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

and

Sixth Annual Report
of
ALFRED HOSPITAL
CLINICAL RESEARCH UNIT
and
RESEARCH FELLOWS

1954

ALFRED HOSPITAL, PRAHRAN,
VICTORIA, AUSTRALIA

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†Died, January, 1955.

ANNUAL REPORT OF THE DIRECTOR

During 1954 the research projects in the research centre have continued to be directed to the broad problems of cardiovascular diseases. Together with a number of studies on other subjects they illustrate the many facets of clinical research. The integration of effort of the staff of the Baker Institute, the Clinical Research Unit and of the Research Fellows is now firmly established and accepted.

It is pleasing to record that the number of workers and the scope of work continues to expand and that, despite some shortage of floor space and the inadequate number of our ward beds, the standard of the investigations carried out continues high. To overcome some of these problems further building extensions are in progress which will enable us to offer better facilities for experimental surgery and will provide a greatly increased space for the library which is rapidly filling. Also more adequate space for study and office work will be available for Research Fellows. These extensions, however, in no way mitigate the bed shortage which will only become aggravated by the increasing number of Fellows who wish to work in the clinical as opposed to the laboratory spheres. This bed shortage makes the research centre unbalanced in two ways. There is a smaller amount of direct clinical observation carried out than is desirable, and there is an undue emphasis on out-patient clinical work.

Details of the investigations carried out during the year are published in the scientific section of this report, but a brief summary is given here so that each may be seen in proper perspective against the background of the general plan of integration.

The cardiovascular system consists of three major components, the heart, the blood vessels and the fluid circulating through the vascular channels. Disorders of the circulation may arise from changes in any of these three components, and various problems relating to each component are being studied.

The efficiency with which the heart changes chemical into physical energy and the effect of adrenaline and noradrenaline in this system is being studied in the hope of elucidating some of the problems of cardiac muscle failure. Towards the same end recordings of the electrical, sound and mechanical activity of the heart are being made by vectorelectrocardiography, phonocardiography and ballistocardiography.

The blood vessels are of three main physical types; arteries, veins and capillaries. Altered behaviour of the arteries may produce conditions of "high" or "low" blood pressure, and both the mechanism of causation and methods of treatment of these conditions are being investigated. Obstruction of arteries in the limbs frequently leads to gangrene, and methods of determining the site of block have been established so that, in conjunction with the thoracic surgical unit, arterial grafts have been used to replace the blocked vessel in a few patients. A small study into methods of treatment of varicose veins has been instituted. Some bleeding conditions are due to failure of the capillaries to seal after rupture and the activity of blood platelets in this regard is under investigation.

Studies of the behaviour of the fluids of the circulation—blood and body fluid in general—continue as in the past to be major studies. Investigation of the clotting mechanism of blood has led to a study of bleeding conditions in general and in particular to a survey of haemophilia. The investigation of the general body fluids has led to the formulation of some general principles which govern the amount of fluid in the body and regulate its intake and output. Using these principles it has been possible to construct a mechanical analogue which qualitatively behaves in the manner seen in patients.

In addition to these studies of the cardiovascular system, investigations into the biological action of some of the anterior pituitary and adrenal hormones, and the physiology of the intestinal tract are being continued.

Facilities to enable members of the staff to visit other centres continue to be provided by the Trustees of the Institute, and the Board of Management of the Hospital. During the year a Fellow from the Postgraduate School of Medicine, London, has been a member of the staff and in the coming year another post-graduate worker comes to us from the University of St. Andrews, Dundee. It is also pleasing to record that one of our recent junior medical officers was awarded a grant to work at the University of California, San Francisco. This interchange of workers is proving most invigorating and I hope that it will continue in future years.

One of the most important tools in research work is a good library, and although we have two excellent libraries at the Hospital their value and usefulness has been enhanced by the formation of a Central Medical Library Co-ordination Committee in Melbourne. The activities of this body have brought us a considerable number of back volumes of journals which in many instances bring about a welcome completion of files.

The National Health and Medical Research Council and the Life Insurance Medical Research Fund of Australia and New Zealand have continued to support several research projects and have allocated grants for additional projects in 1955. The help of these bodies is gratefully acknowledged.

Many organisations have made gifts to the Institute Library during the year, and our thanks are expressed to them, and to various libraries that have loaned us journals, and particularly to the librarians, whose assistance is greatly valued.

As in previous years, much assistance has been given to us by members of the Honorary Medical Staff, by all Hospital departments, by various members of the University staff, by Dr. F. G. Morgan (C.S.L.), Dr. A. W. Turner (C.S.I.R.O.), and by various members of the staff of Kodak A/sia Pty. Ltd. The members of the Institute Advisory Panel have always been very ready to help, and I wish to thank all these persons for their assistance.

It is a pleasure for me to thank the Trustees of the Institute and the Board of Management of the Hospital for their continued generous support, and to thank members of the staff for their co-operation during the past year.

T. E. LOWE, Director.

31st December, 1954.

**LIST OF ORGANISATIONS WHO HAVE MADE GIFTS TO THE
LIBRARY DURING THE YEAR**

Alfred Hospital Library.
Commonwealth Department of Health.
Hallstrom Institute of Cardiology.
L'Institut Bunge.
Institute of Dental Research, Sydney.
Institute of Medical and Veterinary Science, Adelaide.
International Anesthesia Research Society.
Imperial Chemical Industries of Australia and New Zealand.
Kanematsu Institute.
Mayo Clinic.
Medical Research Council, London.
Middlesex Hospital Medical School.
National Health and Medical Research Council, Canberra.
Organisation for Scientific Research, Indonesia.
Queensland Institute of Medical Research.
Rockefeller Institute of Medical Research.
Statens Seruminstitut, Copenhagen.
South African Institute of Medical Research.
U.S. Army Medical Library.
Walter and Eliza Hall Institute.

REPORT OF SCIENTIFIC INVESTIGATIONS

BLOOD COAGULATION

THROMBIN FORMATION IN SHED BLOOD IN RELATION TO THROMBOPLASTIN AND PROTHROMBOPLASTINS:**

P. Fantl, A. G. Marr and H. Ward.

In continuing the studies on blood coagulation mechanisms experiments were undertaken to provide an understanding of the defect in the haemorrhagic diseases, due to a derangement of the blood thromboplastin complex, which are clinically grouped as haemophilia. When blood clots thrombin is formed, and the amount which is present in the clotting blood at any given moment depends on the balance between its formation and destruction. It was found that phenols delay the inactivation of thrombin by plasma antithrombin. With this device the relationship between thromboplastin activity and rate of formation and yield of thrombin was investigated. The experiments were carried out with blood samples from normal donors, and have given support to the assumption that at least two plasma precursors termed alpha- and beta-prothromboplastin, as well as calcium ions and thrombocytes, are required for adequate blood thromboplastin activity. Certain physico-chemical properties of the surface with which the precursors come in contact are also essential for this activation. In the absence of thrombocytes clotting can take place, but the amount of thromboplastin formed is only sufficient to convert a fraction of the prothrombin into thrombin. In cases of severe thrombocytopenia, sufficient thromboplastin is formed from the plasma factors, but thrombin formation is delayed to an extent which makes adequate haemostasis impossible. The experiments have shown that thrombocytes do not contain active thromboplastin because adequate numbers of them in the absence of either alpha- or beta-prothromboplastin did not produce any thrombin in diluted blood. Blood thromboplastin activates prothrombin in a different way to tissue thromboplastin, as is indicated by the different rates of thrombin formation in the two instances. This is due to the fact that blood thromboplastin has to be formed from precursors, a complex reaction which requires time, whereas tissue thromboplastin is preformed, and can react immediately with the prothrombin complex. The role of the thrombocytes in the process of thromboplastin formation seems to be catalytic and due to a specific, relatively heat stable, property of the thrombocytes. Regarding the capacity of the thromboplastin precursors in plasma to convert prothrombin, it was found that normal blood has at least a fourfold excess of potential thromboplastin. From this it is concluded that a bleeding tendency can occur with plasma levels below 25% of each of the plasma thromboplastin precursors. Quantitative determination of the blood thromboplastin components therefore should give an indication of haemostatic efficiency. It was shown that under the experimental conditions used, maximum thrombin formation in normal diluted blood, in the presence of pyrocatechol as a thrombin stabiliser, occurred between 14-19 minutes with a yield of 120-260 units of thrombin per ml of oxalated blood. A prolongation of the reaction time and a diminution of thrombin yield is considered as pathological.

In this report of Scientific Investigations, those projects marked () were supported wholly or in part by grants from the National Health and Medical Research Council and those marked (*) were supported by grants from the Life Insurance Medical Research Fund.

ALPHA- AND BETA-PROTHROMBOPLASTIN**

P. Fantl and R. J. Sawers.

In examining blood specimens from patients with the "haemophilic" syndrome, in addition to the more common tests, the coagulation properties were determined by the rate of formation and amount of thrombin formed in diluted blood in the presence of pyrocatechol, which acts as a thrombin stabiliser. These patients are found to fall into two categories with regard to their clotting defect.

The first have a deficiency in alpha-prothromboplastin (anti-haemophilic factor). This blood deficiency could be corrected by the addition of barium sulphate treated plasma (Ba-plasma) which is a source of alpha-prothromboplastin. It was noted in this group of 65 patients that alpha-prothromboplastin deficiencies can vary in intensity from complete absence to minor deficiencies.

In the second group in contrast to the first, a bleeding tendency due to beta-prothromboplastin deficiency was observed. This cannot be corrected by Ba-plasma but can be corrected by stored plasma, and by serum as well as by whole blood and fresh plasma. Ten patients have been observed in whom the beta-factor was completely absent.

Reported experiments have shown that the rate of thrombin formation can be determined by the addition of normal blood or blood derivatives to patients' blood. From the volume of addition required to correct a deficiency *in vitro* the degree of the defect is determined. Repeated examinations of patients' blood and of blood of their male affected relatives indicated the same and a constant degree of deficiency in a pedigree.

From the *in vitro* experiments it was possible to establish both the diagnosis and the degree of the deficiency. However when a plasma or serum volume corresponding to that which corrected the defect *in vitro* was introduced into the circulation, activity of either alpha- or beta-prothromboplastin in blood specimens taken between ten minutes and 2½ hours after the transfusion were far lower than that calculated from a simple dilution of the particular factor in the assumed blood volume. As plasma prothromboplastins are very probably complex proteins, it might be possible that they are metabolised at greater speed than the other blood proteins, or that alpha- or beta-prothromboplastin after intravenous infusion are diluted into a space far greater than the blood volume. The practical outcome of these experiments is that it is not advisable to rely on a single plasma transfusion to maintain haemostasis in a patient in the post-operative period, but to apply a continuous drip infusion of fresh plasma in the case of alpha-prothromboplastin deficiency, or fresh plasma or stored plasma, or serum in a case of beta-prothromboplastin deficiency. With this procedure it was possible to maintain haemostasis in a patient suffering from a severe beta-deficiency.

DETECTION OF HAEMOPHILIA IN FEMALES**

P. Fantl.

The previously reported investigations were mainly carried out on the blood of male patients. However an opportunity allowed the examination of a family with alpha-prothromboplastin deficiency in which there was a female haemophilic. These investigations were carried out with the assistance of Dr. J. Margolis in the Pathology Department of the Royal Alexandra Hospital for Children, Camperdown, Sydney. It was found that a congenital haemorrhagic

tendency of moderate severity in the mother was due to a partial alpha-prothromboplastin deficiency (haemophilia) in her blood.

This woman has two children; a girl, who shows no bleeding tendency at all, and a son who is suffering from the same type of deficiency as his mother, but in contrast to her his blood is completely devoid of alpha-prothromboplastin. These findings indicate that the mother is not only a carrier of the disease but is herself a haemophilic, although clinically of a mild nature. This is the first instance of an established heterozygous state of alpha-prothromboplastin deficiency in a female.

HAEMOPHILIA

R. J. Sawers.

The investigation of some aspects of haemophilia which was started in 1952 has continued and a majority of the available material has been studied. For the purpose of this study haemophilia is regarded as a syndrome and the disease entities are referred to as alpha-haemophilia and beta-haemophilia, and correspond to plasma deficiencies of alpha-prothromboplastin (antihemophilic globulin) and beta-prothromboplastin (Christmas Factor).

Up to the present in Victoria 60 patients have been found to suffer from alpha-haemophilia and nine from beta-haemophilia. Of the patients with alpha-haemophilia, 25 have a complete absence of alpha-prothromboplastin and 35 have amounts of this factor varying from a trace to approximately 20% of normal. The nine patients with beta-haemophilia have complete deficiency. A general correlation between the clinical severity of the disease and the quantitative assessment of the deficiency has been noted. It is apparent that the clinical severity is an expression of undetermined mechanisms in addition to the plasma abnormality. It appears probable that one of these is dependent on the behaviour of small blood vessels.

Study of the genetic aspects has indicated that the defect is inherited without alteration in severity. The high incidence of mutation to the more severe form of alpha-haemophilia accounts for the large number of patients without a known family history of the disease. Population statistics and calculations based on collected data indicate that new genetic data should result from the study.

Therapeutic management of these patients has proceeded under laboratory control and it is apparent that with our available means only very temporary correction of a plasma deficiency is possible. In spite of this, the control of bleeding in both minor and major surgical procedures has been gratifying. Dental extraction offers no hazard with the present methods used.

As our social study of this disease indicated the need in the community for the parents of affected children to be able to meet, for mutual discussions and elementary instruction, the recent formation of such a lay society has received personal support and assistance. It has been apparent that many parents are overprotective, and have little regard for suitable education and occupations for their children. The problem of women belonging to haemophilic families is being studied in conjunction with the genetic data in an attempt to determine a basis for suitable advice.

Patients with bleeding diseases other than haemophilia are being studied to obtain a greater understanding of the many mechanisms concerned in haemostasis.

CONTROL OF BODY FLUID VOLUME**

GENERAL STUDY

T. E. Lowe and J. Uppill.

In a number of papers from this centre over the past five years certain salient observations on the control of body fluid volume in man have been recorded. It has been suggested on the basis of these observations that the total fluids of the body represent an open system, into which a continuous inflow and outflow occurs, and that the amount of fluid stored in the body at any instant influences both the intake and output of fluid. Further, this hypothetical system must be complex and contain at least two components. The observations made indicate that unless a circulation is incorporated in this hypothetical system, some of the clinical observations cannot be explained.

From clinical observations an hypothesis concerning the mechanisms of control has been proposed. This hypothesis postulates a complex open system with a storage of fluid within the body through which passes a continuous flow of fluid. The fluid is stored in various compartments separated by semipermeable membranes. The inflow sites (alimentary canal and tissue cells), the various parts of the body and the outflow site (the kidney) are linked by the circulatory system. The body fluid is an electrolyte solution, both the solvent and solutes of which are to some extent independently controlled. The total volume and the electrolyte concentration of body fluid is normally kept within a narrow range by regulation of inflow and outflow of water and electrolytes. This regulation is actuated by changes in volume of some part of the body fluid compartments and by changes in the osmotic pressure of some portion of the body fluid.

As this postulated mechanism, whilst simple in concept, is too complex to allow of easy mathematical analysis, a mechanical model has been constructed to study its implications.

This model has been developed from these previously described, and is a complex hydraulic open storage system, with a circulation and inflow and outflow mechanism and controls suggested by physiological studies. The outflow mechanism contains valves which represent glomerular filtration of solvent and solute and the effluent then passes through feedback valves which represent tubular reabsorption of glomerular filtrate. The inflow of water is controlled both by volume and the "osmotic pressure" of the system. The feedback is controlled by the "osmotic pressure." However it was necessary to make assumptions concerning some controls for which there is no physiological evidence available as to their nature. In particular the control of electrolyte inflow and the flow of water and electrolytes through the glomerular valves is unknown. After experimenting with various linkages it was found that the best correlation with clinical findings was obtained when the inflow of electrolytes was determined by the "osmotic pressure" of the system and the flow through the glomerular valves by the fluid volume. Possibly these are the sites of the afferent parts of these mechanisms in man.

In studying the behaviour of the model no attempt to get quantitative results has been made because we are ignorant of the quantitative relationships of the various components. Thus no evidence is available to indicate the relationships between volume of fluid and osmotic pressure on the one hand and the inflow and outflow of water or electrolyte on the other. The importance of these

relationships is apparent, for any change in them, by disease for example, will alter the equilibrium point of the system and could lead to oedema or dehydration, to increase or decrease of osmotic pressure.

With this model it has been possible to reproduce qualitatively the water and electrolyte changes seen in the clinical states of water diuresis and deprivation, salt ingestion and deprivation, diabetes insipidus and the exhibition of antidiuretic hormone, Addison's disease and the exhibition of adrenal cortical hormone, cardiac and nephritic oedema and the action of mercurial diuretics.

The qualitative agreement between the behaviour of the model and the observed behaviour of fluid storage and control in man, both normal and in the presence of disease, is so good that it suggests that the basic principles incorporated in the model are a close approximation to those occurring in man.

It is of interest to note that the hypothetical system provides a basis for synthesis of the rival hypotheses of "forward" and "backward" cardiac failure, and shows a mechanism which includes the heart pump and circulation as an integral part of the fluid regulation. This provides a concept which overcomes the paradox noted by many writers that the heart could be fitted (only with difficulty) into the scheme of things in the production of oedema in cardiac failure.

DIURETIC RESPONSE TO A WATER LOAD IN OEDEMATOUS PATIENTS :

M. Hamilton.

One of the implications of the hypothesis proposed to account for the control of body fluid volume in man is that in oedematous patients there should be a reduced "turnover" of fluid in a given time. Further, as the ingestion of water by oedematous patients leads to an increased urine formation, it has often been assumed that these patients have a normal response to water loading. Prolonged observation of such patients has suggested that this might be so, in that they show the fluctuations in weight and water balance exhibited by normal individuals. However, the long term observations give no indication of the immediate response to an ingested water load. A series of observations was therefore made on both normal and oedematous subjects to determine the immediate response to such a water load.

In these observations water was withheld overnight and in the morning the subjects drank one litre of water in 15 minutes. In the nonoedematous subjects 60% of this water load was excreted within 3 hours. In 11 oedematous patients with cardiac failure the amount excreted in 3 hours ranged from 11 to 58% of the load. When five of these eleven patients were retested after they had recovered from oedema they all showed considerable improvement in the proportion of the load excreted in 3 hours, some in fact then gave normal responses. Similar results were obtained in two patients with nephrotic oedema.

These observations confirm the view that water ingestion increases urine output in oedematous states but they also demonstrate that the rate of water turnover is considerably reduced in the presence of oedema in cardiac failure and the nephrotic syndrome. A finding predicted by the hypothesis outlined.

EFFECT OF METHONIUM DRUGS ON FLUID BALANCE :

T. E. Lowe and J. R. E. Fraser.

In the course of treatment of patients with hypertensive disease it was noted that at times fluid retention occurred. From a study of 17 patients with severe hypertension in whom this phenomenon occurred it was concluded that under some circumstances methonium therapy can precipitate fluid retention. Although the mechanism of this phenomenon has not been demonstrated it is thought that a combination of rapid reduction in blood pressure and renal impairment is a predisposing factor.

ANIMAL STUDIES :

R. Fowler.

As the majority of the observations in this study of the control of body fluid volume had been obtained from oedematous patients, it was considered necessary to define the behaviour of normal individuals, man and animal, in this regard.

Longterm observations of fluid balance in normal subjects and rabbits indicate that the general overall oscillating behaviour of fluid balance is not peculiar to oedematous patients. Violent fluctuations in this balance are seen wherever the normal controlling mechanisms are disturbed.

The normal range and pattern of day to day fluctuations in fluid balance were determined from 303 observations on twelve patients in normal fluid balance and from 164 observations in six rabbits.

Having established the normal pattern and the differences between man and rabbit, the effects of overhydration, dehydration, mercurial diuretics, intravenous fluid loading and anaesthesia were studied in rabbits. These observations showed that any of these disturbances produced excessive fluctuations in body fluid volume which took several days to subside. The fact that the fluctuations following over-hydration and dehydration frequently overswing is presumptive evidence of an open system mechanism.

HYPERTENSIVE STATES

CLINICAL TRIAL OF HYPOTENSIVE DRUGS :

A. J. Barnett and M. Hamilton.

(a) Methonium Compounds:

The trial of methonium compounds in severe hypertension, particularly in the malignant phase, has been continued and the number of patients in the series has progressed to 65 (a number of whom, however, have died). Analysis of records made in 1953 indicated the value of this treatment over a period of six months to three years. An attempt is now being made to evaluate the effects of the treatment over a longer period, now that some patients have been treated for as long as four years.

A comparison of the effect of different types of methonium compounds and of the addition of other drugs is being made. Patients are given a particular treatment for a period of six months, and the type of treatment only altered at

these intervals unless the patient's clinical condition indicates that a change is imperative. Previous analysis of results showed that injection of "Vegolysin" was superior to oral treatment with pentamethonium bromide ("Lytensium") or hexamethonium bromide ("Vegolysin"). These drugs are no longer being used. Patients being treated with "Vegolysin" by injection have been put on to treatment with "Ansolysen" by injection. Patients well controlled by injection treatment have been changed to "Ansolysen" by mouth. In those in whom control by "Ansolysen" has been unsatisfactory because of inadequate reduction in blood pressure or severity of side effects, a new anti-hypertensive compound "Serpasil"† has been added to the treatment. The results from the modifications of treatment have not been analysed as yet, but our experience to date indicates that (1) "Ansolysen" by injection has much the same effect as "Vegolysin" by injection, although sometimes better control has been obtained by "Ansolysen," (2) oral "Ansolysen," although not as effective as "Ansolysen" by injection, is superior to oral "Vegolysin" and gives satisfactory control in about a third of the patients in whom it is tried and (3) in patients not controlled by "Ansolysen," the addition of "Serpasil" gives great benefit—causing more lowering of blood pressure and allowing reduction of the dose of "Ansolysen" to a level where side effects are no longer troublesome.

With the use of "Ansolysen," supplemented if necessary by "Serpasil," it is found that there are very few instances in which severe hypertension cannot be controlled. As a result of the experience gained, a plan for the treatment of patients with severe arterial hypertension, particularly with Grade IV eye signs, has been formulated.

Experience from this trial indicates that a new attitude should be adopted to arterial hypertension. Patients with significantly raised diastolic blood pressures, even if still in the benign phase, should be reviewed at intervals of about six months, so that if there is any indication that the hypertension is entering the accelerated phase, effective treatment involving the use of "Ansolysen" may be commenced.

(b) Serpasil:

Although hypertension in the malignant phase or with left ventricular failure warrants urgent treatment by the most effective remedy available, the indication for treatment in hypertension in the benign phase and without left heart failure is less definite. It is known that patients with such hypertension may live for many years without severe incapacity and it is doubtful whether it is justifiable to use methonium compounds in them because the unpleasant side effects of the treatment may outweigh the possible benefit. However "benign" hypertension is by no means innocuous and if an effective treatment devoid of side effects can be found it should be used.

For this reason a trial has been devised of the effect of "Serpasil" and a combination of "Serpasil" and "Apresoline." After a preliminary observation period to establish the fact of persistent diastolic hypertension, patients in the trial are treated in turn by each of these regimes and by a placebo of inactive substance, the order of the treatments being determined by random selection. The trial is only half completed but certain facts have become apparent. Several of the patients with initially high diastolic blood pressure proved unsuitable because the blood pressure returned to normal during the preliminary observation period. All the patients treated with "Serpasil" alone or combined with

†"Serpasil" is being supplied by Ciba Ltd.

"Apresoline" experienced a fall in diastolic blood pressure. However a similar fall was noted in a high proportion of patients given a placebo of inactive substance. When treatment, either with an active substance or with placebo was discontinued for four weeks prior to commencing the next treatment, the blood pressure often failed to rise to its original level and so it was not possible to compare different treatments given in sequence owing to the different base lines. The main conclusions to date are that both the observation period and exhibition of a placebo have a powerful anti-hypertensive effect, and that because of this it is difficult to conduct an investigation into the effect of a particular drug or to compare the effects of different drugs in one patient.

RENAL HYPERTENSION :

D. G. Duffy.

Following on the previous investigation of symptoms occurring in patients with hypertensive states, various hypotensive agents were used alone or in combination to assess their value in producing symptomatic relief on the one hand and lowering of blood pressure on the other.

At the same time, cases were grouped according to whether they had evidence of past or present urinary tract diseases. Of 157 cases, 62 gave a past history of urinary tract diseases or had current evidence of it. This was a higher proportion than was anticipated. However, the greater numbers of female patients, 37 of whom had had pyelonephritis compared with only seven males, accounted for this preponderance.

It became apparent during treatment with various hypotensive agents that the most effective relief of symptoms and control of blood pressure could be established by means of "serpasil" and "ansolysen" in combination given by the oral route. No adverse effect was observed when "ansolysen" was used in cases showing marked impairment of renal function.

ORTHOSTATIC HYPOTENSION

A. J. Barnett, M. Hamilton and H. B. Kay.

An intensive study has been made of three patients with idiopathic severe orthostatic hypotension, particularly with a view to discovering the mechanism of the lesion. In two patients there was evidence for a widespread loss of sympathetic nervous activity involving not only vasomotor but also other sympathetic functions. Evidence was produced that the lesion was in efferent pathways.

In the third patient, there was deficiency in maintaining blood pressure in the face of changes in posture and other disturbing factors and also deficiency in the pressor reflexes. However, sympathetic activities not concerned with maintenance or changes in blood pressure were intact. It was shown that vasomotor impulses were passing normally along peripheral nerves. Because there was some other evidence of central nervous dysfunction, it was probable that the lesion causing the postural hypotension was centrally situated in the nervous system—involving the vasomotor centre.

In the past there has been much discussion as to whether the lesion in severe postural hypotension with sympathetic nervous insufficiency is central or peripheral. Study of our patients has indicated that there are two distinct types—one in which the lesion is central, the other in which it is peripheral.

THE PHARMACOLOGY OF ADRENALINE AND NORADRENALINE**

G. A. Bentley.

ASSAY OF NORADRENALINE IN URINE :

During the past year, we have assayed a number of urine samples from suspected cases of phaeochromocytoma. These have come from five States, as well as from Victoria. In four cases a diagnosis of phaeochromocytoma has been made as a result of the assay, and these have been confirmed by operation. After removal of the tumour, the urinary output of noradrenaline returned to normal levels in three cases. In one case the output of noradrenaline remained high and secondary growths were subsequently demonstrated.

MODE OF ACTION OF ADRENALINE :

Almost nothing is known of the biochemical changes which cause the inhibitory effects of adrenaline and noradrenaline. This problem has been investigated on the assumption that a drug could act on a smooth muscle cell only at three points, i.e. (a) at the cell membrane (b) on the contractible mechanism, or (c) on the energy-providing systems. These three possibilities were investigated as follows:

(a) Cell Membrane:

If adrenaline produced its effect by altering the membrane permeability to one or other ions then alteration of the ionic constituents of the perfusing fluid might be expected to modify the response of the organ to adrenaline. Therefore, isolated rabbit intestine was perfused with Tyrode solution modified in various ways. It was found that none of the modifications had any qualitative or quantitative effect on the gut's response to adrenaline or noradrenaline. Hence it seems likely that these hormones do not produce their inhibitory effect through any action on cell membrane permeability.

(b) Contractile Mechanism:

The investigation of the possible action of adrenaline on the contractible mechanism was approached as follows: since there is much evidence to connect the hydrolysis of A.T.P. by actomyosin with the contraction-relaxation cycle in muscle, it seemed important to test whether adrenaline had any effect on the rate at which tissue extracts hydrolysed A.T.P. Crude buffered extracts of heart and intestine were used, as well as partially purified actomyosin from both sources, and the enzyme was activated by calcium.

It was found that neither adrenaline nor noradrenaline up to concentrations of $1:10^4$ had any effect on the rate of hydrolysis of A.T.P. Further, in the absence of calcium, neither adrenaline nor noradrenaline was able to activate the enzyme.

Hence, these experiments do not provide any evidence that adrenaline or noradrenaline act directly on the contractible mechanism.

(c) Energy Producing Systems:

It was also investigated whether adrenaline produced its inhibitory effects via the energy supplies of the muscle, either via the carbohydrate sources, or via the high-energy phosphate compounds. To investigate a possible action on carbohydrate metabolism, the following experiments were performed. After recording the responses to adrenaline and noradrenaline of an isolated rabbit intestine in Tyrode solution containing glucose, the gut was allowed to exhaust itself in a medium without any organic energy supply. Various carbohydrate intermediates were then added, in the hope that they would restore the beat of the gut. If they did so, the response to adrenalin and noradrenaline was then tested. It was found that various members of the tricarboxylic acid cycle (i.e. citrate, succinate etc.) would not support the beat, but that lactate and acetate would do so. Moreover, it was found that the response to adrenaline and noradrenaline of a gut supported solely by lactate or acetate, was quantitatively and qualitatively identical with the response in the presence of glucose.

Investigations into possible actions of adrenaline and noradrenaline on the phosphate metabolism were grouped under two headings, i.e. (i) the effect of adrenaline on the inorganic phosphate uptake by isolated intestine, and (ii) the effect on the gut's response to adrenaline of drugs known to influence the production of high energy phosphate compounds. It was found that adrenaline and noradrenaline, when added to a piece of perfused rabbit gut, caused a rapid uptake of inorganic phosphate from the Tyrode solution. However, this does not appear to be fundamentally related to the mode of action of adrenaline and noradrenaline, since calcium also causes a relaxation of the perfused intestine without having any influence on the phosphate uptake.

Since phlorhidzin and 2,4, dinitro-phenol (D.N.P.) have been shown to exert many of their pharmacological actions by virtue of their ability to reduce the formation of high energy phosphate compounds, it seemed important to test whether these compounds could alter the perfused gut's response to adrenaline or noradrenaline. It was found that even high concentrations of phlorhidzin and D.N.P. had no effect on the activity of the isolated rabbit gut, nor on its response to adrenaline or noradrenaline. It is planned to assay pieces of isolated gut, both normal, and after treatment with phlorhidzin, D.N.P., adrenaline and noradrenaline, for their content of high energy phosphate compounds.

(d) The Interaction of Thyroid Hormone and Adrenaline:

There is much evidence in the literature that conditions of high thyroid activity give rise to an increased sensitivity to the excitant actions of adrenaline. Hence it seemed important to test whether the presence of thyroxine would potentiate the inhibitory actions of adrenaline, and it was also attempted to determine whether gut taken from hypothyroid animals responds to adrenaline differently from normal gut.

It was found that even high concentrations of thyroxine had no influence on the isolated gut's response to either adrenaline or noradrenaline.

Other experiments using tissue from hypothyroid animals are in progress. It has been found difficult to suppress significantly the basal metabolic rate of rabbits by oral administration of propylthiouracil. Therefore, it is planned to remove the thyroids surgically from a group of rabbits, and to compare their sensitivity to adrenaline and noradrenaline with that of normal rabbits.

DISEASES OF THE PERIPHERAL BLOOD VESSELS

LIMB VESSELS :

A. J. Barnett.

Occlusive Arterial Disease of the Hands:

The case notes of thirty successive patients who presented with ischaemia of the fingers have been analysed. In most cases clinical tests had been performed to discover whether the ischaemia was due to functional constriction of vessels or due to structural block and in many cases the heat elimination was measured both resting and following release of sympathetic tone by reflex heating. In some instances further information of the state of the vessels of the hands was obtained by arteriography and, in one, by postmortem study.

In only twelve patients was the ischaemia due to Raynaud's disease, as this is generally understood to imply a functional disorder of the vessels. In the others there was evidence of some other underlying disease or of structural arterial occlusion. Unexpectedly, scleroderma was present in five of the patients.

Lumbar Sympathectomy for Occlusive Arterial Disease of the Legs:

The results of lumbar sympathectomy on the ischaemic features in thirty such patients subjected to this operation between five years and six months ago have been assessed, in most cases with personal interviews and clinical examination. Broadly, this study showed that sympathectomy is very valuable in relieving features of distal ischaemia (nutritional changes, coldness, rest pain) but of little, if any, value in relieving intermittent claudication.

Arterial Grafting:

Vascular grafting for occlusive arterial disease of legs has now been performed in ten of our patients by members of the thoracic-surgical unit and the results followed for up to twelve months. The immediate results were uniformly good. One patient has died (seven months after operation) and in two the grafts have become occluded. The other seven are still deriving benefit six to twelve months after operation. It is considered that arterial grafting is a worth-while method of treatment in a small proportion of patients with occlusive arterial disease of the lower limbs. Careful selection of cases is necessary.

Intermittent Claudication:

H. C. Newman.

Intermittent claudication has been studied in some detail during the year, attention having been paid to the clinical features, the appearances obtained with arteriography and particularly the natural history, of which a better understanding has been obtained. The progress of the disease has been followed by means of a step-test, it being considered that objective assessment of the condition is essential. Whereas it has been known for a long time that claudication of recent onset may undergo spontaneous remission or even cure as the collateral circulation develops and by-passes the thrombosed artery, it has not been sufficiently appreciated that even long-standing cases may improve rapidly without any treatment. It has been suggested that fibrosis of the affected muscles occurs, thus leading to diminished oxygen requirement; however, improvements have been observed which were only temporary and may therefore be due to changes in function rather than structure.

The study on the effect of heparin as a therapeutic agent in this disease has been concluded and it has been shown that heparin is unlikely to have any

effect on intermittent claudication other than that of a placebo. In the course of the study with this drug and with intra-arterial injections of vaso-dilators, it has become apparent that the claudication responds to a placebo in about one case in three. Several patients have benefitted considerably from a course of injections of placebo, both subjectively and objectively. Clearly, any clinical trial of a new form of treatment in intermittent claudication would be invalid unless it recognised the importance of prolonged observation and of a placebo-treated control group.

Studies on the calf blood flow in patients with intermittent claudication have been instituted. Following preliminary experiments a plethysmographic technique has been developed whereby the calf blood-flow during and following standard exercises is recorded on a kymograph. More work is still needed to elucidate whether there are specific patterns in such records in this condition. To date it appears that the post-exercise hyperaemia is maintained for a longer than normal time in subjects with intermittent claudication. Resting blood flows have not been found to be abnormal, but in severe cases a limitation of reserve has been demonstrated.

UNSUSPECTED DIABETES MELLITUS IN PERIPHERAL VASCULAR DISEASE :

M. Hamilton.

The high incidence of vascular disease complicating diabetes is well established: the part played by diabetes in the production of vascular disease is less well established. Attempts have been made in the past to estimate the incidence of diabetes among groups of patients with vascular disease, but the results have been far from uniform, and the conclusions drawn from the investigations have not proved entirely acceptable. It was therefore decided to attempt to assess the incidence of diabetes in a group of such patients, and to use an adequate control series of subjects.

The interesting feature that has emerged from this investigation is the altered form of the blood glucose tolerance curve seen with increasing age—the alteration being the increase of the 2 hour blood sugar level over the fasting level. Not seen in healthy young adults, this alteration was demonstrated over 30 years ago, but its finding has apparently been ignored by many recent authors, and I believe accounts for the discrepancies existing between the different authorities in their attempt to assess the incidence of diabetes in patients with vascular disease.

The mean curve for all the patients with vascular disease shows little difference from the mean curve for the control group. However, if the group of patients with vascular disease is divided into those with claudication alone, and those with gangrene, it is seen that whereas the curve for the patients with claudication closely follows the control curve at all ages, that for the patients with gangrene behaves very differently. In the younger age groups (less than 70 years old) this curve becomes higher than the control curve, only to return to control level in the group over 70 years of age.

Although this series was highly selective in that all known diabetics were excluded, it is clear that an incidence of diabetes higher than that existing in the normal population, occurs only in the younger patients with gangrene. The incidence of diabetes amongst patients with claudication alone is no higher than in the control series.

CEREBRAL VASCULAR DISEASE :

R. McD. Anderson.

A clinico-pathological study has been made of two hundred and twenty-eight consecutive autopsies on cases of spontaneous intra-cranial haemorrhage.

In view of the high mortality of these cases (70% in this hospital), and the high general incidence of cerebral vascular disease as a cause of death (one in eight of the Australian population) the underlying lesion is of importance in the management.

The site of haemorrhage was found to be as follows:

Intracerebral	121
Subarachnoid	62
Pontine (primary only)	18
Intra-cerebellar	13
Subdural	13
Ventricular (primary)	1
	<hr/>
	228
	<hr/>

The over-all age incidence showed that over half of the patients were under sixty years of age.

Intracerebral group: Hypertension was present in ninety of the one hundred and twenty-one cases. In half of the remainder some other exciting cause such as blood dyscrasia or subacute bacterial endocarditis was present. Three patients had been on oral "vcgolylin" therapy. Atheroma was prominent in seventy-eight cases out of one hundred and two in which it was noted.

Subarachnoid group: In fifty-three cases there was an aneurysm found as the causal lesion. In nine cases there were multiple aneurysms. One third of the aneurysms occurred on the anterior communicating artery. Hypertension was present in over half of the cases. Apart from two deaths in the teens, no patient died under the age of thirty years. The age incidence was therefore much the same as for intracerebral haemorrhage in the autopsy series. Atheroma was present in over half of the cases and this may have an important bearing on surgery for this condition.

Subdural group: Eight out of twelve patients gave no history of trauma. In the other cases trauma was remote. Hypertension was present in ten of the twelve cases.

VARICOSE VEINS :

W. Stern.

It is common clinical knowledge that sclerosing agents introduced into varicose veins frequently do not produce permanent occlusion of the vein, for recanalisation occurs. In a search for a method of producing permanent occlusion of the veins, floss silk was threaded into ear veins of a series of rabbits. This produced venous thrombosis and the occluded veins were examined histologically at intervals varying from a few days to three months after insertion. Histologically there was a marked foreign body reaction in the vein tissues followed by fibrosis of the involved segment. In no case could recanalisation be demonstrated.

Thirty-nine patients with varicose veins in one or both legs have been studied, and many treated surgically. It is noteworthy that at operation five or more venous branches were found in the sapheno-femoral region whereas only three are usually described. Although at operation bleeding from the veins was sometimes brisk and arterial in type, suggesting an arterio-venous anastomosis, this condition could not be predicted clinically.

THE HEART'S ELECTRICAL ACTIVITY

VECTORELECTROCARDIOGRAPHY ;**

T. E. Lowe and J. M. Gardiner.†

During this year further use has been made of the 2 channel V.C.G. In general a large variety of clinical conditions are being examined to obtain data for an assessment of the value of this technique and its merits relative to scalar electrocardiography.

In particular a small series of each left and right bundle branch block have been analysed. There were twenty cases in each group selected from routine scalar electrocardiograms by standard criteria. This method of selection was necessary for bundle branch block is an electrocardiographic phenomenon not yet satisfactorily correlated with physical conditions in the heart.

The features characteristic of the V.C.G. in these conditions may be summarised—

In R.B.B.B. there is an increased duration of the QRS complex with the increase due to a terminal slowing in inscription of the loop and a run-in to the origin from the right.

In L.B.B.B. there is an increased duration of the QRS complex due to general, often irregular, slowing in inscription of the loop. The horizontal projection of the QRS loop is figure-of-eight with the distal loop inscribed clockwise. The frontal and sagittal projections are open and have a general resemblance. The QRS-T junction is displaced to the right and forwards of O.

It was noted that in right bundle branch block coexistent lesions can be identified but that this cannot be done with left bundle branch block cases.

A series of V.C.G's of patients with myocardial infarction is being collected for analysis at a future date.

SPATIAL MAGNITUDE ELECTROCARDIOGRAPHY :

B. McA. Sayers, F. G. Silberberg and R. Fowler.

The construction of apparatus to study the spatial magnitude of the heart's electrical activity was described in the last report. Owing to the departure for overseas study by the senior workers concerned the only work performed this year has been the collation of existing records. It has been possible to define some of the normal variations in the records obtained and in some instances to relate changes in the curves to existing pathological lesions. It is clear from the studies that the higher frequency components of the electrocardiogram are of some importance in interpreting records.

†Cardiovascular Diagnostic Service, Alfred Hospital.

STUDY OF CARDIAC VIBRATIONS*

J. R. E. Fraser.

The technique of phonocardiography has been established clinical practice for some years. The instruments used have been designed to reproduce graphically what the average observer should hear through the stethoscope. This procedure deliberately modifies the heart sounds to a considerable degree.

The range of vibrations associated with the heart's activity extends from the gross movement of the apex beat through a number of intense but inaudible (infrasonic) vibrations into the sonic range at 30 cycles per second, to which the ear is relatively insensitive, and up to a maximum frequency of 1000 cycles per second, to which the ear is most sensitive.

A study of these vibrations in terms of intensity and frequency, ignoring the arbitrary modifications of ear and stethoscope should therefore give information of a character different from that gained by standard phonocardiography or clinical auscultation. Studies of this nature have been undertaken in the past: usually as separate studies in the sonic and infrasonic ranges, the latter by a variety of methods. These studies have not been pursued widely, in the first instance due to the bulk of apparatus and the apparent lack of practical application, in the second instance, because the records were not considered to give any significant information regarding heart disease.

The present study has been undertaken to extend these observations with a view to gaining further information regarding cardiac physiology, and to seek any practical applications in diagnosis of heart disease. The past year has been spent in constructing and perfecting the technique and apparatus, which will be briefly described. The currents generated by a microphone placed on the chest wall are passed through a series of amplifiers and electronic filters which separate the sound components into a series of frequency bands, each of these being recorded simultaneously in a battery of double-gun cathode ray oscilloscopes. The electrocardiograms and venous or arterial pulse waves can be recorded on the same tracing. The permanent records are made with a high speed camera designed for cathode ray oscilloscopes. Provision is made for comparative or absolute measurement of intensity of the various component vibrations.

Numerous theoretical and technical problems were uncovered during the construction of the instrument. Only limited help was obtained from published studies, due to the different purposes of the various instruments; for example, microphone casings have often been deliberately constructed to introduce acoustical attenuation, which we wished to avoid.

The microphone housing chosen was shown by measurement and physical calculation to be free of resonance in the range of cardiac vibrations. A special adaptation of the crystal microphone was necessary for recording infrasonic vibrations. The chief difficulties lay in constructing suitable electronic filters; the design finally selected was adapted from one recently introduced for telegraphic communications, and appears to have the necessary selectivity, stability and freedom from inherent noise.

The records obtained so far have necessarily been limited in scope, but previous observations regarding the relative intensities of the various frequency components, and the temporal separation of components in the normal heart sounds have been confirmed. The method seems to allow clearer separation of

the latter than is possible with standard techniques, and the records taken in cases of heart disease suggest that there may be characteristic frequency patterns in some of the abnormal sounds. The field of infrasonic vibrations has not yet been explored, but the recent clinical reevaluation of the significance of precordial pulsations lends particular interest to this aspect of the study.

The project is now approaching the stage when an extensive clinical study can be undertaken.

ENERGY PRODUCTION IN THE MYOCARDIUM*

T. E. Lowe, G. A. Bentley, F. McCallum and D. McKelvie.

Last year the construction of a Warburg type apparatus in which the functioning of the intact cold blooded heart could be studied was reported. During the past year exploratory work on this apparatus has been carried out and techniques for measuring various aspects of the heart's functioning have been developed.

Although many cardiac drugs have for many years been used successfully in the alleviation of abnormal heart conditions, very little is known of the way in which they bring about their effects. The heart is an organ in which chemical energy in the myocardium is converted into mechanical energy for contraction and relaxation of the myocardial elements themselves and also into mechanical energy in the blood stream. Cardiac drugs might act by improving either the production of chemical energy or the transformation of chemical into mechanical energy at either of these two points. It is clear that a full investigation into the mode of action of such drugs can only be carried out on an intact heart. Experiments confined to drug action on pieces of heart muscle take into account only factors involved in transfers of chemical into mechanical energy in the myocardium itself.

The apparatus we are using makes possible the simultaneous measurement of the mechanical and chemical functioning of an intact circulating heart. Chemical efficiency is estimated by measuring the gaseous exchange of the recycling heart. This is done by enclosing the heart preparation in a perspex box immersed in a thermostatically controlled water bath and connected with a Warburg manometer. Carbon dioxide given off is absorbed in a potassium hydroxide bath so that oxygen is the only gas phase present within the apparatus and therefore oxygen consumption can be measured at constant temperature and pressure. Determinations carried out on a number of hearts have shown that this method gives reproducible results, oxygen uptake for a total of 12 hearts being between 400-500 micro-litres per hour.

A technique is being developed for measuring carbon dioxide output. This depends upon the fact that as carbon dioxide dissolves in the potassium hydroxide forming potassium carbonate, the resistance of the solution alters and the amount of carbon dioxide evolved can be calculated from this change in resistance. This technique has not as yet been used on a heart but has been developed to the requisite sensitivity. By simultaneous measurement of oxygen uptake and carbon dioxide output it will be possible to estimate the amount and type of chemical fuel being used by the heart.

Mechanical efficiency of the heart preparation is estimated by measuring aortic pressure and fluid output. The measurement of output is achieved by means of a drop counter consisting of a pair of platinum electrodes arranged in

such a way that as each drop leaves the aortic cannula it hits the electrodes thus completing a circuit and giving an electrical response. The drop volume for any given arterial cannula can be estimated and, on the assumption that the drops have a constant volume, output of fluid from the heart can be calculated. In the majority of hearts so far tested, output is about 0.3-0.4 ml per beat.

Aortic pressure is measured by means of a capacitance manometer which is connected to the heart by means of a needle tied into one side of the aortic arch. Pressure measurements on a number of hearts have been very variable and pressures as high as 600 mms of water and as low as 80 mms of water have been recorded. Knowing the fluid output and the aortic pressure of the recycling heart preparation, it will be possible to arrive at an estimate of the mechanical performance.

Since all these measurements of carbon dioxide output, oxygen uptake, aortic pressure and fluid output can be carried out simultaneously on a single preparation, it will be possible to correlate chemical and mechanical efficiency for a given set of conditions. The apparatus has now been developed to the stage when such measurements can be carried out on normal hearts and when this information is available, the way will be open for investigations into the manner in which cardiac drugs may separately affect the production or utilisation of chemical energy.

THE PHYSIOLOGY AND PATHOLOGY OF THE STOMACH AND SMALL BOWEL

R. R. Andrew and J. Meagher.

Further studies by balloon kymography on gastric and intestinal motility under the influence of synaptic-blocking drugs have been done during the year on six subjects. The results of these experiments have been reported elsewhere.

A follow-up of the patients with cholelithiasis in whom gastric biopsy has been performed has been done, but the lapse of another year will be necessary before the effect of operation on those with concurrent cholelithiasis and gastritis is known.

One case of portal hypertension was investigated and attempts made to measure portal pressure by splenic puncture, and also to display radiologically the portal system by injection of radio-opaque medium.

HORMONE-INDUCED EOSINOPENIA

Bryan Hudson.

During the past twelve months investigations concerning the nature of hormone-induced eosinopenia have been along three lines. The first series of experiments have shown that when blood is incubated with varying concentrations of compound F† (hydrocortisone) there is no significant alteration in the number of eosinophils after 4-6 hours. These *in vitro* observations would suggest that it is unlikely that simple lysis of these cells is the cause of hormone-induced eosinopenia.

Others have claimed that if the cells which comprise the reticulo-endothelial system are "blocked" by the use of particulate carbon (India ink) or colloidal

†The Compound F used in these studies was made available by Merck and Company, Inc. Rahawz, New Jersey, U.S.A., and The Upjohn Company, Kalamazoo, Michigan, U.S.A.

dyes (Trypan blue) the fall in eosinophils following the administration of corticotrophin is prevented. It has been agreed that the cells of this system are responsible either by active phagocytosis or sequestration for the eosinopenia. A series of experiments in which the guinea pig was the experimental animal showed that reticulo-endothelial blockade produced no effect on the ability of cortisone to cause a pronounced fall in circulating eosinophils. The results of both these series of experiments have been published recently.

The series of experiments which are being currently undertaken involve a study of the form of the curves which can be constructed when eosinophils are disappearing from the peripheral blood. These curves are constructed by plotting the total number of eosinophils at any given instant against the time. The aim of this study is to try to identify eosinophil disappearance with a particular type of curve. If it can be shown that the form of the curve following an eosinopenic stimulus is linear it would be reasonable to assume that the nature of the process is one of senescence (c.f. red cell survival studies). If eosinophil disappearance is in fact linear, the hypothesis that steroid-induced eosinopenia was due to an effect on the bone marrow with temporary cessation of eosinophil production would appear to be a valid one. If on the other hand the curves are found to be mainly exponential it would seem then that these cells disappear on the basis of concentration and that the phenomenon is the result of an active process involving destruction or sequestration (or both).

PIGMENTATION IN ADDISON'S DISEASE

Bryan Hudson.

During the past twelve months the method which has been previously described for the assay of melanophore expanding hormone (M.E.H.) has been developed to the stage of a routine assay procedure. The assay has been used to test many methods of extraction of melanophore expanding hormone from blood.

The procedure which has been found to yield the greatest recovery when known amounts of M.E.H. are added to blood *in vitro* is one which involves the use of extraction of the blood with pure acetone and adsorption of the active principle on to oxidised cellulose in the presence of 0.1 N acetic acid. When adsorption has occurred the M.E.H. is eluted from the cellulose with 0.1 N HCl. Recoveries of the order of 80-90% are obtained from the procedure when M.E.H. is added to blood. At no stage have we been able to extract this hormone from the blood of patients suffering from Addison's disease when this method is used. In the belief that this hormone might be intimately adsorbed onto large lipoprotein molecules preliminary treatment with N-Butanol has been tried. In one instance, that of a patient who had received a large amount of M.E.H. intravenously preliminary butanol treatment enabled us to recover some activity from the blood, but continuation of this observation is necessary.

We have been able to show in addition that the human pituitary gland contains a melanophore expanding principle. Thus fresh human pituitary tissue was obtained from a patient who was undergoing hypophysectomy and extracted according to the method of Astwood and colleagues. This extract was shown to contain considerable melanophore expanding activity. We believe that this is the first occasion in which such activity has been demonstrated as far as human pituitary tissue is concerned.

PTERYGIUM

R. Fowler.

Pterygium is very prevalent in this country, especially in its hotter regions, so there is strong presumptive evidence that heat is a major factor in the aetiology of this condition.

At the suggestion of Dr. J. Ringland Anderson an attempt was made to produce experimentally a pterygium or some similar change in a rabbit's eye.

A simple surgical technique was devised to convert a rabbit's nictitating membranes for use as eyelid retractors.

One eye served as a control, the nasal side of the limbus of the other eye being exposed to a stream of air at 40-44°C for no longer than half an hour a day. This amount of heat is below the threshold for a thermal burn. After three weeks of this treatment a vascular opacity had appeared in the cornea. The rabbit was sacrificed after another two weeks during which time the lesion did not appear to have progressed.

A meridional section through the limbus showed connective tissue overgrowth with many new blood vessels beneath the bulbar conjunctiva, and a zone of epithelial hyperplasia, with some degenerate sub-epithelial fibrous tissue, in the adjacent cornea.

These changes resemble a pterygium in many respects.

The finding of epithelial hyperplasia after intermittent exposure to moderate heat may have a wider significance for other tissues.

HEAD INJURIES

K. Jamieson.

Several aspects of the physiology of patients suffering from head injuries have been studied.

Study of case histories and circulation and respiration charts showed that respiratory disturbances have a profound deleterious effect on the clinical course of patients with head injuries. In a series of 30 patients measurements of pulmonary function were undertaken. A most striking finding was that many patients with rapid shallow respiration had tidal volumes of only some 300 mls and an effective pulmonary exchange of some 3-4 litres per minute. In these, attention to the airway produced rapid improvement. It was also noted that the prognosis in cases of "secondary haemorrhage" in the hypothalamus and brain stem with increasing coma and shallow respirations depended on the ability to improve the respiratory function. A series of patients with traumatic or naturally occurring cerebral haemorrhage was also investigated.

Examination of a series of patients with intracranial space-occupying lesions showed that these were accommodated by shrinking of the surrounding brain. These observations were made the basis of a paper on cerebral shrinking.

PUBLICATIONS DURING 1954

- T. E. Lowe: "MERCURIAL DIURETICS," *Medicine Illustrated*. Vol. 8 (1954), p. 599.
- T. E. Lowe and J. M. Gardiner: "THE VECTORELECTROCARDIOGRAM IN BUNDLE BRANCH BLOCK," *A/sian Ann. Med.*, Vol. 3 (1954), p. 289.
- P. Fantl: "THE USE OF SUBSTANCES DEPRESSING ANTITHROMBIN ACTIVITY IN THE ASSAY OF PROTHROMBIN," *Biochem. J.*, Vol. 57 (1954), p. 416.
- P. Fantl and R. J. Sawers: "B-PROTHROMBOPLASTIN DEFICIENCY CAUSING A HAEMORRHAGIC TENDENCY RESEMBLING HAEMOPHILIA," *Med. J. Aust.* Vol. 1 (1954), p. 925.
- P. Fantl and R. J. Sawers: "'HAEMOPHILIA': A SYNDROME UNDER REVIEW. INVESTIGATIONS OF ALPHA AND BETA PROTHROMBOPLASTIN DEFICIENCIES," *A/sian Ann. Med.*, Vol. 3 (1954), p. 245.
- A. J. Barnett: "LUMBAR SYMPATHECTOMY FOR OCCLUSIVE ARTERIAL DISEASE," *A/sian Ann. Med.*, Vol. 3 (1954), p. 295.
- A. J. Barnett and J. R. E. Fraser: "MECHANISM OF ARTERIAL HYPERTENSION. A COMPARISON OF THE EFFECTS OF HEXAMETHONIUM BROMIDE IN HYPERTENSIVE AND NORMOTENSIVE PERSONS," *A/sian Ann. Med.*, Vol. 3 (1954), p. 152.
- "METHONIUM TREATMENT OF ARTERIAL HYPERTENSIVE DISEASE," *Alfred Hospital Clinical Reports*, Vol. 4 (1954), p. 35.
- Bryan Hudson: "THE INFLUENCE OF RETICULOENDOTHELIAL BLOCKADE ON HORMONE INDUCED EOSINOPENIA," *Aust. J. exp. Biol. & Med. Sci.*, Vol. 32 (1954), p. 689.
- "THE EFFECTS OF 17-HYDROXYCORTICOSTERONE (Compound F) ON HUMAN EOSINOPHILS," *Aust. J. exp. Biol. & Med. Sci.*, Vol. 32 (1954), p. 601.
- Roderick Andrew: "GASTRIC AND INTESTINAL MOTILITY STUDIES WITH MORPHINE, ATROPINE, HEXAMETHONIUM BROMIDE AND 'BANTHINE'," *A/sian Ann. Med.*, Vol. 3 (1954), p. 305.
- "GASTRIC, DUODENAL AND JEJUNAL MOTILITY IN MAN: PHYSIOLOGICAL STUDIES BY BALLOON-KYMOGRAPHY," *Aust. J. exp. Biol. & Med. Sci.*, Vol. 32 (1954), p. 479.
- D. G. Duffy and H. B. Kay: "SYMPTOMATIC ASSESSMENT IN HYPERTENSION," *Alfred Hospital Clinical Reports*, Vol. 4 (1954), p. 23.
- J. R. E. Fraser and T. E. Lowe: "FLUID RETENTION DURING METHONIUM THERAPY," *A/sian Ann. Med.*, Vol. 3 (1954), p. 234.
- J. R. E. Fraser and A. J. Barnett: "THORACIC OUTLET SYNDROME: CASE ASSOCIATED WITH SHORT 'FIRST' RIB, ANEURYSM OF THE SUBCLAVIAN ARTERY AND OCCLUSION OF BRACHIAL ARTERY," *Med. J. Aust.*, Vol. 2 (1954), p. 739.
- "SECONDAL SEDATION TEST IN ARTERIAL HYPERTENSION, LIMITATIONS OF ITS VALUE," *A/sian Ann. Med.*, Vol. 3 (1954), p. 146.

- J. M. Gardiner: "THE EFFECT OF PRISCOL IN PULMONARY HYPERTENSION," *A/sian Ann. Med.*, Vol. 3 (1954), p. 59.
 "PATENT DUCTUS ARTERIOSUS WITH ATYPICAL SIGNS," *Med. J. Aust.*, Vol. 2 (1954), p. 388.
- J. M. Gardiner and T. E. Lowe: "THE SPATIAL VECTORELECTROCARDIOGRAM IN RIGHT VENTRICULAR HYPERTROPHY," *A/sian Ann. Med.*, Vol. 3 (1954), p. 18.
- Kenneth Jamieson: "CEREBRAL SHRINKING," *A/sian Ann. Med.*, Vol. 3 (1954), p. 312.
- F. G. Silberberg: "TIGER-SNAKE VENOM: ATTEMPTED RESUSCITATION IN RABBITS," *Med. J. Aust.*, Vol. 2 (1954), p. 139.

PAPERS ACCEPTED FOR PUBLICATION

- T. E. Lowe: "A MODEL REPRESENTING THE CONTROL OF BODY FLUID VOLUME IN MAN," *A/sian Ann. Med.*
- P. Fantl: "THROMBIN FORMATION AND YIELD IN SHED BLOOD IN RELATION TO THROMBOPLASTINS AND PROTHROMBOPLASTINS," *Aust. J. exp. Biol. & Med. Sci.*
- P. Fantl and J. Margolis: "ALPHA-PROTHROMBOPLASTIN DEFICIENCIES (Haemophilia) OF DIFFERING DEGREES IN A MOTHER AND SON," *Brit. Med. J.*
- A. J. Barnett: "OCCLUSIVE ARTERIAL DISEASE OF THE HANDS," *Med. J. Aust.*
- A. J. Barnett and J. R. E. Fraser: "SUBCLAVIAN ATHEROSCLEROSIS, CORONARY ATHEROMA AND ANGINA PECTORIS WITHOUT ELECTROCARDIOGRAPHIC CHANGES," *Med. J. Aust.*
- Bryan Hudson and G. A. Bentley: "THE MELANOPHORE-EXPANDING ACTIVITY OF HUMAN PITUITARY," *Lancet.*
- R. Fowler: "AN UNEXPECTED SLOW PHASE IN THE EQUILIBRATION OF BODY WATER CONTENT," *A/sian Ann. Med.*
 "CONTROL OF BODY WATER CONTENT: A STUDY OF DAY TO DAY VARIATIONS IN HUMANS AND RABBITS," *A/sian Ann. Med.*
- R. Fowler and J. Uffill: "THE SODIUM THIOSULPHATE SPACE AS AN ESTIMATE OF EXTRACELLULAR FLUID VOLUME IN RABBITS," *Aust. J. exp. Biol. & Med. Sci.*
- M. Hamilton, A. J. Barnett and T. E. Lowe: "ISCHAEMIC EPISODES IN CARDIAC FAILURE: ACUTE ARTERIAL INSUFFICIENCY WITH AND WITHOUT STRUCTURAL BLOCKAGE," *Med. J. Aust.*
- B. McA. Sayers: "SPATIAL MAGNITUDE ELECTROCARDIOGRAPHY," *Amer. Heart J.*
- B. McA. Sayers, F. G. Silberberg and D. F. Durie: "THE ELECTROCARDIOGRAPHIC SPATIAL MAGNITUDE CURVE IN MAN," *Amer. Heart J.*

MONOGRAPH IN PUBLICATION

- A. J. Barnett and J. R. E. Fraser: "PERIPHERAL VASCULAR DISEASE," *M.U.P.* (Stawell Memorial Prize Essay for 1952).

LECTURES DELIVERED DURING 1954

- "SELF-REGULATION IN OPEN SYSTEMS" T. E. Lowe
Victorian Society for Pathology and Experimental Medicine.
- "VECTORELECTROCARDIOGRAM IN BUNDLE BRANCH BLOCK"
T. E. Lowe and J. M. Gardiner
Australasian Cardiac Society, Melbourne.
- "SOME PROBLEMS IN THE MANAGEMENT OF HAEMORRHAGIC DIS-
ORDERS" P. Fantl
Alfred Hospital Clinical Society.
- "CONGENITAL HAEMOPHILIA IN A FEMALE" P. Fantl
Victorian Society for Pathology and Experimental Medicine.
- "DIFFERENTIATION BETWEEN ALPHA- AND BETA-PROTHROMBO-
PLASTIN DEFICIENCY DISEASES" P. Fantl
Royal Alexandra Hospital for Children, Sydney.
- "SOME ASPECTS OF SYMPATHETIC FUNCTION IN MAN AS REVEALED
BY TWO CASES OF SEVERE POSTURAL HYPOTENSION," A. J. Barnett
Victorian Society for Pathology and Experimental Medicine.
- "LUMBAR SYMPATHECTOMY FOR OCCLUSIVE ARTERIAL DISEASE"
A. J. Barnett
Royal Australasian College of Physicians, Melbourne.
- "OCCLUSIVE ARTERIAL DISEASE OF THE HAND" A. J. Barnett
Anstralasian Cardiac Society, Melbourne.
- "THE DIAGNOSIS AND TREATMENT OF ADDISON'S DISEASE"
Bryan Hudson
Alfred Hospital Clinical Society.
- "RENAL ACIDOSIS WITH OSTEOMALACIA," Bryan Hudson and D. G. Duffy
Royal Australasian College of Physicians, Melbourne.
- "ENDOCRINE DISORDERS" Bryan Hudson
Australian Association of Physiotherapists (Victorian Branch).
- "GENETIC CONSIDERATION IN THE HAEMOPHILIA SYNDROME"
R. J. Sawers
Victorian Society for Pathology and Experimental Medicine.
- "HAEMOPHILIA: A SYNDROME UNDER REVIEW" R. J. Sawers
Royal Australasian College of Physicians, Melbourne.
- "HEXAMETHONIUM AS A CAUSE OF OEDEMA" J. R. E. Fraser
Australasian Cardiac Society, Melbourne.
- "THE REGULATION OF BODY WATER CONTENT" R. Fowler
Victorian Society for Pathology and Experimental Medicine.
- "BLOOD SUGAR CURVES IN PATIENTS WITH PERIPHERAL ARTERIAL
DISEASE" M. Hamilton
Alfred Hospital Clinical Society.

THE THOMAS BAKER, ALICE BAKER AND ELEANOR SHAW MEDICAL RESEARCH INSTITUTE
Balance Sheet at 31st December, 1954.

LIABILITIES.		ASSETS.	
Current Liabilities—		Current Assets—	
Sundry Creditors	£215 9 7	Cash in Bank	£850 19 11
Endowment Fund	8,500 0 0	Sundry Debtors	40 0 0
Capital Grants and Gifts—			£890 19 11
Balance as at 31st December, 1953 ..	£772 18 5	Endowment Investments—	
Add Grants received during year ..	2,257 12 10	Grain Elevators Board Inscribed Stock—	
	3,030 11 3	4% maturing 1/5/1964	2,500 0 0
Less Amount expended during year ..	1,630 19 6	Commonwealth Government Inscribed	
	1,399 11 9	Stock—	
Life Insurance Medical Research Fund of		3% maturing 15/10/1960	5,000 0 0
Australia and New Zealand Reserve—		3% maturing 15/10/1963	500 0 0
Balance as at 31st December, 1953 ..	859 18 4	Australian Consolidated Treasury Bonds—	
Add Grants received during year ..	2,358 19 0	3% maturing 15/9/1961	500 0 0
	3,218 17 4		8,500 0 0
Less Amount expended during year ..	1,286 3 10	Restricted Funds—	
	1,982 13 6	Cash in Bank—	
Revenue Account—		Capital Grants and Gifts	1,399 11 9
Surplus as at 31st December, 1953 ..	2,044 11 7	Research Grant from the Life Insurance	
Add Recoup of Deficit for year ended		Medical Research Fund of Australia	
31st December, 1953	605 0 8	and New Zealand	1,932 13 6
Add Surplus for year ended 31st			3,332 5 3
December, 1954	125 18 1	Fixed Assets—	
	2,775 10 4	Furniture and Fixtures	2,100 0 0
		NOTE: In addition to receiving interest from the Invest-	
		ments as shown on the Balance Sheet, the Institute	
		receives the income from 3% Commonwealth	
		Government Inscribed Stock face value of £17,000,	
		which is inscribed in the name of the Trustees	
		of the Estate of the late Thomas Baker for the	
		benefit of the Institute.	
	£14,823 5 2		£14,823 5 2

AUDITORS' REPORT TO THE TRUSTEES OF THE THOMAS BAKER, ALICE BAKER AND ELEANOR SHAW MEDICAL RESEARCH INSTITUTE

We have examined the above Balance Sheet with the books of the Institute and have obtained all the information and explanations we have required. In our opinion the Balance Sheet presents a true and fair view of the state of the affairs of the Institute at 31st December, 1954, according to the best of our information and the explanations given to us and as shown by the books of the Institute.

Melbourne,
22nd March, 1955.

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

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

Revenue Account for the Year Ended 31st December, 1954.

EXPENDITURE.		INCOME.	
Salaries and Wages	£12,552 8 2	Donations—	
Drugs	205 16 7	Thomas Baker (Kodak), Alice Baker and Eleanor Shaw Benefactions	£10,200 0 0
Instruments and Glassware	660 10 9	Mr. Edgar Rouse	91 0 0
Special Maintenance	791 10 6		£10,291 0 0
Repairs and Renewals	49 16 7	Grant—Life Insurance Medical Research Fund of Australia and New Zealand— 1953 Grant brought for- ward 1/1/54	£859 18 4
Miscellaneous and Administration—		Less carried forward 31/12/54	179 12 9
Fuel and Lighting	£117 10 7		680 5 7
Insurance	147 2 9	1954 Grant received during year	2,358 19 0
Library	409 19 5	Less carried forward 31/12/54	1,753 0 9
Printing and Stationery	160 16 6		605 18 3
Telephone	95 6 10		1,286 3 10
Laundry	32 19 8	Government Grants—	
Sundries	391 9 11	National Health and Medical Research Council	3,099 10 6
Balance—Surplus for year	1,355 5 8 125 18 1	Interest from Investments—	
		Trustees of the Thomas Baker Estate: Commonwealth Government Inscribed Stock held for the benefit of the Institute	551 0 0
		Endowment Investments—	
		Commonwealth Government Inscribed Stock	178 2 6
		Australian Consolidated Treasury Bonds	16 5 0
		Grain Elevators Board Inscribed Stock	103 2 6
			848 10 0
		Sundry Sales	216 0 0
			£15,741 4 4
	£15,741 4 4		£15,741 4 4