BAKER INSTITUTE

RESEARCH

1955

ALFRED HOSPITAL

The Baker Medical Research Institute derives its main financial support from the Thomas Baker (Kodak), Alice Baker and Eleanor Shaw Benefactions. It is also dependent upon donations from private sources. The latter may be allocated to an Endowment Fund.

The Clinical Research Unit is a department of Alfred Hospital, and is recognised by the University of Melbourne for the purpose of providing facilities for candidates proceeding to the degrees of M.Sc. and Ph.D.

The scientific activities of the Baker Institute and Alfred Hospital Clinical Research Unit are co-ordinated. Both are accepted as "approved research institutions" by the National Health and Medical Research Council, from which grants are received for specific research work.

Research Fellowships are awarded by the Appointors for Research Scholarship Funds of the Hospital in consultation with the Research Advisory Committee of the Board of Management.

Twenty-Ninth Annual Report

of

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

and

Seventh Annual Report

of

ALFRED HOSPITAL
CLINICAL RESEARCH UNIT
and
RESEARCH FELLOWS

1955

ALFRED HOSPITAL, PRAHRAN,
VICTORIA, AUSTRALIA.

BAKER MEDICAL RESEARCH INSTITUTE

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Director of Clinical Research Unit (ex officio).

‡Appointed from the University of Melbourne.

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Biochemists	C. C. CURTAIN, PH.D., M.SC., A.R.A.C.I. H. A. WARD, B.SC. A. G. MARR, B.SC., A.R.A.C.I. MISS J. SHEATH, B.SC.
Physiologist	MRS. W. G. NAYLER, B.SC.
Ward Staff	SISTER S. A. CITROEN. SISTER J. DETTMAN (from 13/12/54 to 3/4/55) SISTER B. HILLMAN (from 4/4/55).
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Animal Farm Supervisor	A. RANKIN.
Laboratory Assistants	MISS R. DIXON (to 20/10/55). MISS W. DONOVAN. MISS J. HUDGSON (to 22/4/55). MISS S. EDGINGTON (from 28/4/55 to 19/8/55). MISS J. MCGAHY (from 21/2/55 to 9/12/55). MISS N. BRAIN (from 1/8/55). MISS E. *HENDERSON* (from 5/9/55). MRS. B. STEDMAN (from 12/12/55). MISS M. NEAVE (from 19/12/55).

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"George Merriman"	E. L. G. Beavis, M.B., B.S., D.G.O., M.R.C.O.G., F.R.C.S.
"J. F. MacKeddie"	D. G. Duffy, M.D., M.R.A.C.P.
"Edward Wilson Memorial"	D. Emslie-Smith, M.B., Ch.B. (Aberd.), M.R.C.P.
"Frederick & Esther Michaelis"	J. C. McNeur, M.B., B.S., F.R.C.S., F.R.A.C.S.
"Victor Y. & Margaret Kimpton"	C. J. McRae, M.B., B.S., M.R.C.P., M.R.A.C.P.
"Sol Green"	L. Murfitt, M.B., B.S.
"Sol Green"	W. A. St. Clair, M.B., B.S.
"R. B. McComas Memorial"	R. J. Sawers, M.B., B.S., M.R.A.C.P.
"A. A. Swallow"	W. Stern, M.B., B.S., M.R.C.S., L.R.C.P.
Sydney W. Jones Medical Research Foundation	G. R. Stirling, M.B., B.S.
Honorary Research Fellowship	R. R. Andrew, M.D., M.R.C.P.
Senior Research Fellowship	Jean C. Tolhurst, M.Sc.

APPOINTED TO RESEARCH FELLOWSHIPS FOR 1956

E. L. G. Beavis, M.B., B.S., D.G.O., M.R.C.O.G., F.R.C.S.	"George Merriman"
D. Emslie-Smith, M.B., Ch.B. (Aberd.), M.R.C.P.	"Edward Wilson Memorial"
J. K. Francis, M.B., M.S., F.R.C.S.	"Frederick & Esther Michaelis"
R. J. Sawers, M.B., B.S., M.R.A.C.P.	"R. B. McComas Memorial"
G. R. Stirling, M.B., B.S.	Sydney W. Jones Medical Research Foundation
W. Quinn-Young, B.Sc., B.E.E., M.B., B.S.	"Victor Y. & Margaret Kimpton"

ANNUAL REPORT OF THE DIRECTOR

Although the projects carried out in the Research Centre change somewhat from year to year our investigations are governed by certain broad principles which apply to all medical research directed towards clinical problems. These are a recognition of the differences between basic and applied research, the dependence of medical research on the state of contemporary sciences and the need for a team of investigators coming from a variety of scientific disciplines.

All research may be classified into pure, basic and applied. *Pure research* may be defined as an enquiry after knowledge for its own sake without consideration or hope of practical gain. This type of research is commonly associated with universities and an organisation such as ours can carry out little of it. *Basic research* is an enquiry carried out, not under the pressure of immediate needs but with a reasonable hope of eventual use in the field of interest (here clinical medicine). *Applied research* is rather different to the foregoing and is an investigation carried out in response to an immediate, direct or obvious need.

Much of the research carried out in this Centre is basic and is represented by the projects concerning blood coagulation, control of body fluid volume and the energy production of the myocardium. A feature, often not appreciated, of this type of research is illustrated by the following quotation—

> "The immediate results of basic research are seldom spectacular. They do not get into the headlines, they do not immediately change the lives of millions, or result in enormous savings, or gain victories or defeats, not in themselves, but in their long term effects they may do all these things."*

The projects concerning diagnostic and therapeutic measures of use in haemophilia, the assessment of the value of hypotensive drugs and much of our earlier work on diagnostic methods used in cardiology represent applied research. This last aspect of research is an important, but not a major function, of a research institute attached to a teaching hospital. It was from this work that the Cardiovascular Diagnostic Service was developed. Of similar character and now in the formation stage is a radioisotope centre for diagnostic, therapeutic and research purposes. The work on the development of diagnostic procedures for endocrine disorders is in this same category.

The second guiding principle is the dependence of medical research on contemporary sciences, a dependence both for investigational tools and methods and for ideas on which to found lines of investigation. An example will make this dependence clear. All living tissue produces electrical activity, and the advances of electronic engineering over the past twenty years and more have given the medical research worker investigational tools, such as the various forms of electrocardiograph, electroencephelograph and the electronic recorders, with which to record this activity. As the electrical activity of tissues in disease is frequently different from normal these devices can also be used diagnostically in clinical medicine. This example can be paralleled from almost every branch of science, thus in the studies of the control of body fluid volume the basic idea of an "open" system storage, which has been shown to give a good working hypothesis, comes from physics and hydraulic engineering.

*Spaght, M. E., Science, Vol. 121, 1955, p. 784.

An extension of this second principle leads naturally to the idea that medical research must, in most cases, employ teams of workers drawn from diverse sciences as well as medical graduates. In this way the knowledge of various scientific disciplines becomes available to the essential clinical problem. The value of this team work is well illustrated by many of the projects discussed in the scientific section of this report. It is indeed fortunate that the generosity of many has permitted this research centre to grow to a size that it is possible to assemble such a team. Clearly a minimum size is necessary to carry out this ideal.

The continuing growth of the activities of the research groups places much strain on accommodation and during the year extensions have had to be added to the buildings. These have provided an excellent theatre suitable for experimental surgery and a new library in which is incorporated a much needed seminar room. However this increase in space only provides for new activities and exaggerates the dominance of laboratory over clinical activities. This must continue until it is possible to provide more beds for clinical work. A plan incorporated in this report shows the layout of the centre and indicates the close integration of laboratory and clinical work.

An important activity of any research group is educational for its findings and ideas must be passed on to others. The list of lectures delivered by members of the Centre indicates that this side of our work is well represented and the diversity of bodies before whom the lectures have been given indicates a wide interest in our activities.

Near the end of the past year the investigations into the pharmacology of adrenaline and noradrenaline were discontinued, it is hoped temporarily, owing to the resignation of the senior worker. However at the beginning of 1955 a physico-chemical study of abnormal blood proteins was commenced and during the year some experimental work on the problems of inducing low body temperatures (hypothermia) as an adjunct to cardiac surgery were also instituted. Both these new projects are progressing satisfactorily and proving profitable to workers on other projects by making available additional techniques and skills which can be availed of by all.

A detailed account of the investigations carried out is given in the scientific section of this report.

As in previous years the Trustees of the Institute and the Board of Management of the Hospital have provided facilities for an exchange of visits between this and other centres. In particular it has been stimulating to have with us a postgraduate Fellow from the University of St. Andrews, Dundee, during his tenure of the Edward Wilson Memorial Fellowship, and also to have a short visit from Dr. J. B. Lowe, of Auckland, New Zealand. On two occasions members of our staff visited research groups and scientific meetings in Sydney. These visits provide opportunity for the exchange of ideas and are essential for progress. I hope it will be possible to continue them in the future.

During 1955 the first Professors in Medicine and Surgery of the University of Melbourne assumed office and the Professor of Surgery is to be located in Alfred Hospital. It is anticipated that fruitful co-operation with these new departments will evolve.

The National Health and Medical Research Council, and the Life Insurance Medical Research Fund of Australia and New Zealand have continued to support general research projects and have allocated grants for continuance of the projects in 1956. The help of these bodies is gratefully acknowledged.

Many organisations have made gifts to the Institute library 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.

During the year the death occurred of Mr. John Kennedy, a member of the Institute Advisory Panel. We have thereby lost a trusted friend and advisor.

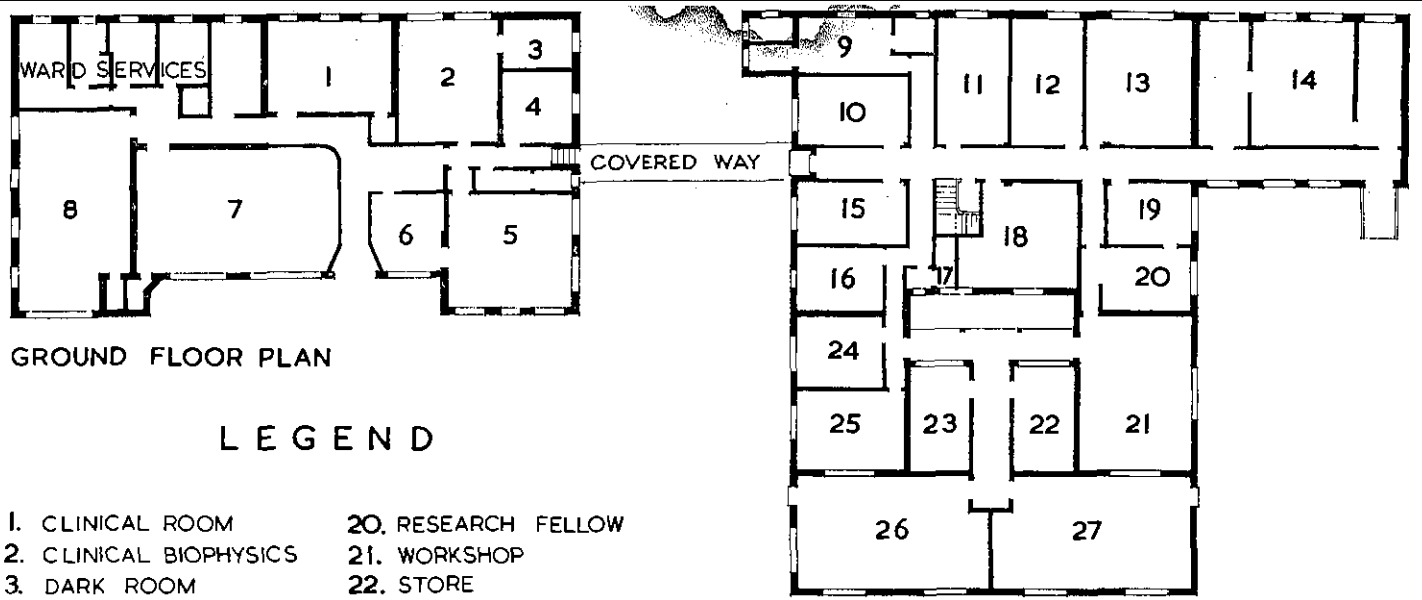
It is a pleasure for me to thank the Trustees of the Institute and the Board of Management of the Hospital for their continued generous support and to thank members of the staff for their co-operation during the past year.

T. E. LOWE, Director.

31st December, 1955.

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

Commonwealth Department of Health.
Hallstrom Institute of Cardiology.
L'Institut Bunge.
Institute of Dental Research, Sydney.
Institute of Medical and Veterinary Science, Adelaide.
International Anaesthesia 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.
Staten Seruminstitut, Copenhagen.
South African Institute of Medical Research.
U.S. Army Medical Library.
Walter and Eliza Hall Institute.



GROUND FLOOR PLAN

GROUND FLOOR PLAN

LEGEND

1. CLINICAL ROOM
2. CLINICAL BIOPHYSICS
3. DARK ROOM
4. CONSULTING ROOM
5. CLINICAL ROOM
6. OFFICE
7. WARD (6 BEDS)
8. WARD (6 BEDS)
9. CHROMATOGRAPHY
10. ASSOCIATE DIRECTOR
11. CENTRIFUGES REFRIG.
12. BIOCHEMISTRY LAB.
13. HAEMATOLOGICAL BIOCHEMISTRY LAB.
14. EXPERIMENTAL SURGERY
15. ASSOCIATE DIRECTOR
16. RESEARCH FELLOW
17. MICROBALANCE
18. ORGANIC CHEMISTRY
19. RESEARCH FELLOW
20. RESEARCH FELLOW
21. WORKSHOP
22. STORE
23. STORE
24. BIOCHEMISTRY LAB
25. ENDOCRINOLOGY LAB
26. CLINICAL BIOCHEMISTRY LAB
27. BIOPHYSICS LAB
28. PHYSIOLOGY LAB
29. PHYSICAL CHEMISTRY LAB
30. BALANCE ROOM
31. PHYSICAL INSTRUMENTS
32. RESEARCH FELLOWS
33. LIBRARY & SEMINAR ROOM
34. GENERAL OFFICE
35. DIRECTOR
36. STAFF ROOM
37. LABORATORY
38. RESEARCH FELLOW

FIRST FLOOR PLAN

RESEARCH CENTRE

SCALE 0 10 20 30 FEET

REPORT OF SCIENTIFIC INVESTIGATIONS

BLOOD COAGULATION

PROTHROMBIN ACCELERATOR DEFICIENCY ASSOCIATED WITH TUBERCULOSIS**

P. Fantl, R. J. Sawers and A. G. Marr.

Prothrombin accelerator is the name given to a plasma globulin which is essential for the conversion of prothrombin into thrombin under physiological conditions. A deficiency of prothrombin accelerator will result therefore in delay of blood coagulation and may give rise to a haemorrhagic tendency. Several workers have connected the haemorrhages occurring in tuberculosis with a derangement of the blood clotting process and it is often found that blood of tuberculous patients shows in certain tests an apparent reduction of prothrombin. With the newer knowledge of the complexity of the prothrombin system it was thought desirable to investigate the clotting defect in tuberculosis. An elderly woman who suffered from pulmonary and peritoneal tuberculosis was admitted to hospital because epistaxis and haematuria had resulted in severe blood loss. It was established that her haemorrhagic state was due to a severe deficiency of prothrombin accelerator, all other clotting factors being present in adequate concentration. The administration of Vitamin K_1 did not influence the deficiency and the only treatment which improved the haemorrhagic tendency was transfusion of fresh blood or fresh plasma. This had to be repeated frequently because of the high turnover rate of prothrombin accelerator. Also it was established that the deficiency was acquired late in life and was not a congenital abnormality.

As most of the clotting factors including prothrombin accelerator are produced by the liver it is remarkable that an extrahepatic disease should be associated with a pronounced deficiency of a hepatic product.

It seems possible that tuberculous lesions are more often associated with prothrombin accelerator deficiency than has hitherto been realised because none of the previous workers have established whether the clotting defect in tuberculosis is in fact due to hypoprothrombinaemia or to a deficiency of prothrombin accelerator.

DIFFERENT PROTHROMBOPLASTIN DEFICIENCIES IN RELATED MALE BLEEDERS**

P. Fantl, R. J. Sawers and H. Ward.

Haemorrhagic diseases connected with the plasma thromboplastin complex diagnosed as haemophilia can be due to deficiencies of either alpha- or beta-prothromboplastin. So far, these deficiences have been observed only as congenital abnormalities in both man and animals. When inheritance can be demonstrated, it has been in the sex-linked recessive manner. Further it has been shown that deficiency of alpha-prothromboplastin may be absolute or partial. Also, affected male relatives show, in laboratory tests, qualitatively the same defect and the same degree of deficiency.

**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.

During an investigation concerned with the distribution of congenital haemorrhagic diseases in the Victorian population the following unusual observations were made. Two male bleeders who are second cousins were examined. It was found that each of them had a complete deficiency of an essential blood clotting factor since their blood did not produce any thrombin at all. The addition of alpha-prothromboplastin (anti-haemophilic globulin) to the one patient's blood corrected the deficiency *in vitro*, but had no effect on the blood of the cousin. Further, the addition of beta-prothromboplastin had no effect on the first patient's blood but corrected the deficiency of his cousin. Finally, in contrast to the individual blood specimens, the mixture of the two deficient specimens produced an apparently normally clotting blood. A likely explanation for two closely related males suffering from unrelated and potentially inheritable diseases is the recent occurrence of mutations either in their mothers or in the foetal period of the patient.

QUANTITATIVE DETERMINATION OF BLOOD PROTHROMBOPLASTINS**:

P. Fantl, R. J. Sawers and H. Ward.

It is desirable that a laboratory diagnosis of any pathological condition should be quantitative as well as of qualitative nature. It is not only essential to know the nature of the defect but it is of value especially in the treatment of a condition to be able to determine the degree of the deficiency. Because haemorrhagic tendencies very often have to be diagnosed and treated as emergencies in hospitals where all laboratory facilities are not available, it is of great help to have tests available which give results without having to resort to elaborate and difficult technical procedures.

With these ideas in mind we have concentrated on the development of reactions which allow identification of the defect and its degree with a minimum of time and equipment. We consider that, after three years' experience with several hundred specimens, the determination of the rate and yield of formation of thrombin with properly taken venous blood will satisfy this demand.

It was reported last year that normal human blood contains approximately a fourfold excess of the two prothromboplastin precursors (alpha- and beta-prothromboplastin). A technique was developed which allows the quantitative determination of the amount of thrombin which is formed during incubation of diluted blood in the presence of pyrocatechol. With this test a quantitative relationship between thromboplastin deficiency and the ability to form thrombin was established. This test has been applied to male bleeders and also to female carriers of inheritable haemorrhagic diseases. In a series of patients suffering from classical haemophilia (alpha-prothromboplastin deficiency) it was noted that the abnormality ranged from a complete absence to a minor deficiency of the particular clotting factor. It was found in a high proportion of female carriers, who themselves show little or no haemorrhagic tendencies, that their blood prothromboplastin level was in the lower region of normal. The test is being used for diagnostic purposes and is applied during treatment of patients with blood and plasma products. We hope in this way not only to establish the most efficient but also the most economical way to diagnose and to treat bleeding tendencies classified clinically as haemophilia.

HAEMOPHILIA :

R. J. Sawers.

Previous reports indicate broadly the outline of the study being made into the problems of haemophilia. This report covers the results obtained by analysing some of the data collected during the past three years.

An important part in the investigation of haemophilia is the conduct of a survey to reveal all cases with the disease born in the State, but it has been difficult to ensure that the survey is as complete as possible. Metropolitan hospital records have supplied the starting point for tracing haemophilic families. Unfortunately no base hospitals in the country keep records which are indexed for the diagnosis, but the proportion of haemophilics traced in country areas is not much less than expected, probably because most cases are referred to a metropolitan hospital for diagnosis and treatment. No vital statistics relating to deaths from haemophilia are available before the year 1950, nor is any record of invalid pensions granted to haemophilics available.

It is believed that there are many cases of mild and very mild haemophilia in the community in which the diagnosis has not been made. Symptoms in such cases are atypical, for they may not suffer joint haemorrhages, and if tested by ordinary laboratory methods, normal results are obtained. The total number of such cannot be estimated.

Records of many pedigrees are available in which however no living haemophilic member is surviving. In such cases, the diagnosis is in some doubt. so that only cases who have a good clinical description of the symptoms recorded and/or have evidence of inheritance in the sex-linked recessive manner can be included in the series.

Finally a number of cases cannot be traced, or are unwilling to provide information or to have investigations performed. A few cases only are awaiting study.

(a) Population Statistics:

With the data obtained, the observed incidence at birth during the past five decades is 1 haemophilic in every 6,600 males born. The most thoroughly studied decade (1940-9) revealed 38 cases with a birth incidence of 1 in 5,500 males.

This is an appreciably higher incidence than found in any previous survey. The previous highest estimated birth incidence was 1 in 7,800 males, in Denmark.

The incidence of living cases is very much higher than previously recorded. Eighty-three cases have been studied, and together with other known cases, it is believed at least 120 cases are living. This gives an incidence of 1 in 10,000 males, which is more than double the highest incidence recorded in Denmark and five times the estimate for Great Britain.

Because of these high estimates for incidence at birth and in living males it is thought that the present survey is more complete than previous ones. This is largely due to the use of newly developed laboratory techniques. An example of the value of these tests is provided by a young man with a mild bleeding state whom we first investigated in 1952. At that time tests revealed no evidence to support a diagnosis of haemophilia. Review of the case this year showed quite easily that he does in fact suffer from a moderate grade of alpha-haemophilia. An alernative interpretation of the high incidence is that haemophilia occurs

more commonly in this country than elsewhere, but as no comparable survey has been reported, no opinion regarding this can be given.

(b) Genetics:

In view of the satisfactory progress with the survey, a review of the methods used to determine mutation rates was carried out. Criticism of methods used to determine the birth incidence and the "reproductive fitness" of haemophilics has been made. Instead of estimating the birth incidence by using indirect methods, direct observations of the birth incidence should be used. "Reproductive fitness" refers to the relative reproductive ability of the haemophilic commnnity as compared with their normal brothers. A "counting heads" method has been used but this is not considered to be as reliable as a method developed which can be called "age at death" method. Statistical data derived from Commonwealth Census reports indicates that this method has disadvantages but in spite of this, it appears to be reliable when dealing with relatively small numbers of pedigrees.

Using the results obtained for both the birth incidence and "reproductive fitness" for the different grades of alpha-haemophilia and for beta-haemophilia, mutation rates have been estimated. The overall mutation rate to haemophilia is somewhat higher than previous estimates.

The individual estimates of the mean mutation rates to complete, and to partial, deficiency alpha-haemophilia and to beta-haemophilia indicate that new pedigrees should appear in the ratios of 66:20:14. The observed ratios during the past two decades closely approximate these figures.

The high proportion of cases of complete deficiency alpha-haemophilia without a family history of the disease suggested the necessity for determining whether the pedigrees collected contained enough detail to reasonably exclude the chance non-appearance of the disease in male members in recent generations. Assistance was sought from the Department of Statistics, University of Melbourne, and a method for analysis of pedigrees has been developed. Its main value lies in determining the most likely place in the pedigrees at which mutation has occurred. Upon this finding advice upon eugenic problems can be planned. The method can be applied also to large numbers of pedigrees to determine other genetic data.

Review of several "new" pedigrees indicates that it is most unlikely that chance non-appearance of the disease in recent generations has occurred in these. This observation gives valuable support to the concept of the occurrence of recent mutations and therefore for the theoretical considerations which have lead to the development of formulae for estimating mutation rates in man.

(c) Clinical Studies:

These studies have been limited to the observation of patients with haemorrhagic episodes and those in need of surgical operations. Study of the concentration and survival of coagulation factors transfused in blood and plasma has been continued. It is evident both clinically and from laboratory study that complete correction of a severe deficiency is not possible with transfusion of unconcentrated plasma unless special methods are used. In spite of this a number of minor procedures such as tooth extraction have been safely carried out. No cases requiring major surgery were encountered during the year.

No progress has been made in developing methods for the detection of female carriers of haemophilia.

(d) Social Studies:

Social problems concerning both parents and sufferer connected with haemophilia are being observed. A few of the problems are peculiar to haemophilia while others are shared with other diseases causing physical handicap. In conjunction with the hospital almoner and the Haemophilia Society, families have been advised on methods of education, suitable types of employment, and eugenic problems.

CONTROL OF BODY FLUID VOLUME**

GENERAL STUDY

T. E. Lowe.

During the past six years the relationship existing between the intake and output of fluid from the body and the volume of fluid stored in the body have been studied in patients suffering from conditions in which fluid storage is abnormal. Most of these patients have been oedematous from cardiac failure or renal disease but some have suffered from endocrine disturbances or hypertension without frank cardiac involvement and in still others the effect of various drugs which influence fluid balance has been observed.

From these observations it is clear that certain well defined and reproducible behaviour patterns exist and that these patterns are influenced by factors such as circulatory efficiency, renal function and the forces governing fluid partition within the body.

As a basis for integrating these observations of the control of body fluid volume it is considered that the storage of fluid within the body can be represented as an "open" or continuous flow system. In such a system there would be continuous inflow and outflow of fluid and if the levels of inflow and outflow are dependent in a reciprocal manner on the volume of storage then the system would be selfregulating with regard to volume. If more than one property of the stored fluid influences inflow and outflow the system will still be self-regulating with regard to volume but the flow/volume relationships will be more complex. In addition should one or more of these "controlling" properties be itself dependent on another open system then both systems must be considered together.

To study the implications of this hypothesis several hydraulic models have been made, as previously described, and the behaviour of the model compared with clinical observations. From this study it has become clear that in a complex compartmented fluid storage, such as exists in the body, a transport mechanism is necessary to link the points of inflow and outflow of the system and to connect the various compartments. The outflow mechanism therefore consists not only of the kidney but also includes the circulation.

To represent the relationship between inflow, outflow, volume and "osmotic pressure" in the model, three-dimensional graphs are necessary. For simplicity it was assumed that these relationships were linear. The relationships were then used to predict clinical behaviour under various specified circumstances and good approximation was obtained between predicted and observed results.

As it was considered that linear relationships probably did not exist in the intact individual the relationships between inflow and volume, and between outflow and volume were determined in patients. The results indicated that when outflow was plotted against volume a sigmoid curve probably represented the relationship but that the central portion of this curve was virtually linear. The relationship between inflow and volume could not however be so clearly defined but it seems probable that it also gives an approximately linear relationship in the midportion of the curve. In the normal individual these curves intersect at normal volume but are very steep in the linear part. This means that large changes of inflow and outflow can occur with very small volume change. In disease states however the slope of the outflow/volume relationship is less and further the whole relationship is frequently depressed. This means that the volume of fluid stored increases (oedema) and control of it becomes broad.

Study of various abnormal states in patients showed that the outflow/volume relationship often changed in a discontinuous manner, being suddenly elevated or suppressed. In many cases these sudden changes could be related to therapeutic procedures; thus, the administration of mercurial diuretics, cardiac drugs such as digitalis and ouabaine, and in one patient aspiration of a haemopericardium, elevated or depressed the relationship, whereas cortisone and phenylbutazone depressed the relationship except in cases of cortisone administered in Addison's disease in which it elevated a depressed function. Hypotensive drugs in some patients depressed the outflow function. In other patients recovering naturally from congestive cardiac failure there were often several steps of improvement noted in outflow function. Sometimes the steps were sudden the change being complete within one day, in others several days were needed for the change from one level of function to another.

It is hoped that this outflow/volume relationship will prove a valuable tool in studying the multitude of factors which may be concerned in the control of body fluid volume. In our studies it has indicated that there are several factors operating to produce oedema in many cases of cardiac failure and that these may return to normal one by one. Probably also it can be used to study the efficacy of various diuretic agents.

As a result of the good agreement found between the results predicted by the hypothesis and those obtained clinically it is considered that the hypothesis concerning the regulations of body fluid volume is useful in that it integrates a large number of uncollated facts and points the way to further investigation. So far it has been necessary to postulate two properties of the stored fluid as having a controlling action in the system. These have been tentatively taken to be the "volume" and "osmotic pressure" of some part of the stored fluid. The observations so far made support the view that "volume" has an important controlling influence. Future work will be directed to testing the validity of the assumption that "osmotic pressure" is the equally important second controlling property. Another line of study will be an endeavour to identify the various factors which are operative in producing abnormalities in the storage mechanism.

ANIMAL STUDIES

W. A. St. Clair and J. C. McNeur.

Observation of patients with a variety of disease states has demonstrated the presence of slow cyclical changes in the state of the fluid balance, in addition to the well-known diurnal fluctuations. These changes are often seen in relation to some disturbance experienced by the individual—such as therapeutically induced diuresis, dehydration and surgical operation, to mention only a few.

Previous work has shown that similar disturbances can readily be produced in normal rabbits by a variety of agents. It was the object this year to collect some observations concerning the effects of specific surgical trauma on fluid balance in normal rabbits.

The procedure selected consisted in fracturing a femur under general anaesthesia and securing immobilization by intra-medullary wiring. This operation has the virtue of being remote from the abdominal cavity and so is less likely to interfere with the processes of fluid intake. Anaesthesia was obtained with intraperitoneal nembutal (75 mg/kg) supplemented with 1% procaine locally. A control series of animals was observed to determine the effects of these agents alone on the control of fluid volume.

The animals employed were male rabbits ranging in weight from 2.0 to 2.5 kilograms. Studies of daily weight change, food consumption and fluid intake and output were made for a week before surgical interference, and continued until the normal pattern of fluid balance was resumed.

Two kinds of disturbance in control of fluid volume were seen. In the first type an increased amplitude of the fluctuations in fluid balance occurred, the rhythm remaining diurnal. Each behaviour seldom lasted longer than three to four days.

In the second type, in addition to the diurnal rhythm (which might or might not show an increase in amplitude), typical, long, slow oscillations were seen, which often lasted for two to three weeks. When expressed as three-day running averages the results exhibited alternating smooth rises and falls about the zero line, each of which might last as long as 3-4 days. These oscillations showed a decreasing amplitude with time.

Usually anaesthesia provoked a change in fluid balance of the first type, although on occasions the second type was seen. Surgical trauma usually produced the second type of behaviour (in five animals out of six). Generalization is difficult, in view of the extreme individuality of the response, but it appears that the prolonged cyclical type of behaviour is more likely to follow more major interference.

The reproducible nature of these findings and their close resemblance to the patterns seen in patients under similar circumstances lends support to the view that these oscillations represent characteristics of the fluid regulating mechanism which are thrown into prominence under conditions of stress.

HYPERTENSIVE STATES

CLINICAL TRIAL OF HYPOTENSIVE DRUGS

A. J. Barnett and C. Crittle.

(a) Ganglionic Blocking Agents in Severe Hypertension:

The trial, commenced over five years ago, of the effect of treatment with ganglionic blocking agents on the symptoms and course of severe arterial hypertension has continued. No new drugs have been used in the past twelve months and the ganglionic blocking agent used most commonly is penta-pyrrolidinium ("Ansolysen," M & B) given either by injection or orally. In some instances, reserpine ("Serpasil," Ciba)† is used in combination with the "Ansolysen."

The number of patients who have commenced treatment is now 80, many of whom have been followed for more than two years and some for approximately five years. A few patients have ceased attending and have been lost sight of and a few have been treated for less than six months. We have reasonably adequate records of 67 patients who have been followed until the time of their death (21 patients) or for more than six months. The records of these patients are at present being analysed to discover the effectiveness of the treatment, both in controlling hypertension and relieving its symptoms on the one hand and increasing the patient's life expectancy on the other. The results confirm the previous impressions that in many cases definite lowering of blood pressure and symptomatic relief is obtained from the treatment. Best results are obtained from the use of "Ansolysen" (by injection or orally) together with "Serpasil." The uncertain prognosis of most cases of hypertension in respect to life expectancy makes it difficult to judge the effect of treatment on survival in hypertensive patients generally. Some 25 per cent. of the patients originally accepted for the trial have died, but they were patients with severe hypertensive disease.

There is one type of hypertensive disease in which the prognosis is fairly well established. Most patients with hypertension in the malignant phase (that is, with papilloedema) die within twelve months from the time this condition is diagnosed and practically all within two years. Of the 33 patients presenting in this phase 23 have survived more than one year and 13 more than two years and 9 more than three years, which is much better than would be expected without treatment. This provides evidence that treatment with ganglionic blocking agents increases the survival time in patients in the malignant phase of hypertension. Some of the patients who died in the early phase of the trial were treated by preparations inferior to those available at present. It would appear that better results than indicated by our figures may be expected in the future.

(b) Reserpine in Benign Hypertension:

A. J. Barnett and M. Down.

The trial of treatment of patients suffering from benign hypertension with reserpine ("Serpasil," Ciba) and of reserpine together with hydrallazine ("Apresoline," (Ciba) has been continued. It was intended that each patient should receive a period of treatment with (a) a placebo, (b) "Serpasil" and (c) "Serpasil" plus "Apresoline," the order of treatment being randomized, with four replications of the six possible orders of sequence of treatment.

†"Serpasil" used in this study was supplied by courtesy of Ciba, Ltd.

Unfortunately, because some patients became normotensive simply with preliminary observation, some patients remained normotensive following one course of treatment, and some patients were unable to complete the three courses, the original plan has not been fully adhered to. Eleven patients have completed the three courses of treatment and seven a course with an active agent and one with placebo. The results show that of the 24 courses of placebo alone, significant lowering of blood pressure (reduction of diastolic blood pressure by 20 mm Hg or more) ocurred in 6, of the 17 courses of "Serpasil" alone, such reduction occurred in 12 cases, and of the 13 courses of "Serpasil" plus "Apresoline" in 10.

Administration of "Serpasil" was often followed by relief of headache. The main side effects were lethargy and gain in weight (apparently due to both fluid retension and deposition of fat); these occurred to some extent in almost all cases.

HYPOTENSIVE STATES

EFFECT OF IMMERSION IN WATER ON BLOOD PRESSURE

A. J. Barnett.

During investigations on the effect of immersion in water on the blood pressure of patients with orthostatic hypotension, the rather surprising observation was made that in two normal subjects used as controls, the blood pressure fell with immersion (in contrast to the patients, in whom it rose). This observation has been confirmed using a larger series of subjects. The fall in blood pressure increases with depth of immersion (up to level of the heart). It does not appear to depend on the differences in temperature between the water and the air, occurring to approximately the same degree with various temperature differences.

DISEASES OF THE PERIPHERAL BLOOD VESSELS

INTERMITTENT CLAUDICATION:

A. J. Barnett and W. A. St. Clair.

Plethysmographic Studies:

New equipment was developed this year which enables the effects of standard exercise on calf blood flow to be recorded. A disadvantage of previous "standard-exercise" apparatus lay in the fact that the work done could be varied by the amount of force applied to the foot piece by the subject. Studies to date on claudicant patients, with this apparatus, have revealed no substantial difference from the blood flow patterns found in "normals."

Natural History of Claudication:

Further studies of the natural history of claudication have been made. A group of twenty patients has been observed at regular intervals and their performance in a standard step-test recorded.

The influence of prolonged dosage of an oral vasodilator has been studied and compared with periods of placebo or observation alone. In only one instance out of 14 subjects did an oral vasodilator appear to be related to considerable improvement in claudication, although other ischaemic symptoms such as nocturnal cramp and cold feet were often relieved.

An analysis of the clinical features presented by 125 claudicant patients seen in the last five years is being made. The study will attempt to relate such features as the peripheral pulse findings, site of claudication, arteriographic findings and the association of other features of occlusive arterial disease.

In this series males predominated in the proportion of 5 : 1. The highest age incidence was between 40 and 70 years. Atherosclerosis was the commonest cause of claudication and about one-fifth of the patients had evidence of cerebral or cardiac vascular disease. Claudication was bilateral in 50 per cent. of cases.

Pulse findings usually indicate, and arteriography usually shows, a block in a large vessel which is most frequently in the superficial femoral or upper part of the popliteal artery. There is usually a patent large vessel below the block and the origins of the tibial arteries are usually patent. The severity of atheroma often decreases with descent of the vessel from the superficial femoral to the lower part of the popliteal.

ARTERIAL GRAFTING:

A. J. Barnett and K. N. Morris.†

Arterial grafting has been performed on 15 of our patients and good results obtained in patients with intermittent claudication. The longest period a graft has remained patent is now two years. The technique has been modified so that the blocked segment of artery is not removed, but is by-passed by the graft without destroying collateral vessels. Also the wound is closed immediately after operation with less resulting discomfort to the patient. Because of these modifications it is now considered justifiable to try the effect of the procedure on patients who would previously not have been considered suitable. These are elderly patients, often in poor general condition and with poor vessels, but in whom amputation appears inevitable without grafting. It is considered that with grafting there may be a chance of saving the limb, and that with the new method, even if the graft is unsuccessful little harm will be done to the patient in the form of discomfort or interference with collateral vessels.

THE EFFECTS OF SYMPATHECTOMY ON FOOT BLOOD FLOW:

W. A. St. Clair.

This year particular attention has been directed towards the long term effects of sympathectomy on the circulation in the lower limb. While the increase in blood flow immediately after sympathectomy is well-known, precise information is lacking as to the permanency of this effect. The answer to this problem is of importance to the surgeon confronted with a patient who has good life expectancy and moderate symptoms of distal ischaemia. Is it justifiable to perform a sympathectomy if it seems likely that its effects will be wearing off at a time when the obliterative arterial disease may well be more advanced?

Since March 1955 studies have been made of the blood flow in the feet in a series of patients who have undergone lumbar sympathectomy for reasons other than occlusive arterial disease. (The most common indications for sympathectomy in this group were Raynaud's disease and ischaemia following old poliomyelitis.) Results have been compared with those obtained from "normals" of the same sex and age group.

†Thoracic-Surgical Unit, Alfred Hospital.

The method employed has been venous occlusion plethysmography, using optical recording. Under standard conditions, observations have been made of the "resting" blood flow, the peak flow during reactive hyperaemia and the time for the flow to return to normal.

	Mean Values from "Normals" 14 Subjects	Mean Values from Sympathectomised Series
Resting Flow:	1.3 cc/min per 100 cc	4.8 cc/min per 100 cc
Maximum Flow:	6.5 cc/min per 100 cc	8.9 cc/min per 100 cc
Resting Flow as Per Cent. of Maximum Flow:	19.9%	56%

The maximum flow during reactive hyperaemia has been assumed to be the maximum of which the vessel is capable. Expressing the resting flow as a percentage of the maximum flow therefore affords an idea of the degree of denervation of the blood vessels—the higher values being indicative of the more complete loss of tone.

In the sympathectomy group the time since operation ranged from ten months to more than twenty years. In this group the resting flows, but for one case, were well above the mean value for the "normals." Although studies are not yet complete, it appears that in many instances the effects of denervation persist for many years. For example, in one woman aged 67 years, the resting flow was 74% of the maximum value *twenty years after sympathectomy* while in another woman aged 40, twelve years after operation the index was 70%. The lowest values obtained were 8% and 18%, operations having been performed eleven and nine years ago respectively.

SCLERODERMA WITH VASCULAR DISTURBANCE:

C. Crittle and A. J. Barnett.

In addition to sclerodermatous changes following a long history of Raynaud's disease in the hands, scleroderma may occur soon after or concurrently with the occurrence of Raynaud's phenomenon. Fourteen cases have been studied in which scleroderma has been early or has spread beyond the region affected by the Raynaud's phenomenon. These cases may be conveniently classified into local and diffuse. A subgroup of the latter is systemic sclerosis in which there is involvement of internal organs. The vascular lesions associated with scleroderma have been studied by digital vascular tests (including the reactive hyperaemia test of Lewis), estimation of blood flow from heat elimination (calorimetry) and by arteriography. In practically all cases, there is structural narrowing of digital vessels indicated by a low heat elimination, even after reflex hyperaemia, and delayed reactive hyperaemia of the finger tips after arterial occlusion. Some patients have also had evidence of structural occlusion of large arteries.

An attempt was made to investigate the hypothesis that there is a personality ("psycho-somatic") factor in scleroderma. Our investigation failed to establish this hypothesis because (a) by psychological testing not only the patients with scleroderma but also all the control group of patients (from a skin clinic) were found to be psychologically disturbed, and (b) there was a low level of concordance between the assessments of a particular patient made by different psychiatrists.

THE PHARMACOLOGY OF ADRENALINE AND NORADRENALINE**

G. A. Bentley.

Research into the pharmacology of adrenaline and noradrenaline has proceeded on two lines, (i) studies on the mechanism of the inhibitory effect of these hormones on isolated rabbit intestine and (ii) an attempt to develop a fluorimetric method for assaying noradrenaline in urine.

INHIBITORY EFFECTS OF ADRENALINE:

The preliminary experiments in the last report have been extended in the following manner.

(a) The ability of various carbohydrate metabolites to support the beat of a piece of perfused rabbit intestine in the absence of glucose was investigated. The effect of adrenaline and noradrenaline under these conditions was then tested. It was found that lactate, pyruvate and to a lesser extent acetate, could support the beat, but that citrate, succinate, B-glycerophosphate, and glycerol could not. In acetate, lactate and pyruvate, the intestine's response to adrenaline and noradrenaline was quantitatively and qualitatively similar to that in glucose. Glycogen estimations showed that intestines perfused with acetate, lactate, or pyruvate could resynthesise glycogen depleted by a preliminary perfusion with Tyrode solution lacking glucose. Attempts were made to block this resynthesis of glycogen from acetate, lactate and pyruvate by perfusion with fluoride, azide, malonate and phlorrhidzin in the hope that the intestine would gain its energy for beatiug by the direct oxidation of the carbohydrate intermediates. Unfortunately, all the means of blocking this resynthesis which were tried also blocked the recovery of the beat. Hence it has not been possible to test the response to adrenaline and noradrenaline of intestine whose beat was supported solely by the oxidation of acetate, lactate or pyruvate.

(b) The effect of adrenaline on the production of lactic acid in perfused, isolated rabbit intestine.

Lactic acid determinations were carried out by the method of Barker and Summerson (1932). The pieces of intestine were removed from the perfusion bath, and rapidly ground up in sand and 10 % phosphotungstic acid. Estimations of lactic acid were then carried out ou the supernatant of this extract. Recovery of small amounts (20 micrograms) of added lactate was checked, and found to be of the order of 85%. To test the effect of adrenaline on the lactate production of perfused intestine, adjacent pieces (2-4 cm in length) were weighed and suspended in an oxygenated organ bath at 37° C. After a standard period of equilibration, they were removed and assayed as above. These constituted the control experiments. Alternate pieces of the same intestine were suspended as above, and after several "priming" doses of adrenaline a "test" dose was given, sufficient to produce complete inhibition of the beat. During the period of inhibition, the piece of intestine was removed and assayed. A minimum of four pieces was taken from each intestine. In a series of eight experiments, no significant difference was noted in the lactate content of the control and the adrenaline-treated intestine. This is in direct conflict with the results of Mohme-Lundholm (1953) who obtained increases in the lactate content of up to 50% of the basal level. However, it is felt that the method of assay used in this series of experiments was more accurate than that used by the above author, and that the method of extraction permitted a much more rapid precipitation of the tissue proteins. Further, the doses of adrenaline used were smaller than those of Mohme-Lundholm, although they caused complete inhibition of the intestine's beat.

Similar experiments were also run in the presence of phlorrhidzin 1:10,000 (a drug which inhibits hexokinase and other enzymes involved in carbohydrate breakdown) and of dinitrophenol 1:2,000,000. This compound markedly increases the lactate content of most tissues. The highest concentration which it was possible to add to the intestine without abolishing the beat was 1:200,000. Again, it was found that completely inhibitory doses of adrenaline had no effect on the lactate content of the intestine.

Hence, it must be concluded that Mohme-Lundholm's results do not explain the inhibitory action of adrenaline. It would seem that the high lactate content found by Mohme-Lundholm is a secondary effect, and is not the cause of the inhibitory effect of adreualine.

FLUORIMETRIC ASSAY OF NORADRENALINE IN URINE:

The fluorimetric methods which are available for pressor amine assay are all more sensitive for adrenaline than for noradrenaline. Since the principle pressor amine in urine is noradrenaline, it seemed important to develop an assay which was more sensitive to noradrenaline than to adrenaline. Previously a modification of Lund's method had been developed which was particularly sensitive to noradrenaline. This method was investigated and applied to uriue extracts.

The conditions for optimal fluorescence were first studied, using pure solutions of adrenaline and noradrenaline. The volumes were adjusted to suit the Uvispec fluorimeter.

The pressor amines, dissolved iu M/1 phosphate buffer, pH 3.0 or pH 4.5, are oxidised for two minutes with 1.0 g manganese dioxide, in the presence of ascorbic acid 1:1,000. The suspension is filtered after two minutes, and 10 ml M/2 potassium tetraborate is added, with 2.5 mg. ascorbic acid, and the volume is made to 25 ml with water. The fluorescence reaches a maximum after 45 minutes then slowly decays. The intensity of the peak fluorescence is dependent on the following variables—(i) molarity of the phosphate buffer (ii) pH of the buffer (iii) molarity of the borate (iv) coucentration of the ascorbic acid present during oxidation (v) concentration of ascorbic acid to the final solution. When all these variables are controlled, accurate results may be obtained. The method appears to be at least as sensitive as Lund's method.

However, when the method is used to estimate the noradrenaline content of urine extracts, high results are obtained. Simultaneous biological assays have given results from 6 to 10 times lower than when the fluorimetric assay is used. Various attempts were made to eliminate this interference. These include (i) preliminary treatment of the urine at pH 4.5 with aluminium hydroxide and with alumina followed by the normal extraction with alumina at pH 8.4; (ii) preliminary extraction with zinc hydroxide and zinc oxide at pH 4.5; (iii) extraction with zinc oxide or hydroxide at pH 8.4.

None of these methods reduced the interference.

However, it was discovered that, when oxidised at pH 3.0, neither adrenaline nor noradrenaline produced any fluorescence, while an extract of urine did fluoresce. It is not known yet whether oxidation at pH 3.0 will provide a satisfactory "blank," enabling a true estimate of the urinary pressor amine content to be made.

It has also been discovered that addition of excess ascorbic acid after the oxidation at pH 4.5 will completely suppress the fluorescence of noradrenaline without affecting that of adrenaline.

THE HEART'S ELECTRICAL ACTIVITY

VECTORELECTROCARDIOGRAPHY

Myocardial Infarction**

T. E. Lowe and J. M. Gardiner.†

This year further data have been collected towards an assessment of the clinical value of this technique, and in particular the electrical changes produced by myocardial infarction have been analysed.

The changes characteristic of myocardial infarction as portrayed by the VCG may be summarised—

In the majority of cases of infarction examined clear cut changes are present in the QRS and T loops and in those examined serially there has been a definite evolution of pattern.

The most usual change is a displacement of a part of the QRS loop, JT segment and the T loop away from the area of infarction. This is particularly so with the initial part of the QRS.

Fairly good correlation has been noticed between VCG and ECG patterns and the morbid anatomical changes when available.

The agreement is better with posterior infarcts than anterior, and this is thought to be due to the fact that precordial ECG leads exaggerate changes in the anterior heart because of their close proximity to the electrode. This may be of value for diagnosis but it does raise a doubt about the value of the precordial leads in attempting an anatomical localisation.

Experience of the technique in general is leading to the conclusion that it has a definite place in the investigation of cardiac disease. It is of no value in the elucidation of abnormal rhythms and because of technical difficulties it is difficult to use for very sick patients, However, the VCG gives a very good representation of the QRS part of the complex and is of value in cases of ventricular hypertrophy, bundle branch block and myocardial infarction.

The angle in space between the QRS and T activity is easily seen and is possibly of significance. Displacements of ST segments are not so clearly visualised in the VCG as the ECG.

Ventricular Complex

C. J. McRae.

A survey of the appearances of the ventricular loop in a series of 400 consecutive VCGs is being made. The loop can be arbitrarily divided into four parts, the initial crochet, the centrifugal limb, the centripetal limb and the "run-in." The tracings have been grouped according to the VCG diagnosis and each part of the loop is being studied in detail to determine the significance of the variation from the normal seen in various conditions.

THE ELECTROCARDIOGRAM IN HYPOTHERMIA

Although ventricular fibrillation is one of the chief risks of hypothermia in both man and dogs, observation of the electrocardiogram at low body temperatures has seldom been reported in man, and in animals the recorded accounts are varied and confusing. The changes in the electrocardiogram during deliberate lowering of temperature have therefore been studied in man, in dogs and in the isolated toad atrium.

†Cardiovascular Diagnostic Service, Alfred Hospital.

Changes in Man:

D. Emslie-Smith.

An eight-lead electrocardiogram has been continuously observed during the production of hypothermia in six anaesthetised patients undergoing craniotomy. Permanent records were made from time to time.

In all cases the heart rate slowed, and PR and QTc lengthened. Consistent changes developed in ST and T in all cases, though differing in degree and in the temperature at which they appeared. In general these changes consisted either of a widening of the base of QRS, with or without the appearance of a ledge on the descending limb of R or the ascending limb of S, or else of a conspicuous, discrete slow deflection early in ST, but apparently separate from the QRS complex. This deflection was upward in leads related to the left ventricle, and downward in aVR. When it was of high altitude T became inverted.

Changes in Dogs:

D. Emslie-Smith, G. R. Stirling, and G. E. Sladden.†

The electrocardiogram of the dog is notoriously variable, but by using unipolar surface leads fairly consistent changes were found on cooling anaesthetised dogs. In lead aVF almost all dogs during cooling show one or more of three basic patterns. If T is upward a slow downward deflection appears soon after QRS, early in the ST segment, and grows in amplitude. If T is downward a similar deflection appears but is directed upward. If T is diphasic, downward and then upward, a diphasic deformity of the early part of the ST segment appears, first upward and then downward so that the whole ST-T segment contains four deflections.

Chest leads generally show T upright at normal temperatures, but at low temperatures a slow, upward deflection appears early in ST, and T is often downward.

Because of the variability in position of the dog's heart during cooling the epicardial electrogram has been studied with particular reference to the ST-T segment. At normal temperatures T is downward over the left ventricle and most of the right ventricle. Over the trabeculated area of the right ventricle, on the ventral surface, it is upright. Over the areas where T is downward ST is not iso-electric, but is elevated to form a more or less peaked, upward deflection immediately following, but more slowly inscribed than, QRS. On cooling, the upward deflection following QRS becomes wider, higher and more rounded, while T remains downward. Over the trabeculated area of the right ventricle there appears early in ST a similar slow deflection which is directed downward, while T remains upward. At low temperatures in electrograms from near the apex of the left ventricle the slow upward deflection becomes inverted.

The development of the two, oppositely directed, basic epicardial patterns appears to explain the changes seen during hypothermia in indirect surface leads. These surface leads reflect one or other basic pattern, or a combination of the two, depending on the relationship of the surface lead to the relevant part of the epicardium.

†Department of Anaesthesia and Resuscitation, Alfred Hospital.

The appearance and growth of the slow deflection early in ST is common to both man and dogs at low temperatures. Whatever the mechanism, it appears that the production of hypothermia alters the total unbalanced electrical activity of the myocardium during the repolarisation process.

Toad Atrium Preparation :

D. Emslie-Smith.

In order to find out whether the appearance, on cooling, of this slow deflection early in ST represents some intrinsic function of cardiac muscle, the effect of temperature upon the electrogram of isolated toad atrium is being investigated. Over the temperature range which is tolerated by the preparation cooling produces no alteration in the form of the SaTa segment. The duration of the spread of depolarisation, and the duration of the depolarised state both appear to lengthen in a manner consistent with the van't Hoff-Arrhenius equation which describes the kinetics of simple chemical reactions as a function of temperature.

STUDY OF CARDIAC VIBRATIONS*

VIBROCARDIOGRAPHY

M. Down.

In the last report the development of equipment to study cardiac vibrations both audible and inaudible was described and during the past year this equipment has been used to study the vibrations of the normal heart. Because the investigations include the inaudible low frequency vibrations this technique has been termed "vibrocardiography."

The vibrocardiograph differs from the phonocardiograph in that it records all vibrations associated with the heart's activity according to their respective physical energy content and this does not parallel auditory loudness. The instrument allows detailed study of vibrations in terms of energy content, intensity, duration and frequency of wave forms. A rapid recording method allows easy analysis of frequencies, which are divided in five bands, or channels, viz.,

Channel	I	0-50	cycles	per	second
,,	II	30-130	,,	,,	,,
,,	III	130-260	,,	,,	,,
,,	IV	260-400	,,	,,	,,
,,	V	480-1000	,,	,,	,,

Study of cardiac vibrations in this way, ignoring the arbitrary modifications of ear and stethoscope, should give information of a character different from that gained by standard phonocardiography or clinical ausculation.

To this end, during the past year, a series of tracings from 53 normal individuals has been made. Of these, 25 were males and 28 were females. Their ages ranged from 17 to 50 years, with only 5 cases over the age of 30 years. The criteria for normality were as follows: no past history of heart disease, normal cardiac function, no signs of abnormal auscultatory findings, heart size normal clinically, blood pressure within normal limits.

The normal vibrocardiogram displayed consistent findings with regard to general form. There were two dominant groups of vibrations—the first group (A) incident to the onset of systole, and the second group (B), incident to the second heart sound.

A. In the first vibration complex three groups of waves were recognizable:

(i) A group of preliminary waves, one or two in number were occasionally seen in the low frequency channel between the P and S deflections of the electrocardiogram. These were of lower amplitude than, and immediately preceded, the principal group of waves.

(ii) The principal vibration complex, the onset of which timed from the Q deflection of the electrocardiogram varied from 0.011 to 0.09 seconds, consisted of complex waves with frequencies varying between 30 and 80 cycles per second. The duration of these vibrations lay in the range of 0.10 to 0.26 seconds.

(iii) Often a third element named for convenience the fundamental vibration could be recognised within the principal vibration complex. This element arose coincidentally with the principal vibration but was of shorter duration, and was often accompanied by components in the higher frequency channels. These components were always pure tones and their onset was always coincident with this third element or fundamental vibration, and had frequencies which were multiples of the fundamental vibration. These components were considered to be harmonics of the fundamental vibration.

B. The second group of vibrations coincident with the second heart sound showed characteristics similar to the first vibration complex, with the exception that there were no preliminary waves. As with the first vibration complex harmonics were present in many cases. The onset of the second group of vibrations ranged from 0.29 to 0.46 seconds from the Q deflection of the electrocardiogram and the duration from 0.07 to 0.143 seconds. This complex was of shorter duration than the complex incident to the onset of systole.

The harmonics seen in association with the first and second vibration complexes may be repeated in the one complex, and where such duplication occurs, the frequency of the two components at the one area is the same in the great majority of cases. With increasing frequency there is always decreased intensity and duration of the components, and in individual channels the intensity and duration of each component may vary. The time separation between components varies from area to area, and may be negligible. On the other hand, time separations up to 0.1 second have been recorded.

In a few tracings some very low frequency, low amplitude vibrations of 5 to 8 cycles per second were seen to run through the entire tracing including the period between the two main vibration complexes.

The recordings suggest that there are four elements in both first and second heart sounds. Attention was drawn to this by Orias and Braun-Menendez (1939). In addition some of the tracings show another element associated with the first sound, viz., the preliminary wave.

Possible structural bases for the different types of vibrations recorded have been postulated, viz., the preliminary wave might be due to myocardial vibrations, auricular or ventricular, or due to vibrations of the auriculo-ventricular valves; the principal vibration complex may arise from myocardial vibrations *per se*, or from vibrations secondary to blood flow, or be contributed to by vibrations in the large arteries. The fundamental vibration and harmonics may be due to movements of the valve flaps.

Further studies are being undertaken to elucidate the origin of the vibrations discussed. Amongst these investigations are recordings of cardiac vibrations in patients with an accentuated first sound, e.g., mitral stenosis, and in patients with an accentuated second sound, e.g., hypertensive heart disease. The possible study of cardiac vibrations by direct application of the microphone to the myocardium of an experimental animal is being borne in mind.

ENERGY PRODUCTION IN THE MYOCARDIUM*

T. E. Lowe, G. A. Bentley, D. McKelvie, and W. G. Nayler.

The construction of the modified Warburg type apparatus in which the functioning of the intact spontaneously beating cold-blooded heart is being studied has been altered to improve the reliability of the carbon dioxide measurement and secondly so that the drug whose action is being investigated can be added to the heart without disturbing the thermal equilibrium of the system.

The reliability of the carbon dioxide measurement has been improved by the addition of an agitator in the absorbing potassium hydroxide solution. This was found to be necessary because of the formation of a surface layer of carbonate and also in order to obtain readings over intervals as short as 15 minutes. A strip of plastic coated iron is suspended into the potassium hydroxide by means of a piece of spring steel. This paddle is vibrated by an alternating current electromagnet outside the respiratory vessel.

Addition of a drug to the perfusate during the course of an experiment, without interrupting the continuous observations being made, is done by tilting a small perspex cup mounted above the inflow reservoir of the circulation system. This cup can be tipped over to expel its contents into the reservoir by turning a spindle sealed through the wall of the respiratory chamber with a rubber gland. The drug is placed in the perspex cup at the beginning of the experiment.

CARDIAC EFFICIENCY :

A series of control experiments under standard conditions (at 25.0 ± .05°C and using standard toad Ringer perfusate) has been made. Oxygen uptake, carbon dioxide output, cardiac performance in terms of maximum aortic pressure, drops per beat, beats per min. and total number of drops have been recorded simultaneously. From these results the work done by the heart in such a system has been estimated and when correlated with the chemical energy utilised by the heart an index of the efficiency has been reached. With an oxygen uptake of 60 microlitres per min. per gm wet weight, the work done by such a heart is approximately 250 g cm per min and the efficiency 5-8%. Respiratory quotient values for the non-hibernating toad heart lie in the range of 0.90-0.98 indicating that carbohydrate is the main metabolic substrate under these conditions.

Whilst there is considerable variation between preparations, within the one preparation a relatively constant work output, oxygen uptake, respiratory quotient and efficiency has been recorded during 6 hours following pithing of the toad.

Since the basic physiological action of adrenaline and noradrenaline are not yet clear, there being much conflicting evidence relating to the action of these two closely related drugs upon cardiac output, a series of experiments has been made to investigate their action on the isolated spontaneously beating heart.

ACTION OF ADRENALINE :

Doses of 0.2μg and 0.05μg adrenaline have been added to the 5ml perfusate in the circulation system and the change in oxygen uptake, respiratory quotient and work output have been measured simultaneously. With both dosages an increase in work output and oxygen uptake has been repeatedly recorded immediately after the addition of the drug and extending for periods up to 30 minutes.

The respiratory quotient does not appear to change significantly. Thus, with a 90% increase in oxygen uptake following administration of 0.2 μg adrenaline the work output increased from 250 gm. cm. per min to 622 gm. cm. per min. This increase in work output is due to an increase in aortic pressure and increase in number of beats per min and not to any change in drops per beat. In some cases a fall in drops per beat was recorded. The rate of oxygen uptake returns to normal coincident with the return of cardiac output to the normal level. Since administration of adrenaline does not significantly alter the respiratory quotient this suggests that adrenaline acts upon the utilization of energy and not upon its generation. A small increase in efficiency of the heart has been estimated in all preparations following the administration of adrenaline.

ACTION OF NORADRENALINE :

A similar series of experiments in which noradrenaline has been added has been carried out. An increase in oxygen uptake coincident with an increase in work output has been recorded. Unlike adrenaline, noradrenaline produces only a small increase in number of beats per min but it does produce a significant increase in number of drops per beat. The efficiency of the heart following administration of noradrenaline at this dose level does not suggest any increase in efficiency.

OPEN INTRACARDIAC SURGERY

G. R. Stirling, G. E. Sladden† and D. Emslie-Smith.

The aim of the project has been to develop experimentally a safe technique for the surgery of intracardiac defects under vision with the chambers of the heart open. The work has been largely concerned with observations on dogs submitted to hypothermia with occlusion of the venae cavae and aorta during the period when the cavities of the heart were opened.

Hypothermia was induced in anaesthetised dogs by immersion in iced water or by the application of chipped ice in plastic packs to the skin. Shivering was readily controlled by pentobarbital or thiopentone anaesthesia or by the combined use of chlorpromazine, promethazine and pethidine—though there appeared to be no special virtue in the last more complex method. Controlled respiration with carbon dioxide absorption has been routinely used.

It has been confirmed that cooling to 25-28°C is attended by little risk and that cooling below these temperatures becomes progressively more hazardous —the development of ventricular fibrillation being increasingly more frequent and more difficult of reversal. With the fall in body temperature there is a steady fall in pulse rate. The blood pressure tends to remain constant at first but, as cooling continues beyond 32-30°C, there is a fall in blood pressure which becomes more severe the lower the temperature. Respiration slows in rate and decreases in amplitude with fall in body temperature. The electrocardiogram shows characteristic changes with falling temperature the most notable being the lengthening of the P-R, QRS and Q-T intervals and the development of changes in the S-T segment. The pH progressively falls in animals allowed to breathe spontaneously but, with vigorous hyperventilation and carbon dioxide absorption, the pH can be maintained at normal levels. Measurements of the pH, the plasma carbon dioxide and the alveolar carbon dioxide suggest that there are two factors in the acidosis of hypothermia unmodified by hyper-

†Department of Anaesthesia and Resuscitation, Alfred Hospital.

ventilation. The first factor is a respiratory one, due to carbon dioxide solubility in body fluids at low temperature, whilst the second factor is metabolic in nature: other workers have shown this to be associated with an increase in the blood lactic acid concentration.

Ventricular fibrillation, the major hazard in hypothermia, has been less common in dogs, which have been hyperventilated with carbon dioxide absorption. It may occur spontaneously at low temperature or it may be precipitated by anoxia, haemorrhage or by interference with the ventricles. It may be reverted by cardiac massage and electrical stimulation applied to the heart, but at temperatures below 28°C this has not been successful often enough in our hands.

It has been shown that at 28°C the circulation can be stopped for ten minutes by caval occlusion with a high survival rate and without obvious sequelae. However when open operations on the interatrial septum were performed during this period of caval occlusion it was found that the mortality rate was significantly higher, most of the animals dying in ventricular fibrillation which could not be reversed.

It was felt that the liability to ventricular fibrillation during the period of caval occlusion might be lessened if the heart were artificially arrested during the period of occlusion as, in this way, the myocardium would not be contracting in the absence of an adequate coronary blood flow. In this series of experiments dogs were cooled to 28°C, the cavae and aorta were occluded, and the heart was arrested by the injection of potassium chloride into the ventricles. Periods of cardiac standstill of 10 minutes duration with caval occlusion for a longer time were well tolerated. The heart was started again, after release of occlusion, by massage and, on occasion, the injection of calcium chloride solution. When ventricular fibrillation did occur under these circumstances it was readily reversed by electrical stimulation. With this combination of hypothermia, caval and aortic occlusion and cardiac arrest the heart is at rest and its chambers are dry so that the operating conditions allow unhurried and precise work to be carried out.

Although the results for creation and repair of interatrial defects by this technique were better than those using the earlier methods, in our hands the mortality is still prohibitively high.

HORMONE INDUCED EOSINOPENIA

Bryan Hudson.

Work during the past three years had not produced any conclusive evidence with regard to the nature of the eosinopenia that follows the administration of cortisone. The results of two series of experiments make it unlikely that either lysis of these cells by cortisone or sequestration within the reticulo-endothelial system are the mechanisms underlying this phenomenon.

During the past year a series of experiments has been performed in which the form of eosinophil disappearance curves following the administration of an active steroid have been studied. It was argued, *a priori*, that such curves, constructed by plotting the number of eosinophils against time, might show either an exponential or linear form. If the form was exponential this would seem to indicate that the cells disappeared from the circulation on the basis of concentration, that is, they underwent lysis or were redistributed into one or more internal organs. If however the rate of disappearance was linear in form, it would

be reasonable to suppose that the cells were disappearing from the circulation on the basis of their age, as is seen in the survival of normal red cells when transfused into a normal recipient.

If the eosinophils do disappear on the basis of age then it follows that the mechanism for their disappearance from the circulation depends upon an inhibition of production in the bone marrow. As a corollary, the point at which the cells have completely disappeared from the circulation will give an index of their life span.

The results of these experiments were such that in a series of sixteen patients, the "best fit" curves were linear in form. The common feature in all these curves was a steady state, reached between three and five hours, in which over 90% of the eosinophils had disappeared from the circulation.

It is concluded from these experiments that the mechanism of hormone induced eosinopenia is suppression of eosinophil production by the bone marrow and that the life cycle of the eosinophil is somewhere between three and five hours.

HORMONAL CONTROL OF PIGMENTATION**

Bryan Hudson.

During the past three years methods have been developed for the assay of melanophore expanding hormone. These methods have involved the use of intact and hypophysectomised toads and detect the presence of this hormone in concentrations of 3-4 microgram per ml of extract. By using this assay procedure a technique of extracting this hormone from blood has been established so that 85-90% of added hormone can be recovered from blood. When blood from normal persons and from patients suffering from Addison's disease was suitably extracted no response could be obtained in either intact or hypophysectomised animals. In view of the reports from Lerner and his colleagues that melanophoric activity could be demonstrated from normal blood and in the blood of patients suffering from Addison's disease by the use of isolated frog's skin, attempts have been made to modify local apparatus and Xenopus toads for this procedure. In the first instance an attempt was made to measure changes in the absorption of light through toad's skin when subjected to varying concentrations of melanophore hormone. For a variety of technical reasons this method proved to be a failure.

More recently the darkening of the skin that takes place with the addition of melanophore hormone has been measured by means of an EEL photoelectric reflectance meter. This method has greatly increased the sensitivity of the assay but at the same time there has been a considerable loss in precision. By this method doses of hormone as low as 0.06 microgram per ml can be measured when the skin from hypophysectomised toads is used. This represents an approximate 50 fold increase in sensitivity.

When this method is used it has been shown that normally melanophore hormone can be detected in the circulation in concentrations between 3-6 microgram per 100 ml blood. Blood taken from patients who had well marked evidence of pituitary failure (a patient with a pituitary tumour and another with post partum pituitary necrosis) showed very little melanophoric activity and it was estimated that the concentration of hormone was certainly less than 1 microgram per 100 ml. Both these patients showed striking pallor of the skin.

By contrast, blood from patients with untreated Addison's disease who manifested classical and well developed skin pigmentation contained melano-

phoric activity to excess. The concentration ranged between 10-16 microgram per 100 ml blood. When these patients were treated with cortisone the hormone concentration fell considerably within 48 hours of treatment, coming within the normal range of values.

Other observations of interest include the finding of a high value in a patient who was five months pregnant and who showed marked darkening of the nipples, and an elevated value in a patient with arthritis, who was receiving 6 g of salicyclate per day. This latter observation would tend to confirm the suggestion that one of the routes by which salicylates act is through the pituitary and adrenals in causing stimulation of the former.

These results would appear to confirm the hypothesis initially advanced at the commencement of this work, that there is a pituitary hormone which influences skin pigmentation in man and which is produced in excessive amounts in patients suffering from Addison's disease.

ENDOCRINE DISTURBANCES

Iu the diagnosis and management of endocrine disorders it is desirable to assay the activity of the glands concerned. To this end several techniques are being investigated and established on a routine basis for clinical use.

11, 17 HYDROXYSTEROIDS IN PLASMA AND URINE

Bryan Hudson.

During the past two years methods have been established for the rapid determination of cortisone and cortisone-like steroids in the plasma and urine. The methods have now reached the stage where several such determinations can be performed in a working day, whereas previously they had been long and tedious. Already such methods have been of value in aiding the diagnosis of certain adrenocortical disorders.

RADIO-ISOTOPES AND THE DIAGNOSIS AND TREATMENT OF THYROID DISORDERS

Bryan Hudson.

In the past six months the necessary equipment for the measurement of radio-iodine uptake and plasma protein-bound-radio-iodine activity have been installed. The various physical characteristics of these instruments have been established and patients with certain thyroid disorders have been investigated and treated.

THE ASSAY OF PITUITARY GONADOTROPHINS

E. L. G. Beavis.

Gonadotrophic hormones are derived from two sources. The assay of those which are placental in origin is a standard and routine laboratory procedure but the assay of pituitary gonadotrophins is very much more difficult. This is due to the relatively minute amounts present, even in specimens of urine obtained from patients in whom the pituitary output is high, and because of the more complicated methods necessary to assess the amount of activity present in any given extract of urine.

During the past twelve months efforts have been made to establish an assay method for pituitary gonadotrophins for the purpose of investigating patients suffering from disorders involving the pituitary and gonads, between which a reciprocal relationship normally exists.

The procedure of extracting the urine has been standardised, and appears to be satisfactory. However the problems involved in estimating the activity of any given extract, within reasonable limits, have so far not been satisfactorily overcome. The chosen index of response is the weight of the uterus of immature female mice, which themselves must be within a limited range of age and weight. It has been difficult to date to obtain an adequate supply of these animals. Within the limitations thus imposed, a small nnmber of patients has been investigated. One patient of particular interest was a young apparently female person, suffering from gonadal agenesis, in whom the excretion of pitnitary gonadotrophins was shown to be high. This information was of considerable clinical importance in establishing the exact nature of the variation from the normal gonad pattern in this case.

ABNORMAL SERUM PROTEINS

C. C. Curtain.

As abnormal proteins appear in the serum in a variety of diseases, techniques for their investigation have been established. Experiments have been carried out with electrophoresis-convection and with zone electrophoresis, using paper, starch gels and sucrose density gradients as stabilising media in order to determine the best ways of using these techniques to study dysproteinaemias. Immunological and histochemical techniques are also being developed as part of the study of the mode and site of synthesis of abnormal serum proteins.

As part of this study the abnormal serum protein fonnd in a patient with cryoglobulinaemia was characterised. This protein was precipitated at temperatures below 28°C and above 42°C.

PUBLICATIONS DURING 1955

T. E. Lowe: "BIFID CARDIAC APEX: A RARE CONGENITAL ANOMALY," *Alfred Hospital Clinical Reports,* Vol. 5 (1955), p. 93.

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P. Fantl: "THROMBIN FORMATION AND YIELD IN SHED BLOOD IN RELATION TO THROMBOPLASTINS AND PROTHROMBOPLASTINS," *Aust. J. exp. Biol. & Med. Sci.,* Vol. 32 (1954), p. 853.

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P. Fantl and R. J. Sawers: "HAEMORRHAGIC DISEASES: THEIR DETECTION AND MANAGEMENT IN DENTAL SURGERY," *Aust. J. Dentistry,* Vol. 59 (1955), p. 327.

A. J. Barnett: "OCCLUSIVE ARTERIAL DISEASE OF THE HANDS," *Med. J. Aust.,* Vol. 1 (1955), p. 455.

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A. J. Barnett, M. Hamilton and H. B. Kay: "SEVERE ORTHOSTATIC HYPOTENSION," *A/sian Ann. Med.,* Vol. 4 (1955), p. 195.

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Bryan Hudson and G. A. Bentley: "MELANOPHORE-EXPANDING ACTIVITY OF HUMAN PITUITARY GLAND," *Lancet,* Vol. 1 (1955), p. 386.

M. Hamilton: "CARBOHYDRATE TOLERANCE OF PATIENTS WITH PERIPHERAL VASCULAR DISEASE," *Alfred Hospital Clinical Reports,* Vol. 5 (1955), p. 39.

M. Hamilton: "THE DIURETIC RESPONSE OF OEDEMATOUS PATIENTS TO A WATER LOAD," *Alfred Hospital Clinical Reports,* Vol. 5 (1955), p. 105.

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.,* Vol. 2 (1955), p. 93.

R. Fowler: "CONTROL OF BODY WATER CONTENT: A STUDY OF DAY-TO-DAY VARIATIONS IN HUMANS AND RABBITS," *A/sian Ann. Med.,* Vol. 4 (1955), p. 123.

R. Fowler: "AN UNEXPECTED SLOW PHASE IN THE EQUILIBRATION OF BODY WATER CONTENT," *A/sian Ann. Med.,* Vol. 4 (1955), p. 128.

R. Fowler and J. Upfill: "THE SODIUM THIOSULPHATE SPACE AS AN ESTIMATE OF EXTRACELLULAR FLUID VOLUME IN RABBITS," *Aust. J. exp. Biol. & Med. Sci.,* Vol. 33 (1955), p. 39.

B. McA. Sayers: "A SPATIAL MAGNITUDE ELECTROCARDIOGRAPH," *Amer. Heart J.,* Vol. 49 (1955), p. 336.

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

Revenue Account for the Year Ended 31st December, 1955

EXPENDITURE.				INCOME.					
Drugs	£264	3	6	Donations—					
Fuel and Lighting	191	17	8	Thomas Baker (Kodak), Alice Baker and Eleanor Shaw Benefactions	£10,450	0	0		
Instruments and Glassware	741	9	11	Mr. Edgar Rouse	91	0	0		
Insurance	318	13	2	Marian and E. H. Flack Trust	400	0	0		
Library Maintenance	560	17	6	Sir William Angliss	200	0	0		
Miscellaneous and Administration	270	2	11	George F. Little Trust	148	6	6		
Printing and Stationery	151	17	10		11,289	6	6		
Repairs and Renewals	134	16	7	Research Grant—Life Insurance Medical Research Fund of Australia and New Zealand—					
Salaries and Wages	13,565	4	11	Brought forward, 1/1/1955	£1,932	13	6		
Special Maintenance	721	6	7	1955 Grant Received during year	1,617	0	0		
Telephone	124	10	11		3,549	13	6		
Sundries	639	19	4	Less Balance carried forward 31/12/1955	2,178	12	9		
					1,371	0	9	12,660	7	3
				Government Grants—						
				National Health and Medical Research Council				3,078	12	10
				Interest from Investments—						
				Trustees of the Thomas Baker Estate—Commonwealth Government Inscribed Stock held for the benefit of the Institute	551	10	0			
				Endowment Investments—						
				Australian Commonwealth Government Inscribed Stock	178	2	6			
				Australian Consolidated Treasury Bonds	16	5	0			
				Grain Elevators Board Inscribed Stock	103	2	6			
								849	0	0
				Sundry Sales				119	15	0
				Deficit for Year				977	5	9
	£17,685	0	10					£17,685	0	10

Spectator Publishing Co. Pty. Ltd., 134a Little Collins Street, Melbourne, C.1.

"GENETICS OF HAEMOPHILIA" . . . . . R. J. Sawers
Pediatric Society of Victoria.

"EUGENICS IN HAEMOPHILIA–THE CLINICAL BACKGROUND" . . . . R. J. Sawers
Victorian Society of Pathology and Experimental Medicine and the Biometric Society.

"GENETICS OF HAEMOPHILIA–ESTIMATION OF MUTATION RATES" R. J. Sawers
Australian and New Zealand Association for the Advancement of Science.

"CLINICAL ASPECTS OF HAEMOPHILIA" . . . . . R. J. Sawers
Alfred Hospital Clinical Society.

"THE ELECTROCARDIOGRAM IN HYPOTHERMIA" . . D. Emslie-Smith
Victorian Society of Pathology and Experimental Medicine.

"CHANGES IN THE ELECTROCARDIOGRAM DURING HYPOTHERMIA" D. Emslie-Smith
Alfred Hospital Clinical Society.

"PATHOLOGY OF CEREBRAL ARTERIAL DISEASE" . . R. McD. Anderson
Australasian Medical Congress, Sydney.

MONOGRAPH SERIES

No. 1. "PRACTICAL ANAESTHESIA."
1932. (A/sian Med. Pub.)

No. 2. "SPREAD OF TUMOURS IN THE HUMAN BODY" . . . . R. A. Willis
1934. (Churchill.)

No. 3. "BLOOD CULTURES AND THEIR SIGNIFICANCE," Hildred M. Butler
1937. (Churchill.)

No. 4. "THE PRACTICAL SIGNIFICANCE OF MODERN CARDIOLOGICAL INVESTIGATIONS" . . . . . T. E. Lowe, H. B. Kay and H. A. Luke
1951. (M.U.P.)

No. 5. "PERIPHERAL VASCULAR DISEASE," A. J. Barnett and J. R. E. Fraser
1955. (M.U.P.)

No. 6. "CHEMOTHERAPY WITH ANTIBIOTICS AND ALLIED DRUGS,"
. . . . . Jean C. Tolhurst, G. Buckle and S. W. Williams
1955. (N.H. and M.R.C.)

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

Balance Sheet at 31st December, 1955

LIABILITIES.			ASSETS.			
Current Liabilities—			Current Assets—			
Sundry Creditors		£844 18 7	Cash in Bank			£543 3 2
Endowment Fund		8,500 0 0	Endowment Investments—			
Capital Grants and Gifts—			Grain Elevators Board Inscribed Stock—			
Balance as at 31st December, 1954	1,399 11 9		4½% maturing 1/5/1964	2,500 0 0		
Add Grants received during year	1,303 12 0		Commonwealth Government Inscribed Stock—			
	2,703 3 9		3¼% maturing 15/10/1960	5,000 0 0		
Less Amount expended during year	1,303 12 0		3¼% maturing 15/10/1963	500 0 0		
		1,399 11 9	Consolidated Treasury Bonds—			
Research Grant—Life Insurance Medical Research Fund of Australia and New Zealand—			3¼% maturing 15/9/1961	500 0 0		
					8,500 0 0	
Balance as at 31st December, 1954	1,932 13 6		Restricted Funds—			
Add Grants received during year	1,617 0 0		Capital Grants and Gifts	1,399 11 9		
	3,549 13 6		Research Grant—Life Insurance Medical Research Fund of Australia and New Zealand	2,178 12 9		
Less Amount expended during year	1,371 0 9					
		2,178 12 9	Represented by Cash in Bank			3,578 4 6
Revenue Account—			Fixed Assets—			
Surplus as at 31st December, 1954	2,775 10 4		Furniture and Fixtures			2,100 0 0
Deduct deficit for year ended 31st December, 1955	977 5 9					
		1,798 4 7				
		£14,721 7 8				£14,721 7 8

NOTE: In addition to receiving interest from the Investments as shown on the Balance Sheet, the Institute receives the income from 3¼% Commonwealth Government Inscribed Stock face vale 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.

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, 1955, 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 (Aust.),
Honorary Auditors.

Melbourne,
5th March, 1956.

B. McA. Sayers, F. G. Silberberg and D. F. Durie: "THE ELECTROCARDIOGRAPHIC SPATIAL MAGNITUDE CURVE IN MAN," *Amer. Heart J.*, Vol. 49 (1955), p. 323.

H. C. Newman and A. J. Barnett: "A COMPARISON OF PLACEBO AND HEPARIN TREATMENT IN INTERMITTENT CLAUDICATION," *Asian Ann. Med.*, Vol. 4 (1955), p. 183.

I. K. Buckley: "SOME UNUSUAL FEATURES IN A CASE OF GOUT," *Alfred Hospital Clinical Reports*, Vol. 5 (1955), p. 109.

J. S. Pettit: "A CASE OF RETROCEDENT GOUT," *Alfred Hospital Clinical Reports*, Vol. 5 (1955), p. 115.

I. S. de la Lande and G. A. Bentley: "THE ACTION OF MORPHINE AND ANTAGONISTS OF THE NARCOTIC ACTION OF MORPHINE ON ACETYL CHOLINE SYNTHESIS IN BRAIN," *Aust. J. exp. Biol. & Med. Sci.*, Vol. 33 (1955), p. 555.

PAPERS ACCEPTED FOR PUBLICATION

T. E. Lowe: "THE RELATIONSHIP BETWEEN BODY FLUID VOLUME AND URINE FLOW IN MAN," *Asian Ann. Med.*

T. E. Lowe: "CONTROL OF BODY FLUID VOLUME IN MAN: FURTHER OBSERVATIONS ON INTAKE, OUTFLOW AND VOLUME OF BODY FLUID," *Asian Ann. Med.*

P. Fantl and R. J. Sawers: "PROTHROMBIN ACCELERATOR DEFICIENCY ASSOCIATED WITH TUBERCULOSIS," *Med. J. Aust.*

P. Fantl and R. J. Sawers: "THE OCCURRENCE OF DIFFERENT PROTHROMBOPLASTIN DEFICIENCIES IN RELATED MALE BLEEDERS," *Brit. J. Haemat.*

D. Emslie-Smith: "CHANGES IN THE ELECTROCARDIOGRAM DURING PREOPERATIVE HYPOTHERMIA IN MAN," *Asian Ann. Med.*

R. Fowler: "THE EFFECTS ON A RABBIT'S EYE OF INTERMITTENT EXPOSURE TO A STREAM OF WARM AIR: AN INVESTIGATION INTO THE AETIOLOGY OF PTERYGIUM," *Brit. J. Ophthalmol.*

Margaret Down: "VIBROCARDIOGRAPHY—A STUDY OF VIBRATIONS IN THE NORMAL HEART," *Asian Ann. Med.*

R. McD. Anderson: "THE THYMUS IN MYASTHENIA GRAVIS," *Med. J. Aust.*

PAPERS SUBMITTED FOR PUBLICATION

R. McD. Anderson: "SPONTANEOUS INTRACRANIAL HAEMORRHAGES."

Winifred G. Nayler and D. McKelvie: "A METHOD FOR THE STUDY OF CARDIAC METABOLISM AND EFFICIENCY IN THE TOAD, BUFO MARINUS."

F. E. Binet, G. S. Watson and R. J. Sawers: "ON THE ESTIMATION OF GENETIC PARAMETERS IN SEX-LINKED RECESSIVE DEFICIENCY DISEASES, WITH SPECIAL REFERENCE TO THE EUGENICS OF HAEMOPHILIA."

LECTURES DELIVERED DURING 1955

"CARDIOVASCULAR RESEARCH" . . . . . T. E. Lowe
Royal Australasian College of Physicians, Sydney.

"RESEARCH, ITS MEANING AND POSSIBLE EFFECTS ON HOSPITALS" . . . . . T. E. Lowe
Australian Institute of Hospital Administrators, Healesville.

"WHAT DOES MEDICAL RESEARCH MEAN TO YOU?" . . . . T. E. Lowe
English Speaking Union—Victorian Branch.

"SOME ASPECTS OF MEDICAL RESEARCH" . . . . . T. E. Lowe
Rotary Club of Melbourne.

"THE MANAGEMENT OF OEDEMA" . . . . . T. E. Lowe
Melbourne Medical Post-graduate Committee, Mortlake.

"SOME ASPECTS OF THE REGULATION OF BODY FLUID" . . T. E. Lowe
Australian and New Zealand Association for the Advancement of Science.

"THE VECTOR ELECTROCARDIOGRAPHIC PATTERN IN MYOCARDIAL INFARCTION" with J. M. Gardiner . . . . . T. E. Lowe
Australasian Cardiac Society, Sydney.

"LABORATORY AIDS IN MANAGEMENT OF HAEMORRHAGIC DISEASES" . . . . . P. Fantl
Alfred Hospital Clinical Society.

"BIOCHEMISTRY OF GENETICALLY CONTROLLED DISEASES" . . . . P. Fantl
Royal Australian Chemical Institute.

"BIOCHEMICAL ASPECTS OF BLOOD COAGULATION" . . . P. Fantl
University of Melbourne.

"DIAGNOSIS OF PERIPHERAL VASCULAR DISEASE" . . . . A. J. Barnett
Royal Australasian College of Physicians, Melbourne.

"USE OF ARTERIAL GRAFTS FOR OBLITERATIVE ARTERIAL DISEASE OF THE LOWER LIMBS: MEDICAL ASPECTS" . . A. J. Barnett
Australasian Medical Congress, Sydney.

"MODERN MANAGEMENT OF ARTERIAL HYPERTENSION," A. J. Barnett
Eye and Ear Hospital Clinical Society.

"LABORATORY AIDS IN THE DIAGNOSIS OF ENDOCRINE AND METABOLIC DISORDERS" . . . . . Bryan Hudson
Laboratory Technicians' Society of Victoria.

"THE PRESENCE OF MELANOCYTE STIMULATING HORMONE IN THE HUMAN PITUITARY GLAND: THE IMPLICATIONS OF THIS OBSERVATION IN RELATION TO THE GENESIS OF ADDISONIAN PIGMENTATION" . . . . . Bryan Hudson
Australian and New Zealand Association for the Advancement of Science.

"NATURE OF ADDISONIAN PIGMENTATION" . . . . . Bryan Hudson
Alfred Hospital Clinical Society.