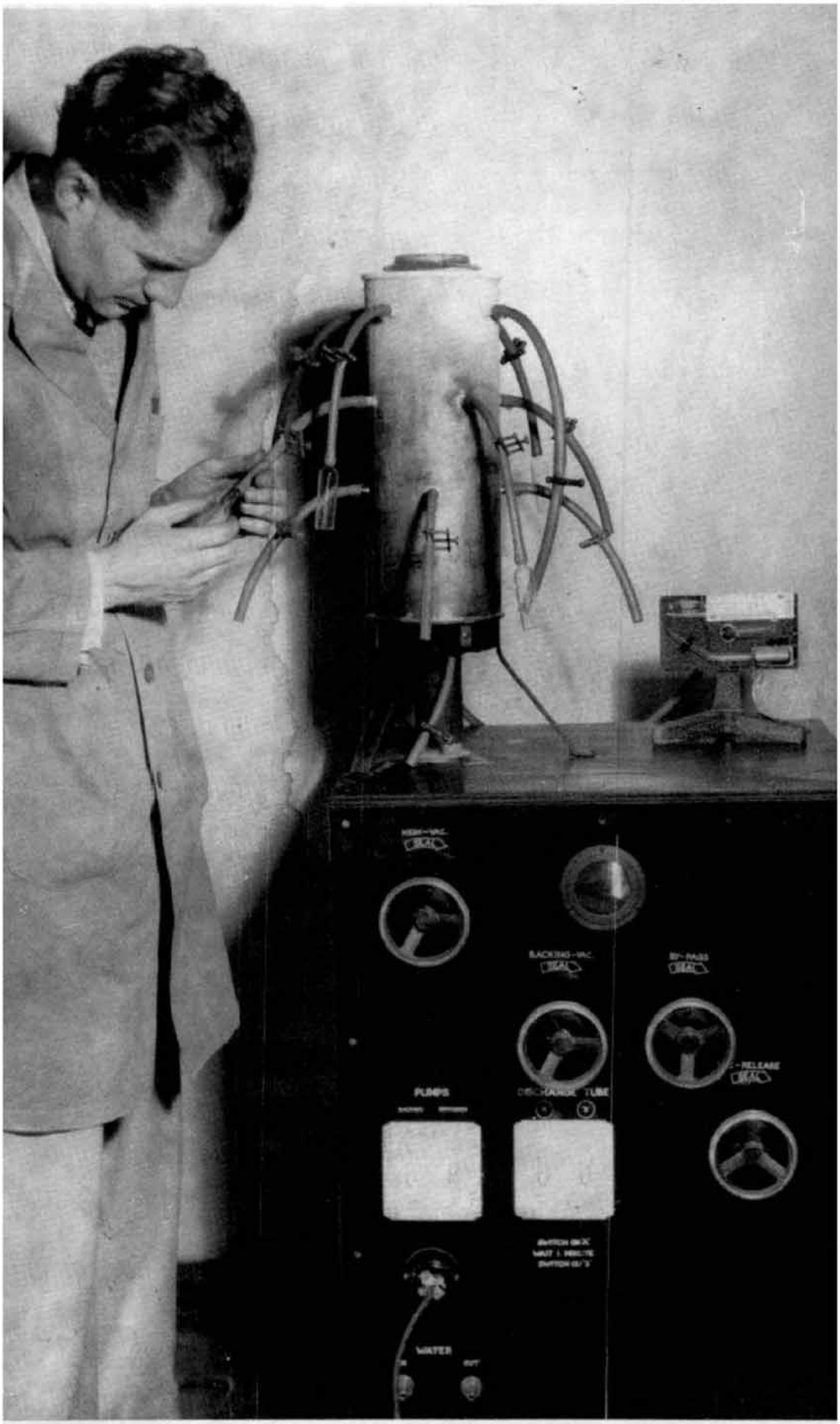
Also, I wish to thank the members of the Advisory Committee, who have been very ready to help whenever their assistance has been sought.

In the following pages a detailed summary of the work of the Institute during 1949 is presented under several headings, together with a chart showing the organisation of the Baker Institute and the integration of its work with that of the Hospital.

T. E. LOWE,
Director.



A Fractionation Column used in Baker Medical Research Institute Laboratories for Purification of Organic Solvents.



Freeze Drying Apparatus used in Study of Blood Coagulation.

BLOOD COAGULATION STUDIES.

Dr. P. Fantl, Miss B. Everard and Miss M. Fitzpatrick.

Fibrinolysis: Isolation of fibrinokinase from human brain.

In the last report it was noted that under the influence of electroconvulsions transient fibrinolytic activity appeared in human plasma whilst fibrinogen was unaffected. Because such a specific fibrinolytic enzyme might have important clinical uses in the prevention of thrombo-embolism, further studies of its characteristics have been made.

As a working hypothesis Christensen's ideas concerning protein breakdown by the enzymes of blood plasma were adopted. He assumes that the enzyme precursor is a normal blood constituent and that it is activated by a kinase produced in response to certain stimuli. The present investigation has been directed to the source of this kinase.

The most consistent results have been obtained by the use of extracts of human brain. These contain a principle that, combined with a serum component, dissolves fibrin. Without the serum component the extracts produced fibrinolysis only in about one-quarter of the cases tested, thus indicating the extracts contain little, if any, fibrin splitting enzymes. It is probable, therefore, that serum contains the enzyme precursor and brain the kinase. In these experiments fibrinogen was attacked rarely.

When brain extract was heated to 70 deg. C. for 15 minutes, its fibrin-splitting activity was destroyed, but its thrombo-plastic property was not greatly influenced.

These results suggest that the brain component required for fibrinolysis differs from thromboplastin. This difference was also demonstrated by using heterologous brain for extraction.

Results from a few experiments indicate that the specificity of the fibrinolytic enzyme produced by combination of the serum precursor with brain fibrinokinase is confined to undenatured fibrin.

This brain fibrinokinase is a saline soluble protein of globulin nature. Its insolubility in distilled water indicates that it is not of albumin nature.

Several workers have stated that there is no difference, in susceptibility to fibrinolysins, between fibrin and fibrinogen. A fibrinolysin was produced by activation of the plasma precursor by streptokinase (form haemolytic streptococci) and studies of its action show again that fibrin is lysed more markedly than fibrinogen.

Salmine Sulphate.

Having found an enzyme specific for the breakdown of fibrin, substances with the ability to split fibrin or fibrinogen were investigated next.

Protamine appeared to be of special interest in this connection, for this compound is now used for the treatment of haemorrhagic conditions due to heparinaemia, and a detailed investigation of its action on the components of the blood system appeared to be advisable.

It is known that the addition of protamine (salmine sulphate was used throughout these experiments) to oxalated plasma in the cold precipitated fibrinogen, but during experiments it was noticed that the fibrinogen precipitated went into solution during incubation. Subsequent addition of calcium ions did

not produce a fibrin clot in the majority of cases. However, in addition to calcium ions, prothrombin and thromboplastin are required for coagulation and protamines inactivate thromboplastin so that no thrombin formation can take place. Addition of thrombin to salmine-treated plasma resulted in the recovery of fibrinogen in most cases.

As these experiments show that the disappearance of the precipitated fibrinogen was not due to its breakdown, the mechanism of the fibrinogen disappearance in the presence of salmine sulphate was studied.

The most likely explanation of the phenomenon is that salmine sulphate is attacked by a plasma enzyme and the breakdown products do not share the fibrinogen-precipitating properties of the original protamine. The extent of protaminolysis could readily be followed by the application of the Sakaguchi colour reaction.

Another method of following the salmine breakdown by the plasma enzyme, based on the measurement of turbidity of the heparin-protamine complex, has been tested.

Colorimetric and nephelometric methods gave only limited information of protaminolysis, so for quantitative purposes, estimation of non-protein nitrogen by the Kjeldahl procedure was selected.

To obtain information with regard to the source of this blood enzyme a total pancreatectomy and splenectomy was carried out in a dog. A post-mortem examination forty days later showed no pancreatic or splenic tissue. In the post-operative period, the animal developed diabetes and ketonuria, which was controlled by twice-daily injections of insulin. Twenty and forty days after the operation, protaminolytic activity of the serum was measured by using the Kjeldahl technique.

As it was found that protaminolysis following the operation was within the physiological range, neither pancreas nor spleen can be considered as a major source of the blood enzyme. The only other organ tested for protaminolytic activity was rabbit's liver. Following incubation with salmine (for 21 hours) all the protein nitrogen appeared as non-protein nitrogen in the filtrate. These results indicate the presence of a very potent protaminolytic enzyme in the liver. When similar experiments were caried out using the Sakaguchi colour reaction as indicator of the breakdown of salmine, negative results were obtained. This observation suggests that liver contains, in addition to protaminase, enzymes capable of breaking down the peptide chain to arginine which in turn is split by arginase into ornithine and urea, neither of which give a positive Sakaguchi test.

The Nature of Arginine Linkage in Basic Proteins.

During the course of the investigation of the breakdown of salmine by an enzyme present in the blood serum, the reaction was followed by the estimation of arginine, using the Sakaguchi test. When salmine sulphate was used as reference substance, the result compared favourably with estimations of non-protein nitrogen. When, however, salmine was replaced by arginine as standard, theoretically impossible figures were obtained. In order to find the cause of these varying results, the Sakaguchi reaction was carried out simultaneously on salmine sulphate (Lilly), its acid hydrolysis products and arginine hydrochloride. The optical densities of the colours obtained were measured in a Beckmann Spectrophotometer.

Experimental results indicated that it is not possible to carry out arginine estimations in native salmine. After acid hydrolysis, however, a reliable estimation of arginine by the use of Sakaguchi reaction is possible.

A discrepancy between the results obtained before and after acid hydrolysis, raises the question of linkage of arginine in the salmine molecule. This problem was investigated by the use of hypobromite. It was found that four-fifths of the guanidine groups of salmine are free and one-fifth not only combined in the usual peptide linkage but also substituted in the guanidine radicle.

Treatment of Thrombo-embolic Conditions.

The clinical application of 3,3'-ethylidene dicoumarol (E.D.C.) in post-operative thrombo-embolic conditions and coronary occlusion has been continued and can be considered as a matter of routine in this hospital. The application of E.D.C. has been extended at the Women's Hospital where this drug is in use for the treatment of thrombo-embolic conditions after child-birth. The transmission of the drug into milk has been investigated in order to find out if there are toxic effects to suckling babies.

The concentration of E.D.C. in both human milk and that of experimental animals was between 0 and 0.3 mg. %. Assuming human milk production to be approximately 600 ml. per day this volume would contain not more than 1.8 mg. of the drug. It is doubtful whether such an amount given daily to a baby would influence its prothrombin level.

The Action of Ovomucoid on Blood Coagulation.

It has been shown by Lineweaver that ovomucoid has very marked anti-tryptic activity, and since other substances capable of inhibiting proteolytic processes have been shown to interfere with blood coagulation, ovomucoid was tested on the various phases of the clotting mechanism. Concentrations of 1.5% ovomucoid were used on human oxalated plasma. No influence was observed on prothrombin-thrombin conversion or the thrombin-fibrinogen reaction, and with concentrations of up to 1.35% no infleunce on plasma coagulation time could be detected.

These experiments were carried out because it has been suggested by several workers that the processes of blood coagulation are comparable to those involving proteolytic enzymes. It has been observed indeed that trypsin inhibitor isolated from soya bean has antithromboplastic and antifibrinolytic properties. It is interesting to note, however, that although ovomucoid is a potent trypsin inhibitor at similar concentrations, it has no effect on the blood coagulation system.

The Influence of p-Amino Salicylic Acid (PAS) on Prothrombin Level.

Drugs of the Salicylic Acid group are capable of inducing haemorrhages due to a reduction of the prothrombin level. In view of the fact that PAS has to be administered in relatively large amounts for long periods in the treatment of tuberculous conditions, the influence of PAS on blood coagulation was investigated. Normally fed rabbits were given orally twice daily the sodium salt equivalent to 1 g. PAS. The prothrombin level after the administration of 10.5 g. of the drug was not altered. The fibrinogen concentration showed in several cases a slight but insignificant drop.

It would appear that even large doses of PAS in normally fed rabbits do not produce prothrombin deficiency.

INTRACELLULAR BREAKDOWN OF FATTY ACIDS.

Dr. P. Fantl, G. J. Lincoln and J. F. Nelson.

The breakdown of fatty acids and their metabolites has been studied in liver slices in the presence of respiratory poisons. The most consistent results were obtained by using 2:4 dinitrophenol. This substance was selected because of its demonstrated ability to increase the oxygen uptake of respiring cells and the claim that it dissociates oxidation from phosphorylation.

It could be established that the breakdown of octanoic acid by rat liver slices was unimpaired by the addition of dinitrophenol and the oxygen consumption in the presence of substrate and dinitrophenol was increased. An investigation of this phenomenon indicated that the amount of octanoic acid disappearing was the same under either condition, but the additional oxygen uptake was accounted for by the formation of corresponding amount of aceto-acetic acid.

In order to establish whether the dinitrophenol concentration used in the above experiments was sufficient to inhibit oxidative phosphorylation, the transformation of fructose to glucose by respiring liver—a reaction known to require phosphorylation—was tested simultaneously with the octanoate breakdown. The result showed that the liver slices were unable to utilise fructose in the presence of dinitrophenol. In contrast to this inhibition the metabolism of octanoate with regard to oxygen uptake and ketone body formation was enhanced under the influence of dinitrophenol.

From these results it would appear that oxidative phosphorylation is not involved in the breakdown of fatty acids.

It has been established that for the enzymatic oxidation of hydroxybutyric acid, in addition to a specific enzyme, cozymase (diphosphopyridine nucleotide) is required which of course is reduced in this oxido-reduction process. It appears that dinitrophenol, under aerobic conditions has the ability to oxidise dihydrocozymase and this accounts for the accumulation of acetoacetic acid in the presence of dinitrophenol and similar respiratory poisons. Further evidence for this view can be obtained from experiments in which liver slices were incubated with b-hydroxybutyric acid. Again in the presence of dinitrophenol the equilibrium between b-hydroxybutyric acid and aceto-acetic acid was shifted towards accumulation of the latter compound.

Another reaction which leads to the same end products as the fatty acid oxidation by isolated liver is the conversion of pyruvate into aceto-acetate. From the amounts of b-keto acid formed it would appear that complete conversion of pyruvate into aceto-acetate occurred in the presence of dinitrophenol. In its absence part of the keto acid was reduced to b-hydroxybutyrate.

An indication that dinitrophenol oxidises preferentially dihydrocozymase is offered from experiments using triphenyltetrazolium chloride. This is a colourless substance which under the conditions of living tissues can be irreversibly reduced to the red triphenyl formazan. When the tetrazolium compound was added as an indicator to respiring liver and also kidney cortex extracts it was observed that in the absence of dinitrophenol a marked reduction of indicator occurred, whilst in the presence of dinitrophenol the reduction was inhibited. The reduction in the absence of dinitrophenol can be explained by the assumption that the reducing agent is dihydrocozymase.

From the experimental evidence obtained it is quite apparent that the breakdown of fatty acids and pyruvate, in contrast to the aerobic breakdown of monosaccharides, is not dependent upon oxidative phosphorylation. This would indicate that the energy level of fatty acids is sufficiently high to be oxidised in the biological system. From this assumption it could be concluded that under adverse conditions the breakdown of fat has a priority over that of carbohydrates in the living cell.

A paper covering this work has been submitted for publication.

BLOOD INSULIN LEVELS IN NORMAL AND DIABETIC SUBJECTS.

Dr. J. Bornstein and Miss P. Trewhella.

A technique to measure the concentration of insulin in human blood has been developed and used to investigate the changes in blood insulin content after glucose administration. It was demonstrated that insulin is secreted in response to a rise in blood sugar levels.

Using this technique in a study of 19 diabetic patients, it was found that in the majority no insulin could be detected in their plasma. The minority had, however, normal insulin concentrations in the plasma, suggesting that some mechanism operates which either creates a demand for more insulin than the body can secrete or prevents insulin from operating normally.

Arising out of this work experiments were conducted to determine the influence of various endocrine glands on glycogen deposition in isolated muscle with the following results:

(i) Alloxan diabetes inhibits the laying down of glycogen in the muscle.
(ii) Hypophysectomy following the administration of alloxan restores the deposition to normal levels.
(iii) Adrenalectomy, following alloxan, raises the deposition to well above normal levels.
(iv) Hypophysectomy and adrenalectomy following alloxan administration (A.D.H.A. animal) raise the deposition to an even greater extent than adrenalectomy.
(v) The injection of diabetic sera rendering the A.D.H.A. animal resistant to insulin, lowers the deposition back to normal levels.

Several techniques for hormone assays have been used to investigate the abovementioned phenomena.

The technique described by Venning for the estimation of adrenal corticoids has been converted to a rapid, simple technique based on the reducing power of such substances and has been applied to the problem.

Results to date are not significant except in the case of one insulin-resistant diabetic where an extremely high excretion rate was found.

In view of the importance of adrenocorticotropic hormone as a diabetogenic agent, a technique for its estimation in blood has been devised and results to date suggest that it may be useful for research and, possibly, clinical use.

In view of Houssay's results stressing the importance of the thyroid in diabetes mellitus, preliminary experiments have been commenced to develop a

technique for the assay of thyrotropic hormone, which may be applicable for research and clinical use.

At the request of the Clinical Research Unit a technique for the assay of desoxycorticosterone-like substances in urine, and possibly blood, has been attempted, and preliminary results suggest that it will be practicable.

Following on discussions with Professor F. M. Burnet (Professor of Experimental Medicine, University of Melbourne) concerning the work of his department on Cholera Bacillus Enzyme (R.D.E.), experiments have started to investigate its effect on carbohydrate metabolism and the action of pituitary hormones.

WORK DONE IN COLLABORATION WITH THE CLINICAL DEPARTMENTS OF ALFRED HOSPITAL.

Considerable work has been carried out by members of the Institute staff together with both the newly-formed Clinical Research Unit and members of the Honorary Medical Staff of the Hospital.

Blood Coagulation.

Dr. Fantl and Dr. John MacLean have continued their collaboration in the study of the disturbances of blood coagulation. Together with Dr. John F. Williams, Dr. Fantl has continued his studies on the blood changes produced by electroconvulsive therapy.

Cardiovascular Physiology.

Members of the Thoracic Surgical Unit have been active during the year studying the physiological effects of operations for congenital heart disease, and the Institute's physiological equipment has been made available for this purpose. Surgeons of the unit have assisted Dr. Fantl in the preparation of his experimental animals.

Sodium estimation in body fluids.

Very close co-operation exists between the Staff of the Institute and that of the Clinical Research Unit. Dr. Fantl elaborated for their use a simple technique for the estimation of sodium in body fluids and subsequently a method of recovering uranium salts used in that assay.

Hormone Assay in Cardiac Failure.

Hormone assays done by Dr. Bornstein and his team have been of considerable value to the Clinical Research Unit in its investigations of cardiac failure.

The Value of Sodium Gentisate in the Treatment of Rheumatism.

It has been known that salicylates are converted in the body into several derivatives. A product of oxidation, Gentisic acid (dihydroxy benzoic acid), appears of special interest. It has been shown by K. Meyer ("Science," Vol. 108, p. 281, 1948) to inhibit the spreading effect of hyaluronidase and was suggested for the treatment of rheumatism. At the suggestion of Dr. Ian McLean, gentisic acid was prepared for a clinical trial in a patient who developed an intolerance towards salicylates. He reports prompt clinical improvement following the administration of sodium gentisate without any side reactions.

THE THOMAS BAKER, ALICE BAKER AND ELEANOR SHAW MEDICAL RESEARCH INSTITUTE.

Report of the Trustees covering the First Quarter-Century of the Institute's Work.

The Thomas Baker, Alice Baker and Eleanor Shaw Medical Research Institute was founded a quarter of a century ago and it is fitting at this stage to review the work of the Institute—its investigations, its many notable achievements, and its place in the ever-widening field of medical research. Accordingly, the Trustees take pleasure and not a little pride in setting out the course of events which has marked the development of the Institute.

Establishment of the Institute was made possible by the late Mr. Thomas Baker, Chairman of Directors of the Kodak organisation and a member of the Board of Management of the Alfred Hospital; his wife, Mrs. Alice Baker; and the latter's sister, Miss Eleanor Show, who at first jointly accepted liability for the maintenance of the Research Department for five years, but later made provision for continued support and maintenance.

Under the terms of the Deed of Settlement executed in 1926 between the Settlors and the Board of Management, Trustees were appointed to conduct the affairs of the new Baker Medical Research Institute. Mr. Baker was the first Chairman of Trustees and the Board of Management was represented by its President, Mr. H. M. Collins. Dr. J. F. Mackeddie was also appointed a Trustee.

The Baker Medical Research Institute developed directly from the laboratory services of the Alfred Hospital and was established to provide an efficient routine hospital laboratory service and facilities for medical research.

From the inception the workers in the Institute developed and maintained efficient laboratories to assist the Honorary Medical Staff in their treatment of the sick. These laboratories covered the fields of pathology, bacteriology, biochemistry and electrocardiography. In the course of time, however, it was found to be more satisfactory for these routine services to be placed under the direct control of the Hospital staff and gradually they have been handed over as well-developed units. This aspect of the Institute's activities illustrates an important phase of medical research—namely, the development of methods of investigating disease and their application to the treatment of individual patients. When that has been done, use of these methods becomes a matter of routine and should be handed over, as has been done, to the medical staff requiring such services.

It was the late Mr. Thomas Baker's wish that workers in the Institute which was to bear his name should direct their efforts to the improvement of the health of the community, and it is interesting to trace the development of work which originated in the Institute's laboratories; progressed through clinical application in wards of the Hospital, and finally became available for use of the medical profession generally.

The first Director of the Institute was Dr. W. J. Penfold, formerly of the Lister Institute, London, and at the time of his appointment, Director of the Commonwealth Serum Laboratories. Upon his appointment to the Institute there commenced for Dr. Penfold a period of intensive activity in medical research

of a very varied kind, mainly in collaboration with various members of his staff and of the clinical staff of the Hospital.

Of the many subjects to which Dr. Penfold devoted attention during his directorship of the Baker Institute, several deserve more than passing notice. His first task was to greatly improve the efficiency of the routine laboratories for bacteriology and biochemistry of the Alfred Hospital. While Dr. Penfold himself speedily ensured this for the bacteriological section, a similar service in the biochemical section was effected by the work of Dr. A. B. Corkill, who was the senior member of the Institute staff.

In 1934, on behalf of the Melbourne and Metropolitan Board of Works, Dr. Penfold undertook (in collaboration with his son, Dr. H. B. Penfold, and Miss Mary Phillips) an extensive research on the subject of tapeworm infestation in the population of Victoria, and the possible risk of infection from the consumption of beef grown on the Werribee sewage farm. These investigations not only established the fact that the alleged risk from the consumption of beef raised on the Werribee farm was negligible, but also produced some significant facts regarding the life history of the parasite and the development of natural immunity in animals infected by it.

Under Dr. Penfold the Institute rendered the Hospital service in biochemistry, bacteriology, serology and pathology, and research work was carried out within these sections. With the expansion of each of these fields, however, it became necessary to readjust the activities of the Institute, and the Pathology Department, under the direction of Dr. R. A. Willis, was transferred to the new Alfred Hospital building during 1938. A year later the routine bacteriological service was transferred to Dr. Willis' new department, and recently the routine biochemistry and electrocardiography services were similarly transferred.

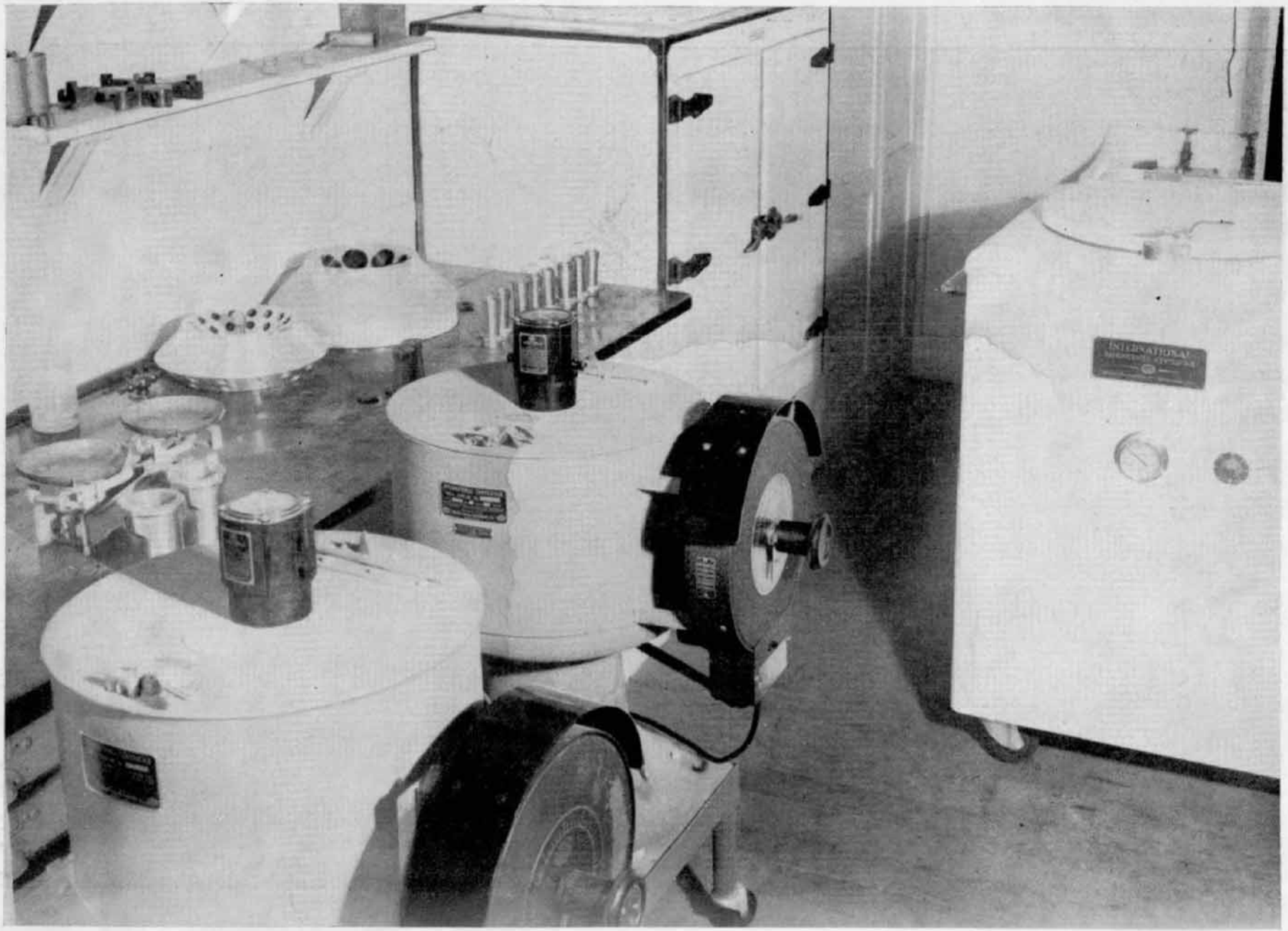
Much basic research into medical problems has been carried out in the quarter century of the Institute's existence. The field in which this has been done has varied from time to time acocrding to the qualifications and training of the workers. Thus, while Dr. W. J. Penfold (the first director) directed the work in pathology and bacteriology and, to a lesser extent in physiology, his successor, Dr. A. B. Corkill, followed the fields of physiology and biochemistry.

Two of many successful pieces of research work done by the Institute Staff were the researches into the biochemistry of diabetes mellitus and the development of the drug E.D.C., widely used in Melbourne in the treatment of coronary occlusion and of blood clots in veins. This drug is considered to be safer to use than Dicoumarol, which is in general use overseas.

The Institute Staff developed and continually increased the biochemical service for the Hospital, using the majority of tests essential for diagnostic purposes. In addition to accepted methods Dr. Fantl introduced several techniques, e.g., the method for estimating sulphanilamide in body fluids, the estimation of male sex hormones for the diagnosis of adrenal cortical tumours, estimation of alkaline phosphatases for the diagnosis of bone diseases, acid phosphatase for the diagnosis of carcinoma of the prostate, citric acid in bone disorders, the estimation of prothrombin levels; and procedures for the diagnosis of haemorrhagic conditions were elaborated.

On numerous occasions other hospitals have made special requests for assistance and technicians for a number of hospitals have been trained in routine methods.

Baker Medical Research Institute Building.



A Bank of Centrifuges and Refrigerators in a Baker Medical Research Institute laboratory, used in investigation of blood coagulation problems. Much of this apparatus was provided by the National Health and Medical Research Council.

Another aspect of the work of a research institution is the training of workers and the dissemination of the facts its workers learn about disease. The Baker Institute sponsored the publication of three monographs which have become standard medical texts. They are "Practical Anaesthesia," "Spread of Tumours in the Human Body," and "Blood Culture."

As a result of the expressed wish of the late Mr. Baker, the Institute launched a campaign in 1929 with the purpose of reducing the mortality from diabetes mellitus in the State of Victoria. The plan of the campaign, which was conducted with the approval of the British Medical Association, and with the co-operation of the State Health Department, consisted in the provision of facilities for the better education of the diabetic patient and in stimulating the interest of the medical profession in the disease.

The Trustees recall with pride that two of its early members have become holders of Professorial Chairs. Dr. Rupert Willis became the Sir William Collins Professor of Pathology, Royal College of Surgeons, and Dr. A. H. Ennor was recently appointed Professor of Biochemistry at the Australian National University.

Published papers emanating from workers in Baker Institute over the past quarter century have been in such varied fields as pathology, biochemistry, general medicine, bacteriology, haematology, diabetes mellitus, general surgery, physiology, neurology and anaesthesia.

During the recent war years members of the staff were actively engaged in work with the Chemical Defence Board of the Munitions Supply Laboratory, thus indicating another aspect of the community service given by the Institute. Dr. Fantl assisted in the production of essential drugs and he developed processes for the manufacture of acetyl sulphonamide, para-amino benzoic acid and local anaesthetics derived from it. Anti-histamine drugs required for work on phosgene poisoning were also prepared for the Chemical Warfare Section.

At the present time the basic research work in the Institute is following two main lines: an investigation of the chemistry of blood coagulation and studies of the relationship of ductless glands and carbohydrate metabolism. In addition laboratory facilities and technical assistance and apparatus are made available to Honoraries of Alfred Hospital in connection with various problems from time to time.

The following brief resume will demonstrate the practical application of some of the work with which the Baker Institute has been associated over the last quarter century:—

Nervous System.—A study of the nervous control of the urinary bladder and colon resulted in considerable advances in the treatment of diseases of these organs by surgeons of the Hospital.

The pathology of cerebral tumours was studied and as a result an outstanding advance was made in the diagnosis and operative treatment of such conditions.

Diabetes Mellitus.—Studies of sugar metabolism and the action of insulin and various other hormones enabled the instruction of the medical profession in the use of insulin in the treatment of diabetes.

Vitamin K.—A vitamin K substance suitable for use by external application was prepared and is now used in the treatment of obstructive jaundice and late pregnancy.

Blood Coagulation.—The development of E.D.C. as an anti-coagulant, and the introduction of methods for estimating the clotting power of blood enabled control of the use of anti-coagulants in the treatment of coronary thrombosis.

Surgery of Heart and Lung.—Physiological studies have assisted thoracic surgery in both partial and total removal of a lung. Surgery of congenital heart disease has also been greatly assisted by blood gas analyses carried out in the Institute.

Allergy.—Workers in the Institute conducted research into pollens and other agents causing asthma in Melbourne, and the physiological basis for asthma was also studied.

This work played an important part in the establishment of the Asthma Clinic in the Alfred Hospital under the direction of Dr. Charles Sutherland.

Sulphonamide Drugs.—Methods of estimating the concentration of sulphanilamide in body fluids have been developed to give a rational basis for the treatment of patients with "Sulpha" drugs.

A clinical research unit has recently been established in the Hospital and it is now possible to envisage a long-term research plan co-ordinating several separate research projects within the Hospital. The core of this plan is the development of a cardiovascular research centre, which will be able to study the problems involved in the investigation and treatment of all types of diseases of the heart and blood vessels. Such problems as the surgery necessary to treat "blue babies," the treatment of congestive cardiac failure, the treatment of coronary occlusion and the treatment of thrombosis of the arteries of the limbs, to mention but a few, will now be studied by a large group of workers. The Baker Institute's present contribution to this scheme is work on blood coagulation, hormone assay and physiological studies on the circulation and blood vessels. A necessary link in the whole plan is the establishment of a pharmacology laboratory in the Baker Institute. A suitable man has been found to take charge of this work and he will take up his duties late in 1950. This new group will study the mode of action of various drugs on the heart and blood vessels. Although many of these drugs, such as digitalis, have been in use for a long time there are many gaps in our knowledge of their action. The results of this work must prove of benefit to all persons suffering from any ailment of the heart or blood vessels.

THE PLACE AND VALUE OF THE INSTITUTE IN THE COMMONWEALTH.

In the foregoing pages sufficient has been written concerning both the valuable work accomplished, and avenues of endeavour contemplated in the Institute's Research programme, to warrant the premise that in the Baker Research Institute there exists a potential in the realm of Medical Science of the utmost value to Australia.

Dav after day reports of scientific investigation the whole world round emphasise the fact that the expansive field of study of human physical wellbeing has been, more or less, merely skirted. The great ocean of knowledge of the body in health and sickness still awaits the brave adventurer in Research, the call is still to the genius and his willing co-operator.

In a world in which the older countries particularly are harassed by the upset and despoliation of World War II and in which ancient and traditional landmarks of scientific pursuits have been at least temporarily obscured, it follows, as an almost natural sequence, that a community such as our own should provide an active and profitable field for research.

The value of such an organisation as the Baker Medical Research Institute can therefore scarcely be over-estimated. In a country, the geographical boundaries of which encompass almost the scope of the sub-frigid, temperate, sub-tropical and tropical, the field of exploration in the interests of human physical well-being is almost illimitable.

What this should mean to Australia should require no elaboration of argument, and doubtless, as the work of the Baker Research Institute becomes more widely and deservedly known and recognised, full advantage will be taken of its potential value to the Commonwealth.

THE INSTITUTE AS AN IMPORTANT MEDIUM FOR BENEFACTIONS.

Melbourne has a creditable record for charitable and philanthropic generosity and a long list of consistently and generously supported movements all attest the eager willingness of the public to assist worthy and approved causes which seek to alleviate human suffering and to solve the ever-recurring question "Why Pain?"

With this most satisfactory reflection upon the attitude of the community, it is surely both justifiable and timely to suggest that the Baker Research Institute constitutes an almost unrivalled object for the receipt of gifts and benefactions.

It should be accepted as axiomatic that the reseach work of the Institute must be related to the financial resources made available to its Director and staff. Therefore the Trustees feel that what is needed to ensure the development of this essential community service to a degree in keeping with the growth of population and increased requirements for medical services is an adequately informed public mind with regard to the work accomplished and in contemplation, and an income in keeping with these added responsibilities.

THE THOMAS BAKER, ALICE BAKER AND ELEANOR SHAW MEDICAL RESEARCH INSTITUTE

Revenue Account for the Year Ended 31st December, 1949.

EXPENDITURE.			INCOME.		
Salaries and Wages		£9,924 12 10	Donations—		
Drugs		157 2 9	Thomas Baker (Kodak), Alice Baker and Eleanor Shaw Benefactions		£7,200 0 0
Instruments and Glassware		322 3 2	Government Grants—		
Special Maintenance		659 19 4	National Health and Medical Research Council		3,045 0 0
Repairs and Renewals		700 3 2	Interest from Investments—		
Miscellaneous and Administration—			Thomas Baker (Kodak), Alice Baker and Eleanor Shaw Benefactions—		
Fuel and Lighting	£165 8 4		Australian Commonwealth Inscribed Stock	£552 10 0	
Insurance	170 6 3		Endowment Investments—		
Library Maintenance	293 3 11		Australian Commonwealth Inscribed Stock	162 10 0	
Printing, Stationery	69 13 11		Grain Elevators Board Inscribed Stock	93 15 0	
Travelling Expenses	18 13 6		Australian Consolidated Treasury Bonds	16 5 0	
Sundries	327 10 11				825 0 0
		1,044 16 10	Proceeds from Sale of—		
			Monographs	11 16 8	
			Sundries	19 10 9	
					31 7 5
			Biochemistry Fees		152 10 2
			Balance—Deficiency for the Year		1,555 0 6
		£12,808 18 1			£12,808 18 1

THE THOMAS BAKER, ALICE BAKER AND ELEANOR SHAW MEDICAL RESEARCH INSTITUTE

Balance Sheet at 31st December, 1949.

LIABILITIES.			ASSETS.		
Commercial Bank of Australia Ltd.	£1,381 1 9		Sundry Debtors		£532 6 1
Endowment Fund	8,500 0 0		Investments—		
Capital Grants and Gifts—			Grain Elevators Board Inscribed Stock		
Balance: 31st December, 1948 £88 6 11			3¾% due 1/5/1952 £2,500 0 0		
Add: Grants made during the year 100 0 0			Australian Commonwealth Inscribed Stock		
188 6 11			3¼% due 15/10/1960 5,000 0 0		
Less: Disbursements during the year 31 14 4			3⅛% due 15/10/1963 500 0 0		
	156 12 7		Australian Commonwealth Treasury Bonds		
Revenue Account—			3¼% due 15/9/1961 500 0 0		
Recoup of Deficits for two years ended 31st December, 1947 and 1948, from the Thomas Baker (Kodak), Alice Baker and Eleanor Shaw Benefactions 2,929 0 0				8,500 0 0	
Less: Deficiencies—			Fixed Assets—		
Balance at 31/12/48 279 7 9			Furniture and Fittings	2,100 0 0	
For year ending 31st December, 1949 1,555 0 6					
1,834 8 3					
	1,094 11 9				
	£11,132 6 1			£11,132 6 1	

Note.—3¼% Commonwealth Government Inscribed Stock face value of £17,000 is inscribed in the names of the Trustees of the Thomas Baker (Kodak), Alice Baker and Eleanor Shaw Benefactions for the benefit of the Institution.

AUDITORS' REPORT TO THE TRUSTEES.

We have examined the above Balance Sheet with the books of the Institute and, having obtained all the information and explanations required by us, we are of opinion that the Balance Sheet shows a true and fair view of the state of the Institute's affairs at 31st December, 1949, according to the best of our information and the explanations given to us and as shown by the books of the Institute.

FLACK & FLACK,
Chartered Accountants (Australia),
Honorary Auditors.

Melbourne,
13th April, 1950.

PAPERS PUBLISHED DURING 1949.

P. Fantl and Betty A. Everard: "THE SIGNIFICANCE OF PROTHROMBIN ACCELERATOR IN THE THROMBIN FORMATION BY RUSSELL VIPER VENOM." Aust. J. Exp. Biol. & Med. Science, Vol. 27 (1949), p. 197.

Leonard B. Cox, P. Fantl and Mildred Fitzpatrick: "THE TREATMENT OF DISSEMINATED SCLEROSIS BY PROLONGED LOWERING OF THE BLOOD PROTHROMBIN LEVEL." Med. J. Aust., Vol. 1 (1949), p. 577.

P. Fantl and G. J. Lincoln: "THE ENZYMATIC DEHYDROGENATION OF FATTY ACIDS." Aust. J. Exp. Biol. & Med. Sci., Vol. 27 (1949), p. 403.

P. Fantl: "AN ASSAY OF PARA-AMINO SALICYLIC ACID." Royal Aust. Chem. Inst. Journal & Proceedings, Vol. 16 (1949), p. 248.

P. Fantl: "THE USE OF ANTICOAGULANTS." Med. J. Aust., Vol. 11 (1949), p. 667.

P. Fantl: "THE SIGNIFICANCE OF PROTHROMBIN ACCELERATOR IN BLOOD COAGULATION." Proc. Royal Aust. College of Physicians. Vol. 4. (1949).

J. Bornstein and J. F. Nelson: "OBSERVATIONS ON THE EFFECT OF HIGH FAT DIET IN ALLOXAN DIABETIC RATS." Med. J. Aust., Vol. 1 (1949), p. 121.

PAPERS ACCEPTED FOR PUBLICATION.

J. Bornstein: "A TECHNIQUE FOR THE ASSAY OF SMALL QUANTITIES OF INSULIN USING ALLOXAN DIABETIC, HYPOPHYSECTOMISED, ADRENALECTOMISED RATS." Aust. J. Exper. Biol. & Med. Science.

J. Bornstein: "NORMAL INSULIN CONCENTRATION IN MAN." Ibid.