

# RES MEDICA

Journal of the Royal Medical Society



## Contents

EDITORIAL	7
JAMES PARKINSON AND HIS DISEASE	8
THE HIP FROM CRADLE TO GRAVE	13
ENDOCRINE ASPECTS OF BREAST CANCER	19
THE SOCIETY	26
COMPUTERS IN MEDICINE	28
DIAGNOSTIC PROBLEM	31
THE HAND IN CLINICAL MEDICINE	33
THE CHOCOLATE COATED PILL	33
RESEARCH TOPIC	45
THE CONTRIBUTORS	46
BOOK REVIEWS	47

Copyright Royal Medical Society. All rights reserved. The copyright is retained by the author and the Royal Medical Society, except where explicitly otherwise stated. Scans have been produced by the Digital Imaging Unit at Edinburgh University Library. Res Medica is supported by the University of Edinburgh's Journal Hosting Service: <http://journals.ed.ac.uk>

ISSN: 2051-7580 (Online) ISSN: 0482-3206 (Print)

Res Medica is published by the Royal Medical Society, 5/5 Bristo Square, Edinburgh, EH8 9AL

Res Medica, Summer 1967, 5(4)

doi: [10.2218/resmedica.v5i4.492](https://doi.org/10.2218/resmedica.v5i4.492)

Vol. V. No. 4.

SUMMER 1967

# res medica

# JOURNAL

*of the*

ROYAL COLLEGE

*of*

SURGEONS

*of*

EDINBURGH

---

*Published Quarterly: October, January, April, July*

*Annual Subscription: 21s. post free*

**Editor: Sir JOHN BRUCE, C.B.E., T.D.**

# LATEST BOOKS FROM EDINBURGH

---

## RECENT RESEARCH ON GONADOTROPHIC HORMONES

E. T. BELL and J. A. LORAINE

346 pages, 169 illustrations, 70s.

## MANUAL OF SURGICAL ANATOMY

SIR JOHN BRUCE, C.B.E., T.D., R. WALMSLEY and J. A. ROSS

574 pages, 307 illustrations, Paperback, 30s.

## THE PRINCIPLES AND PRACTICE OF MEDICINE

SIR STANLEY DAVIDSON

Eighth Edition, 1,352 pages, 139 illustrations, 40s.

## TROPICAL DISEASES

Supplement of "The Principles and Practice of Medicine"

F. J. WRIGHT and J. P. BAIRD

Second Edition, 164 pages, 15 illustrations, 10s 6d.

## DISEASES OF THE NOSE, THROAT AND EAR

I. S. HALL and B. H. COLMAN

Eighth Edition, 442 pages, 111 illustrations, 30s.

## THE EYE IN GENERAL PRACTICE

C. R. S. JACKSON

Fourth Edition, 182 pages, 59 illustrations, 27s 6d.

## THE EEG IN CLINICAL PRACTICE

J. P. LAIDLAW and J. B. STANTON

128 pages, 147 illustrations, 40s.

## CLINICAL EXAMINATION

J. MACLEOD

Second Edition, 596 pages, 235 illustrations, 45s.

## NOTES ON CLINICAL SIDE-ROOM METHODS

Prepared by the Subcommittee in Medicine of the Medical Education Committee of the University of Edinburgh.

Second Edition, 104 pages, 30 illustrations, 10s 6d.

## AN INTRODUCTION TO DERMATOLOGY

G. H. PERCIVAL

Thirteenth Edition, 402 pages, 278 illustrations, 75s.

## CLINICAL VIROLOGY

R. H. A. SWAIN and T. C. DODDS

324 pages, 241 illustrations, 75s.

## PARAPLEGIA AT HOME

M. A. THOMPSON and W. A. MURRAY, O.B.E.

52 pages, 18 tables, 10s 6d.

## TRANSACTIONS OF THE SECOND INTERNATIONAL CONGRESS ON RESEARCH IN BURNS

A. B. WALLACE, C.B.E. and A. W. WILKINSON

652 pages, 227 illustrations, 90s.

## ELECTROCARDIOGRAPHY

R. W. D. TURNER, O.B.E.

Second Edition Reprint, 164 pages, 181 illustrations, 21s.

1967 Catalogue now available

---

**E. & S. LIVINGSTONE LTD., 15-17 TEVIOT PLACE, EDINBURGH**

---

# it's here!



## Colour-coded by **ETHICON**\* The new suture packaging system

Ethicon Ltd have simplified the problem of suture storage with a new system based on colour-coding. ETHICON overwrap sutures are packed in a plastic box with sliding lid, colour-coded to indicate the material from which the sutures are made, then wrapped in clear cellulose film.

The new SUTURE CABINET provides a compact storage and dispensing system which can

be built to whatever size is required. Each colour-coded box of ETHICON sutures becomes a drawer in the cabinet. Plastic extenders allow the basic 16 drawer unit to be increased in multiples of 8 drawers. This revolutionary system minimises the risk of error and provides you with sutures at your fingertips.

**ETHICON** LTD.

Bankhead Avenue Sighthill Edinburgh 11

\*Trade Mark

D5728sr

# ***Res Medica***

## ***Journal of The Royal Medical Society***

VOL. V. NO. 4.

SUMMER 1967

### **Editorial Committee**

#### **Honorary**

*Sir John Bruce, C.B.E*  
*Sir Derrick Dunlop, M.D.*  
*R. J. Kellar, M.B.E.*

#### **Editor**

*M. F. Macnicol, B.Sc.*

#### **Advisory**

*I. M. C. Macintyre*  
*D. Beamish*

#### **Sales**

*C. J. Eastmond*

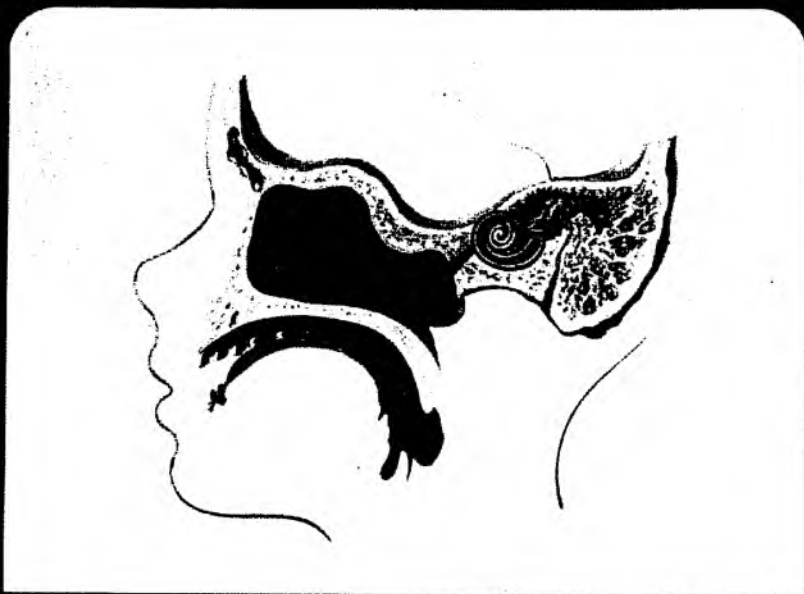
#### **Advertising**

*Mackenzie & Arthur Ltd.*  
*53 George St., Edinburgh, 2.*

ONESHILLING AND SIXPENCE

PUBLISHED TWICE YEARLY BY THE ROYAL MEDICAL SOCIETY

FIVE YEAR SUBSCRIPTION — ONE POUND



## Lincocin penetrates/Lincocin works

efficacy through depth of  
penetration in  
tonsillitis/otitis media

and the difficult-to-reach infections—  
sinusitis/mastoiditis



**available as:**

**Lincocin Syrup 250** Each 5 ml. contains 250 mg. lincomycin (as lincomycin hydrochloride monohydrate) in bottles of 60 ml.

**Lincocin Capsules** Each capsule contains 500 mg. lincomycin (as lincomycin hydrochloride monohydrate) in bottles of 12 and 100.

**Lincocin Sterile Solution** Ampoules (2 ml.) 600 mg. Each 2 ml. ampoule contains 600 mg. lincomycin (as lincomycin hydrochloride monohydrate).

UPJOHN LIMITED • CRAWLEY • SUSSEX

**Upjohn**

University of Edinburgh Pfizer Medical  
Monographs :

# DIABETES MELLITUS

EDITED BY L. J. P. DUNCAN

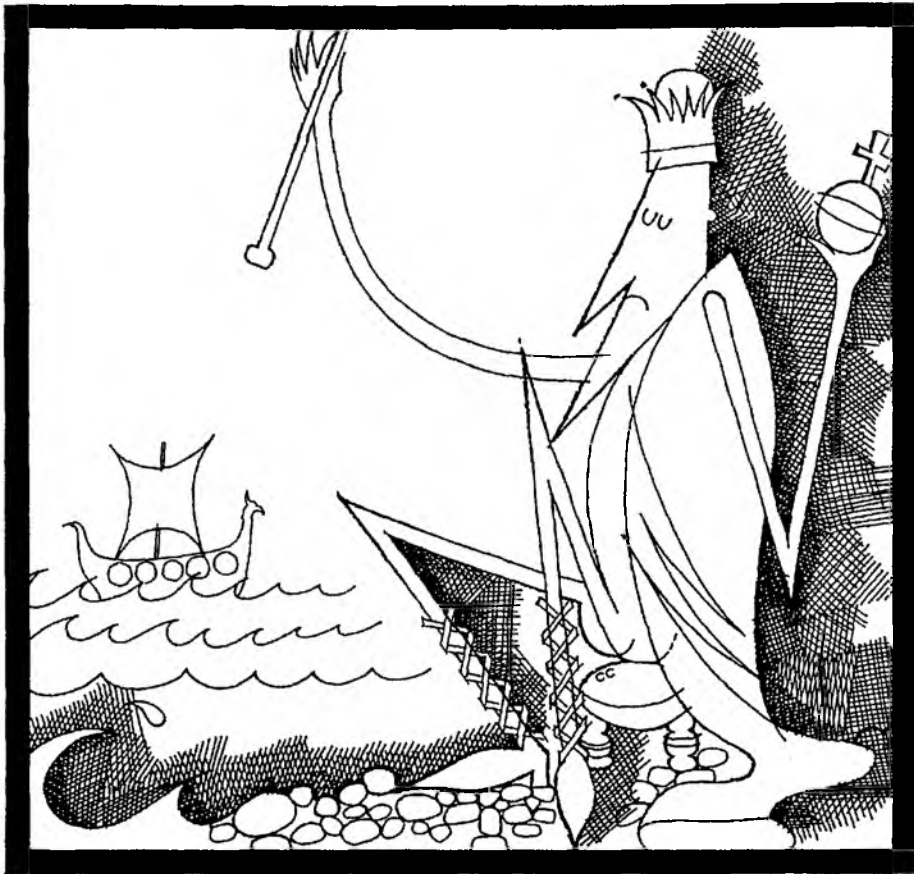
Diabetes is a disease which leaves no organ or tissue of the body unaffected. ¶ Its study is therefore of importance to all medical practitioners. ¶ This book, deriving from the opening symposium of the University of Edinburgh Pfizer Foundation for Post-Graduate Medical Research, discusses the disease under 4 headings: INSULIN, DIABETIC ANGIOPATHY, EPIDEMIOLOGICAL and THERAPEUTIC ASPECTS. ¶ Recent research in these fields is discussed in papers by leading authorities from Britain, U.S.A., Germany, Switzerland and Africa. ¶ This book carries on Edinburgh University Press's reputation for excellent production and aims to set a new standard in the design and production of medical books. ¶ 189 pp. 44 plates & drawings, 42s.

Edinburgh University Press, George  
Square, Edinburgh 8

## CONTENTS

EDITORIAL . . . . .	7
JAMES PARKINSON AND HIS DISEASE . . . . .	8
THE HIP FROM CRADLE TO GRAVE . . . . .	13
ENDOCRINE ASPECTS OF BREAST CANCER . . . . .	19
THE SOCIETY . . . . .	26
COMPUTERS IN MEDICINE . . . . .	28
DIAGNOSTIC PROBLEM . . . . .	31
THE HAND IN CLINICAL MEDICINE . . . . .	33
THE CHOCOLATE COATED PILL . . . . .	39
RESEARCH TOPIC . . . . .	45
THE CONTRIBUTORS . . . . .	46
BOOK REVIEWS . . . . .	47





## Canute couldn't stem the tide

**We can tide you over when you are sick**

Whoever you are—whatever you do—we have a wide range of personal insurances designed to meet your needs. Our long term **Sickness and Accident Insurances** have bonuses allotted irrespective of claims. We offer **Life Assurances** to provide for your old age and your dependants. There are **Special Policies** for Students and newly qualified Practitioners.



*The Medical and Dental Profession's own Insurance Company*

**MEDICAL SICKNESS ANNUITY AND  
LIFE ASSURANCE SOCIETY LIMITED**

PO Box 449, 7-10 Chandos Street, Cavendish Square, London W1  
Telephone Museum 1686

## EDITORIAL

Ask an etymologist or even a schoolboy with the Latin still tingling in his ears about the word hospital. You might glean more meanings subsumed under the word than bargained for; but care for the homeless is one interpretation that has fallen by the wayside. This is as well when the scene of the overcrowded, understaffed Health Service is surveyed. Yet how much in fact is the care for the homeless (a matter of community health) the province of the medical profession?

In this context the spectrum extends from the tramp, the vagrant, the ultimate social casualty, to the flatly intolerable conditions of some 30,000 families — a conservative one per cent of the three million families in Britain who live, according to the Ministry of Housing, in “slums, near-slums or grossly-overcrowded conditions”. Between the extremes are those who have lost their homes, mostly by eviction:

for these it is the hostel, insecure “furnished” lettings, or worse.

Risks to health, mental and physical, are appalling, more especially among the larger families of young children. As a sociomedical problem the case presents with an extremely poor prognosis, and nomadic, insecure (and often structurally dangerous) environments guarantee to see our hospitals, and law courts, in business till well out of this century. Perhaps it is asking too much to expect our hospitals, and more particularly those doctors and social workers critically aware of domiciliary conditions, to turn the problem into one of national urgency. But if steps are not taken in this direction hospitals will find themselves coping, however indirectly, with those 30,000 families.

---

The aim of this Journal continues to be that of an informative vehicle of the Society's activities; additionally, articles are published which should be of interest to medical undergraduate and postgraduate readers alike. It is hoped that supporters of the Journal will encourage others to subscribe, and to make

subscription easier a bank order system will be available next session.

The resourceful help of Sir John Bruce and Miss Hannah Harkins, assistant editor of the Journal of the Royal College of Surgeons, has never been more appreciated, and the Journal is grateful to them for their advice.

# **JAMES PARKINSON AND HIS DISEASE**

**John Gillingham, M.B.E., M.B., B.S.,  
F.R.C.S., F.R.C.S.E., F.R.C.P.E.**

*Professor of Surgical Neurology, Royal Infirmary of Edinburgh, and The  
Western General Hospital*

James Parkinson was born in 1755 in Shore-ditch, close to the City of London and like his father practised medicine there as an Apothecary and Surgeon. His earlier years in practice were disturbed by a rebellious spirit, roused by the poverty and injustices he saw around him. Inevitably he was drawn into politics and joined the provocative London Corresponding Society. He wrote a number of highly critical pamphlets under the pseudonym of "Old Hubert". His criticisms of government and administration were at times so bitter and fearless that eventually they led to his being subpoenaed and examined by the Privy Council. During the course of these examinations he had to answer to the Lord Chancellor, the Prime Minister, Mr. William Pitt and others in high office. Fortunately his explanations impressed his interrogators by their honesty and sincerity and he escaped imprisonment. By the time he was 40, with the increasing demands of a busy practice and a young family, he seemed to turn all his efforts to his own work and writings. His interests were broad. His first book was on "The Organic Remains of a Former World". Later he wrote on medical education, the preservation of health, and a brilliant criticism "Observations on Doctor Hugh Smith's Philosophy of Physics". Nevertheless it was not for another 22 years that he wrote his classic essay on "The Shaking Palsy" which was published in 1817 (Critchley 1955).

It is not surprising that this energetic compassionate man with a keen sense of observation

and flair for detailed recording, should turn his attention to that hitherto neglected group of patients suffering from the disease later to be called by his followers "Parkinsonism".

On Pages 15 and 16 of his monograph, (Parkinson 1817) he describes how the tremor of an aged patient disappeared following the onset of a "stroke" — a capsular hemiplegia. In about a fortnight the limbs had regained most of their movement. He says — "During the time of their having remained in this state, neither the arm nor the leg of the paralytic side was in the least affected with the tremulous agitation; but as their paralysed state was removed, the shaking returned."

The first surgical attempts to treat Parkinsonian tremor were in the early 1930's by destructive lesions at various levels of the cortical spinal pathways — the motor cortex, the internal capsule, the cerebral peduncle and later the posterior lateral quadrant of the upper cervical spinal cord. However, had this original observation of James Parkinson been carefully considered, a more successful surgical approach to this problem might have been achieved earlier. He clearly stated "As their paralysed state was removed, the shaking returned". These first operations often led to considerable disability from paralysis and neither the results nor their physiological basis encouraged pursuit of the problem in this way.

Nevertheless it was his experience with these procedures that led Russell Meyers (1942) to put forward his hypothesis that tremor and rigidity might be relieved by interruption of

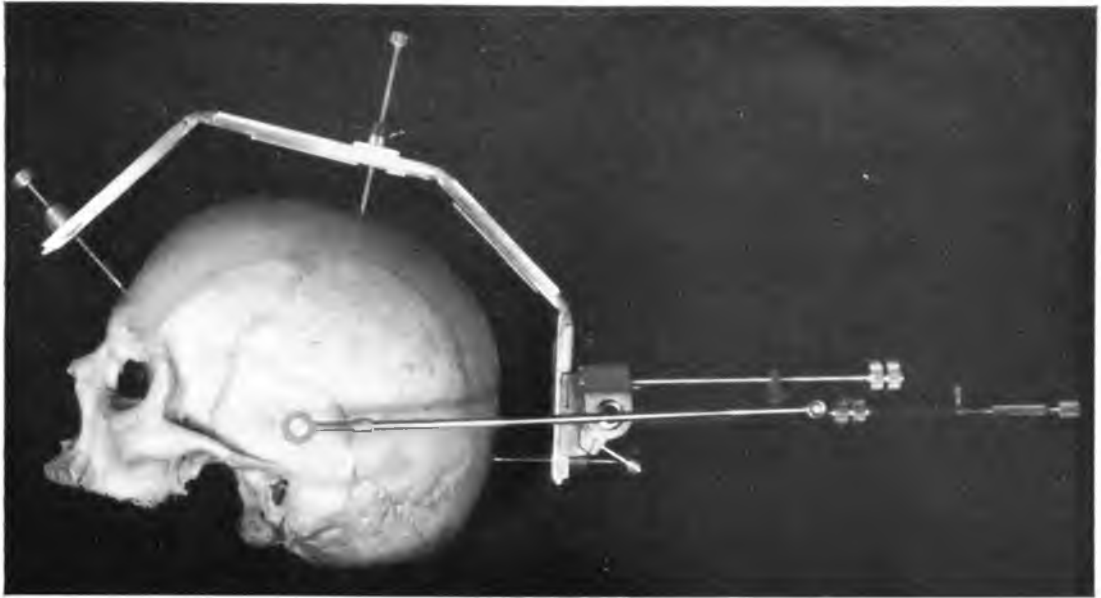


Figure 1

the pallido-fugal fibres and without any involvement of the cortico-spinal tract. This marked the great step forward but unfortunately his operation, designed to interrupt these fibres through the lateral wall of the third ventricle, was ill-conceived. The results although encouraging in some respects, were disappointing because of injury to diencephalic structures adjacent to the third ventricle with stupor and a high mortality and the operation fell into disrepute. Because of this and preoccupation with the medical problems of the Second World War, nothing more was done. Later Fenelon (1949) in Paris took up Russell Meyer's original observation and devised a new operative approach using a sub-frontal route. He followed the optic tract backwards beneath the frontal lobe to the point where the tract begins to merge with brain. Using this landmark and by directing his electrode upwards and slightly laterally for 1 cm., he was able to create an electro-coagulation lesion of the pallido-fugal fibres — the ansa lenticularis and adjacent globus pallidus. The results of this procedure were encouraging. Tremor and rigidity were often reduced and occasionally abolished, yet without any untoward side effects. In particular

there was no evidence of stupor, paralysis, sensory deficit or akinesia. This work was soon taken up by Guiot who published a series of successful results in 1953 and it was Guiot who demonstrated this exciting new operation to me in Paris in 1954 (Guiot 1953).

Early in 1955 our first patient was treated. A miner of 50 with post encephalitic Parkinsonism, he had been unable to work for 10 years because of severe tremor and rigidity of left limbs. At least half of each week was spent in bed because of an exacerbation of akinesia, sweating and tremor. Over the years he had lost 2 stones in weight and had become gravely disabled. Following operation which of necessity had to be performed under local anaesthesia to observe the effect and effectiveness of the lesion, he rapidly improved. He lost his tremor and rigidity completely and there was no paresis. His sense of well-being and weight were quickly restored, his kyphosis lessened and he returned to surface work at the pit in two months. He has remained well since although some mild rigidity in the left limbs has returned in the last few years. However for twelve years he has been without tremor and a

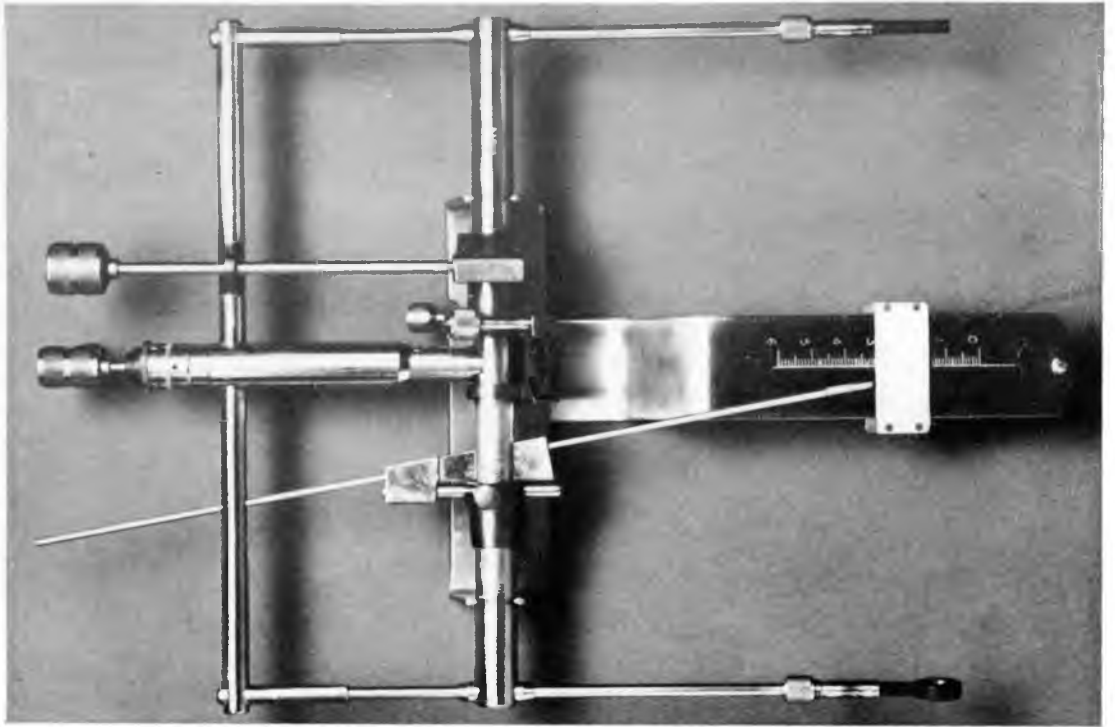


Figure II

steadily deteriorating condition has been greatly slowed or halted.

A further patient was treated in the same way shortly afterwards and a similar result obtained which has been maintained after twelve years.

In the meantime we were becoming increasingly interested in the development of the first stereotaxic human instrument devised and used by Spiegel and Wycis of Philadelphia in 1947 for the treatment of psychiatric disorder (Spiegel et al. 1947). This was designed very much on the pattern of that devised and used by Horsley and Clarke with such precision for animal work in 1908 (Horsley and Clarke 1908). The open operation of Fenclon, although very successful, was difficult and hazardous. If a discrete lesion could be sited accurately at a predetermined target through a burr hole by means of a suitable guiding apparatus fixed to the head, then much would have been achieved. This was the great contribution of Spiegel and Wycis for the field of stereotaxic surgery is now one of the major branches of surgical neurology not only in Parkinsonism and the dyskinesias,

but also in epilepsy, intractable pain and some of the psychiatric disorders.

Guiot was soon to follow with a much simpler yet very precise apparatus, a modified version of which has been used in my own department for many years (Figs. I and II). I remember the early discussions we had in Paris with great pleasure and how ultimately we decided that the posterior stereotaxic approach using an occipital burr hole, even though it meant a longer track, would probably be the best. As subsequent events have shown it was a fortuitous decision not only because the best results were obtained in this way, but also because it led to a greater understanding of the basic problems of Parkinsonism and the effectiveness of the different lesions used.

These early procedures were sometimes inaccurate and we came to realise the stereotaxic method was fallible. The problem was not that of imprecise instrumentation or lesion making but of the anatomical variation of one brain to another and even of one hemisphere to another. We had to rely upon radiologically determined landmarks such as the septum pellucidum and

the third ventricle (the mid sagittal plane) and the anterior and posterior commissures shown by means of a radio opaque dye or air. These landmarks gave only a reasonable bearing for our target and we began increasingly to look for physiological methods such as electric stimulation and reversible lesions to help us. By fractionating the electro-coagulation lesion using low heat initially it was possible to show the damping down of tremor or the relief of rigidity and of equal importance, side-effects such as speech, motor or sensory disturbances, before the permanent lesion was created; this method has proved to be more reliable in our hands than stimulation. Gradually as a result of the marking of all lesions at operation by detaching the tiny stainless steel tip of the electrode, taking a skull X-ray afterwards, then charting them on stereotaxic atlases, the sites of the most effective lesions for the relief of tremor and rigidity were soon determined. This was further helped by making as small a lesion as would be compatible with maintained improvement. We also began to map out for the first time the various tract systems such as the corticospinal fibres, the parieto-sensory projection within the posterior limb of the internal capsule and the tract systems concerned with speech. The results of this work using scattergram techniques have been published elsewhere (Gillingham 1962).

In 1955, when most of us were working on the globus pallidus and the pallido-fugal fibres, Hassler suggested that the most effective lesion for the relief of tremor should lie in the ventro-lateral nucleus of the thalamus (Hassler 1955). This was subsequently proved by Riechert, Cooper, ourselves and many others as successful operations on the thalamus were reported (Riechert 1955, Cooper 1959, Gillingham 1960). Nevertheless with follow up the lesion of the globus pallidus remained the most effective for the relief of rigidity. By elevating our posterior track to the globus pallidus, we found that a double ipsilateral lesion 15 mm from the mid-sagittal plane could be made quite successfully with only one insertion of the electrode. The posterior lesion for tremor was made first in the ventro-lateral nucleus posterior to the capsule, and the second for rigidity in the globus pallidus anterior to the capsule. This technique even after some 700 operations has been performed for Parkinsonism has remained the most effective.

There still seemed to be room for error and our restless search for further accuracy was eventually rewarded. For some years the

neurophysiologists had relied on electrical recording rather than stimulation for locating the electrode tip and this was beautifully demonstrated to me by Professor David Whitteridge during explorations of the external geniculate ganglion of the cat. The borders of grey and white matter were clearly defined with a degree of accuracy which so far we had not known. The subsequent development of the technique and its value in stereotaxic surgery has been published elsewhere (Gaze et al. 1964) and followed very closely the work of Albe-Jessard (1962). Since then, depth micro-electrode recording has become almost standard practice as further information has accumulated from greater experience and the use of smaller electrodes (1 to 10 $\mu$  tips). The borders of the thalamus and its sensory relay nucleus, of the internal capsule and the globus pallidus, are identified with confidence and target siting is no longer a problem.

Detailed study of electrical activity from the basal ganglia is continuing for there is much to learn about sensory mechanisms and the basic pathology of Parkinsonism. Of particular interest has been the recognition of spontaneous rhythmical activity arising in the thalamus synchronous with tremor yet not evoked by any sensory stimulus. It is not always found and as yet its relation to tremor has not been fully determined. The more sophisticated techniques of frequency analysis of the various patterns of cell activity may give some of the answers.

Perhaps of equal importance to the understanding of the basic pathology of Parkinsonism is the biochemical changes which occur. Recently Barbeau (1962) and others have shown a disturbance of dopamine metabolism and we have followed this work by a study of this substance in the cerebro-spinal fluid of the lateral and third ventricles in patients with Parkinsonism and in controls. The team responsible for this study, working in my department and that of Professor Perry, will be reporting about it shortly. Future research in the field of the Dyskinesias would seem to depend very much upon the pursuit of the abnormal electrochemical changes which are present.

The surgeon, stumbling as he does, often in an empirical way, responds to each challenge thoughtfully and with the improvement of the patient as his primary concern. The rewards of such an exercise in understanding the problems of Parkinsonism have been considerable, and in particular perhaps in the outlining of a "pathway" which lies within the diencephalon,

interruption of which at any point relieves tremor and rigidity and to a greater or lesser extent some of the other associated symptoms as well, such as oculogyric crises and the compulsive thinking that sometimes go with them. This "pathway" which has been defined by a whole series of differently sited yet successful lesions by surgeons across the world, extends from the inferior aspect of the globus pallidus anteriorly, upwards and posteriorly through the globus pallidus, across the posterior limb of the internal capsule at and above the inter-commissural plane into the ventro-lateral nucleus of the thalamus. There it turns downwards through the zona incerta just lateral to the red nucleus to the substantia nigra. Its distance from the mid-line and its width varies from point to point and there would seem to be "bottlenecks" within it. A lesion placed strategically within it brings immediate relief of symptoms and signs but if it is poorly placed the results are inadequate and side effects follow. Its connections with the cortex above and spinal cord below have not yet been defined but in the diencephalon we would seem to have shown "the pathway" to be the ansa and fasciculus lenticularis (Gillingham 1966).

Much of what I have said has been about research and the solution of our problems of

accurate placement of effective lesions for the relief of this relentlessly progressive disease, but we must now look at the results and the indications and contraindications of operation.

Not all patients are benefitted by stereotaxic surgery. Those who are deteriorating rapidly with bilateral tremor and rigidity and who show widespread effects of their disease, notably intellectual impairment, gross reduction of voice volume and disturbances of micturition, cannot be improved and are often made worse. Fortunately the majority are not so severely affected and in these patients operation will always effect some increase in independence, and in a reasonably high proportion great improvement, particularly in those with strictly unilateral rigidity and tremor. Bilateral operations, if staged with at least a month between them, are being carried out increasingly as precision has increased. (Gillingham 1964).

Post-operative drugs are usually necessary although the dosage is often progressively reduced as the months and years pass. It is the accumulating evidence, with prolonged follow-up, now of twelve years in some patients, of the greatly slowed or halted disease process which is perhaps the most exciting observation of all and which now poses the important question "How has it happened?"

## REFERENCES

- Albe-Fessard, D., Arfel, G., Guiot, G., Hardy, J., Vourc'h, G., Hertzog, E. and Aleonard, P. Precise delimitation of the subcortical structures and identification of thalamic nuclei in man by stereotaxic electrophysiology. *Neurochirurgia*, 5, 1-18, 1962.
- Barbeau, A. The pathogenesis of Parkinson's disease. A new hypothesis. *Canad. Med. Ass. J.* 87, 802-807, 1962.
- Cooper, I.S. *Proc. roy. Soc. Med.*, 52, 47, 1959.
- Critchley, McD. James Parkinson. Macmillan & Co. 1955.
- Gaze, R. M., Gillingham, F. J., Kalyanaraman, S., Porter, R. W., Donaldson, A. A. and Donaldson, I. M. L. Microelectrode recordings from the human thalamus. *Brain*, 87, 691-706, 1964.
- Gillingham, F. J. et al. The surgical treatment of Parkinsonism. *Brit. Med. J.*, 2, 1395, 1960.
- Gillingham, F. J. Small localised surgical lesions of the internal capsule in the treatment of the dyskinesias. *Confin. Neurol.*, 22, 385-392, 1962.
- Gillingham, F. J., Kalyanaraman, S. and Donaldson, A. A. Bilateral stereotaxic lesions in the management of parkinsonism and the dyskinesias. *Brit. Med. J.*, 11, 656-659, 1964.
- Gillingham, F. J. Stereotaxic Surgery — Past, Present and Future. *Proceedings Congress of Neurological Surgeons (U.S.A.)*, Clinical Neurology, Vol. 13, Chap. 10, 189-203, 1966.
- Guiot, G. Le traitement des syndromes parkinsoniens par la destruction du pallidum interne. *Neurochirurgie*, 1, 94-98, 1958.
- Hassler, R. *Proceedings of the Second International Congress of Neuropathology*, London, Part I, pp. 29-40; Part IV, pp. 637-642, *Excerpta Medica*, Amsterdam, 1955.
- Horsely, V. and Clarke, R. H. The structure and functions of the cerebellum examined by a new method. *Brain*, 31, 45-124, 1908.
- Meyers, R. Surgical interruption of the Pallidofugal fibres. *New York J. Med.*, 48, 317, 317-325, 1942.
- Parkinson, J. *An Essay on the Shaking Palsy*, 66 pp. Sherwood, Neely and Jones, London, 1817.
- Riechert, T. and Hassler, R. Klinische Effekte bei Reizung einiger Thalamus-Kerne am Menschen. *Nervenarzt*, 26, 35-40, 1955.
- Spiegel, E. A., Wycis, H. T., Marks, M. and Lee, A. J. Stereotaxic apparatus for operations on the human brain. *Science*, 106, 349-350, 1947.

# THE HIP - FROM CRADLE TO GRAVE

**Ian R. Williams, M.B., Gh.B.**

From a dissertation read before the Society on Friday, 26th November, 1965

From birth to old age the hip joint provides a fascinating spectrum of disease processes; this provides a useful starting point for a study of the interaction of development of structure with development of function and the pathological variants of this interaction. Because of limitations of space only a few disease processes will be chosen and much of the review will be devoted to normal structure and function.

## ANATOMY

The general anatomy of the adult hip joint is well known and will therefore only be briefly mentioned. It is a synovial ball and socket joint in which the almost spherical head of the femur sits in the deep cup of the acetabulum, the two

apposed surfaces being almost congruent. The neck of the femur is angulated medially on the shaft at an angle of  $135^\circ$  and is anteverted  $25^\circ$  at birth.

The anatomy of the blood supply is important both during development and later life. The arterial supply is from two main sources in the adult; the artery of the ligamentum teres and the retinacular vessels which ascend the neck of the femur in the fibres of the joint capsule, entering the synovial cavity at the upper part of the neck. The relative importance of these vessels varies greatly during development; the following table attempts to show which vessels are responsible for supply at each age:—

---

Retinacular vessels — Posterolateral — Superior Metaphyseal; Lateral Epiphyseal.		
Posteromedial — Inferior Metaphyseal.		
Age	Vessels	
Foetal — 4 months .....	Lat. epiphyseal Inf. metaphyseal Artery of lig. teres	All are end arteries
4 months — 4 years .....	Transitional period	
4 years — 9 years .....	Lateral epiphyseal	
7 years — 10 years .....	Transitional period	
10 years — Maturity .....	Lateral epiphyseal Artery of lig. teres	Anastomoses begin Anastomoses across epiphyseal line

---



After maturity has been reached all the vessels take part in the supply but the relative importance of each is disputed; the artery of the ligamentum teres has been said to be capable of supplying the whole head (Waldenstrom 1934, Wolcott 1943.) Strange (1965) believes that this would be possible in only 20% of the population; in a further 20% he suggests that it has no function and in 60% its supply is restricted to 10% of the head. Likewise the contribution of the Nutrient artery of the femur has been variously assessed: Tucker (1949) and Trueta and Harrison (1953) do not believe that it has any role in supplying the head.

Racial variations occur especially with respect to the importance of the artery of the ligamentum teres in the negroid, the supply being much greater in the 4 - 9 years period.

The importance of these facts should become more apparent on considering pathological processes later in the review.

#### PHYSIOLOGY

The articular surfaces of the joint are of hyaline cartilage which, in spite of its name, has strands of collagen running in a basket work fashion, serving to prevent lateral expansion as a result of vertical compression. The load on these surfaces is high and thus perfect distribution is required, as is a low coefficient of friction. The coefficient of friction has been calculated by many people with results ranging from 0.0075 to 0.023; the average of Charnley's experiments was 0.013. This compares with 0.03 for ice on ice and 0.1 for mechanical ball bearings.

In spite of this low coefficient of friction the movement of the surfaces, one over the other, produces continual abrasion of surface layers — this may be considered as wear and tear or simply as replacement; the result appears to be the same. The other important effect which movement has, is the compression and expansion of the cartilage and this may be important in lubrication, the synovial fluid entering and leaving the cartilage as it would a sponge. The flow of fluid in and out of the cartilage may also be important to the nutrition of the avascular tissue.

The lubrication has been thought to occur in many different ways; a combination of several would seem to be possible. A hydrodynamic method in which one surface floats on a film of fluid on the other surface is the simplest, but Tanner (1949) believed that the nature of the fluid precludes this under the

conditions existing in the hip joint. A refinement of this has been suggested by Charnley (1959) who favours a form of boundary lubrication; in this form the lubricant fluid has an affinity for both surfaces enabling a thin film of fluid to be present even at high pressures. A further refinement combines all that has so far been described with the expression of the fluid from the cartilage under pressure.

The viscosity of the fluid itself may be important in that the extent of polymerisation is reduced in several diseases of the hip joint (Matsunaga, Ioki and Aoki 1958). Depolymerisation is associated with decreased viscosity. Many of the disease processes of the hip involve physical displacement of one form of another and hence a brief consideration of the forces acting on the joint is essential. When a person is standing on both legs the weight on each joint is half the body weight excluding the legs, which would be about 72 lbs. in a 12 stone man. This would act vertically through the head of the femur. When walking, however, the weight is borne on one leg at a time, leading to enormous forces acting at the hip joint; in the figure this can easily be seen.

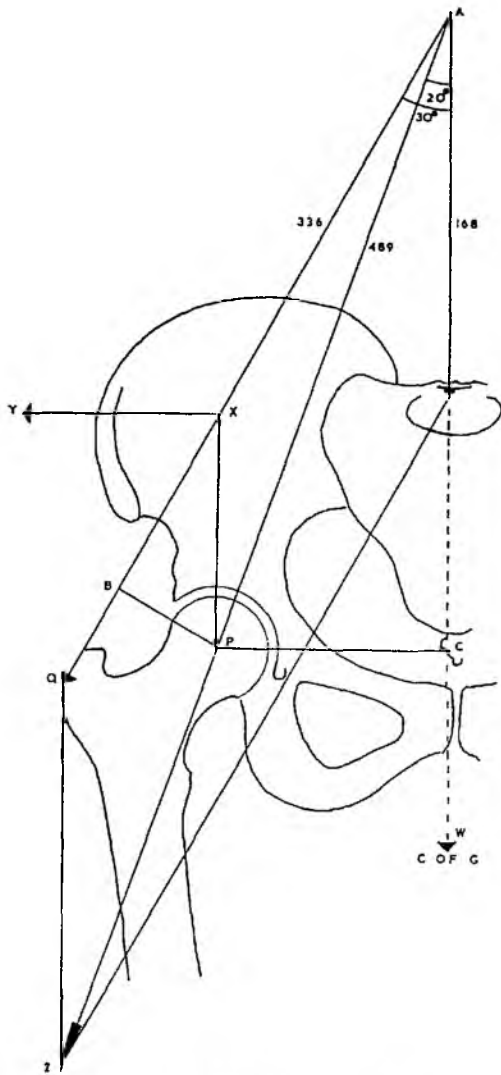
The centre of gravity passes slightly to the same side as the weight bearing hip; this leads to an adduction moment  $W \times PC$ . To balance this the abductors, gluteus medius and minimus, must exert an equal moment and because their line of action is much nearer the centre, P, the force must be correspondingly greater. In fact PC is at least twice PB (Inman 1953 gave 2.4 - 2.6) so that the muscles must achieve a force of at least twice the body weight; this means that the total load on the hip, the resultant, is almost three times the body weight, acting downwards and 20° outwards.

Balance in the antero posterior direction is controlled by gluteus maximus.

The aetiology and pathogenesis of several disease processes will now be considered in order to illustrate the importance of some of the above factors.

#### CONGENITAL DISLOCATION OF THE HIP

This disorder occurs in 15 per 10,000 live births in this country, but in countries such as Japan, North Italy and Brittany the incidence is as high as 40 per 10,000 live births. The incidence is much lower in countries where mothers carry their babies astride their backs. Girls are affected four times more frequently than boys and the left hip three times more than the right; it is bilateral in only 25% of cases. Dislocation at birth and dislocation as



—by courtesy of Heineman Publ.

part of a general disorder, e.g. athrogyphosis, are not considered here.

The typical dislocation is not a primary developmental defect because the joint develops by cleavage of a solid block of mesoderm which is complete by the tenth week of intrauterine life.

Among the many factors suggested are hereditary and familial influences but it is not clear whether this represents a genetic predisposition to dislocation as such or merely a tendency to

predisposing factors such as placental site. Gill in 1948 suggested a disturbance of the maternal environment; perhaps after the discovery of the effects of Thalidomide this may seem a possibility. Dennis Brown (1948) postulated intra-uterine mechanical stress as a cause; pressure of the uterus on a flexed knee in a breech presentation forcing the head down and back out of the acetabulum. In 1962 Barlow produced results to suggest that the incidence was increased in breech presentation but it was not possible to say which was cause and which effect. Acetabular hypoplasia and increased anteversion of the femoral neck have both been suggested as primary factors but both are more likely to be secondary. Von Rosen showed, in 1962, that in babies with C.D.H. the pubic symphysis could be distracted twice the distance of that of a normal child; he also found an increased excretion of Oestrogens in the urine of these babies, for the first three days of life. Hence it seems possible that hormonal factors may relax ligaments which allows the mechanical stresses in the uterus to produce subluxation or dislocation and increased anteversion. Consequent upon this the limbus, consisting of cartilage and a fold of capsule, turns into the joint and this together with hypertrophy of the ligamentum teres and capsule leads to difficulty in reduction. With delayed reduction hypoplasia of the acetabulum becomes apparent and the inturned limbus may calcify (Somerville 1953). After a good early reduction almost normal structure and function will be achieved. In a variable proportion of patients an epiphysitis develops probably due to interference with the blood supply to the ossific nucleus of the normal side. The pathogenesis is not clear but the long intracartilagenous course of the vessels would render them liable to compression in the Frog or Bachlor positions used for reduction.

#### PERTHES' DISEASE

Between the ages of 3 and 16, but especially 4 and 10 years, children are at risk to Perthes' disease; it is 2 or 3 times more common in boys and bilateral in about 10% of cases. It is more common than C.D.H. but its aetiology and treatment are subjects of great mystery. Hereditary and familial influences have been suggested but are not generally thought to be important; likewise infection, trauma and hormonal factors have been suggested. The most acceptable theories implicate vascular disturbances leading to an avascular necrosis, although Ratliff (1962) compared the process

**Q What are the positive benefits of ATROMID-S to patients with angina pectoris, or with biochemical evidence indicating enhanced liability to myocardial infarction ?**

**A** ATROMID-S has been shown to correct or favourably affect all the blood lipid (cholesterol and triglyceride) and thrombogenic factors which are correlated with enhanced liability to myocardial infarction.

Figures from controlled trials of ATROMID-S are not available yet but it would certainly seem more than justifiable to use ATROMID-S at least selectively at this stage.

*In long-term but uncontrolled trials in patients with angina pectoris and a history of myocardial infarction, the mortality and recurrence rates are lower than those of other published series of cases.\**

\* Prog. in Biochem Pharmacol 1966 (In press)

250 mg. clofibrate  
in red soft capsules

The usual dosage is  
2 or 3 capsules after  
food (average 8  
capsules daily)



*A product of original ICI research*



Imperial Chemical Industries Limited    Pharmaceuticals Division  
Alderley Park    Macclesfield    Cheshire

Ph 515/3m

with that following fracture of the neck of the femur and said that they were not the same.

At this stage in life the epiphysis is dependent on the lateral epiphyseal vessels alone for its blood supply; compression of these vessels would lead to necrosis. This is supported by the fact that the process is most common at the anterior margin which is furthest from the blood supply, and that it does not occur in negroes, who have a supply from the ligamentum teres (Trueta 1959).

Experimental findings are mainly extrapolation from animals because of the innocent nature of the condition; in general these support a loss of arterial supply as the primary event. This is followed by multiple fractures of the trabeculae, but because of the avascularity no reaction occurs except in the synovial membrane — swelling of this membrane and the ligamentum teres leading to lateral displacement of the head. If fibrosis occurs at this stage the displacement will be more marked and prolonged. The inflammatory response causes a decalcification in the area but the ossific nucleus, having no blood supply, does not take part, giving an appearance of increased radio density of the head.

From surviving tissue the repair begins and thus at this stage may be found areas of necrotic bone and of new bone; because some superficial subchondral layers of bone are supplied with nutrients through the surviving cartilage it is also possible to find areas of new bone overlying necrotic bone.

The pain caused by the inflammatory reaction around the joint causes the patient to adopt a limp in which the centre of gravity moves laterally decreasing the work demanded of gluteus medius and thus the load on the hip joint. In fact the load in this position is only the body weight and acts vertically through the femoral head; this in turn means that the load is spread over a much smaller area of the head, increasing the pressure. This immense pressure is associated with indentation of the head at every step causing trabecular fractures. During repair the pressure and the enlarged soft tissue lead to flattening of the head followed by flattening of the acetabulum if treatment is not prompt and effective.

#### **SLIPPED EPIPHYSIS**

Displacement of the upper femoral epiphysis is a not uncommon problem affecting boys more than girls between the ages of 12 and 15 years. At this time the adult sex hormones are just beginning to be secreted at a higher level

and this may be important. The ratio of the Growth Hormone and the Gonadotrophic Hormones appears to control the rate and duration of growth, with a fall of G.H. and increase in sex hormones occurring through puberty. A delay or fall in the production of sex hormones by the anterior pituitary which later returns to normal or continued high output of G.H. both give rise to a relative increase in the amount of G.H. The former gives a mild Fröhlich's syndrome and the latter a mild pituitary gigantism.

In 1950 Harris showed the effect of this to be a widening of the layer of cartilage cells in the epiphyseal line which is a structurally weaker zone and is rendered even weaker. Scott (1956) showed that 70% of the patients had Fröhlich-like features and 30% had signs of G.H. excess, in his series of patients.

The weakened epiphysis is then exposed to the stresses of weight bearing and of progression: the tendency to leave the epiphysis with the pelvis is increased. The pain so caused produces a limp in which the weight is transferred laterally and acts vertically on the head of the femur as described above. This change in the direction of the force greatly increases the shearing strain at the epiphyseal line, and the femur becomes more vertical, again increasing the strain; these changes act to displace the epiphysis downwards and backwards.

The displacement is not sudden but gradual usually, and in 25% of cases becomes bilateral.

#### **OSTEOARTHRITIS**

Osteoarthritis is the major disease of the limp in adult life and may be roughly divided into primary and secondary; the aetiology of the primary form is rather a mystery, most attempts to explain it using a secondary theory.

A normal joint can survive normal work for a hundred years, whereas an abnormal joint will show changes at an earlier age. Wolff's Law may be considered alongside this observation: just as normal function gives rise to normal structure, abnormal function may be expected to give rise to abnormal structure; thus osteoarthritis may represent a change in structure related to a limp (abnormal function) from some primary pathological change.

In the gluteus medius limp, described above, the weight of the body is seen to act on a much reduced area of the femoral head, so that in spite of reduced load there are areas of very high pressure and areas of very low pressure. This loss of the normal compression and expansion of cartilage results in decreased

nutritional supply, first in the deeper layers, and this undernourished tissue disrupts under high pressure giving rise to fibrillation and erosion. This allows a further shift of the head, accentuating the pressure differences and leading to damage to the bony articular surface. The trabeculae undergo changes to counteract the changes, becoming thickened; this requires an increase in vascularisation in a wedge shaped vascular supply area which becomes apparent radiographically. In spite of strengthening, trabecular infractions still occur and local hyperaemia denotes the start of repair processes. At the same time some trabeculae lose their blood supply, as in all fractures, and synovial fluid enters the necrotic areas giving rise to the cyst formation seen on X-ray pictures. With a loss of fine structure comes a loss of gross structure and flattening of the head,

proportional to the extent of devascularisation. The fluid trapped in the bone transmits pressure to the cyst walls causing a reactive schlerosis.

Strange suggests that the size of the head and acetabulum now increases in an attempt to reduce the pressure; this is the process of lipping and osteophyte formation which Harrison et al (1953) considered to be primarily due to increased vascularisation. Harrison et al considered osteoarthritis to be primarily a vascular reaction to degeneration of articular cartilage and that abnormalities resulting, e.g. osteophytes, are evidence of persistent attempt at repair.

The theories presented above are really all involving a secondary mechanism though a primary disease process may not always be obvious.

#### REFERENCES :

- |   |   |
|---|---|
| <p>Waldenstrom, H. (1934) Act. Chir. Scand., 75, 185.<br/>         Wolcott, W. E. (1943). Surg. Gynae and Obstet., 77, No. 1, 61.<br/>         Tucker, E. R. (1949). J. Bone Jt. Surg. 31. B, 82.<br/>         Trueta and Harrison (1953) J. Bone Jt. Surg. 35. B, 442.<br/>         Charnley, J. (1959) Symposium on Biomechanics, 12. London, I.M.E.<br/>         Tanner, R. I. (1959) Appendix IV to Charnley J. (1959) above.<br/>         Matsunago, H. et al, (1955) J. Bone Jt. Surg. 37, A, 1314.<br/>         Gill, A. B. (1948) Editorial J. Bone Jt. Surg. 30A, 526.</p> | <p>Browne, D. (1948) Proc. Roy. Soc. Med. (Sect. Orth.) 41, 388.<br/>         Barlow, T. G. (1962) J. Bone Jt. Surg. 44, B, 292.<br/>         Von Rosen, S. (1962) J. Bone Jt. Surg. 44, B 284.<br/>         Somerville, E. W. (1953) J. Bone Jt. Surg. 35 B, 368.<br/>         Ratliff, A. H. C. (1962) J. Bone Jt. Surg. 44 B 528.<br/>         Harris, W. R. (1950) J. Bone Jt. Surg. 32 B, 5.<br/>         Scott, J. C. (1956) In, Modern Trends in Orthopaedics 2nd series London.<br/>         Harrison et al (1953) J. Bone Jt. Surg. 35 B 598.<br/>         Strange, F. G. St. C. (1965) The Hip, Heineman, London.</p> |
|---|---|

### Dubious Philosophy?

“The reader will find that the opium-eater boasteth himself to be a philosopher; and accordingly, that the phantasmagoria of his dreams (waking or sleeping, day-dreams or night-dreams) is suitable to one who in that character,

HUMANI NIHIL A SE ALIENUM PUTAT.

The true philosopher, de Quincey affirms, possesses “that constitution of faculties, in short, which (amongst all the generations of men that from the beginning of time have deployed into life, as it were, upon this planet), our English poets have possessed in the highest degree, — and Scottish professors in the lowest.”

from the Society's copy of  
 “Confessions of an English Opium-Eater”  
 (1853 ed.) by Thomas de Quincey.

# ENDOCRINE ASPECTS OF BREAST CANCER

**Thomas Hamilton, M.B., Ch.B., F.R.C.S.Ed.**

*Research Fellow, Department of Clinical Surgery*

## INTRODUCTION

A relationship between the endocrine system and breast cancer was first demonstrated by Beatson in 1896, when he obtained some benefit from oophorectomy in two patients with advanced disease. Until that time the treatment of breast cancer was limited to removal of the mamma and excision of superficial metastatic or recurrent nodules. The practice of castrating cows to maintain lactation after calving suggested to Beatson that the ovaries must be concerned in some way with the regulation of the physiological processes of the breast.

Reporting his findings to the Medico-Chirurgical Society of Edinburgh, Beatson summed up :

“The conclusion I draw from two cases I have brought under notice is this — that we must look in the female to the ovaries as the seat of the exciting cause of carcinoma, certainly of the mamma . . . .”

He further emphasised :

1. “That there seems to be evidence of the ovaries and testicles having control in the human body over local proliferation of epithelium”.
2. “That the removal of the tubes and ovaries has effect on the local proliferation of epithelium which occurs in carcinoma of the mamma . . . .”

3. “That the effect is best seen in cases of carcinoma in young people, a class of case where local removal of the disease is often unsatisfactory.”

Within the next decade, Boyd (1900) and Lett (1905) confirmed Beatson's observations and showed that about one-third of patients responded favourably to oophorectomy. It is interesting that no improvement in this figure has taken place since then, for the Joint Committee of the American Medical Association on Ablative Procedures in Breast Cancer reported that objective tumour regression occurred in 29% of women castrated before or during the menopause (Taylor, 1962).

In the seventy years since Beatson's pioneer effort the concept of hormone-dependence has become an accepted biological characteristic of certain tumours, particularly of the breast and prostate. It had its origin in the classical observations of Huggins and his colleagues who demonstrated that in dogs not only are the physiological processes of the prostate under endocrine control but that tumours of the glands regress after castration or in response to the administration of oestrogens (Huggins and Clark, 1940). It was subsequently shown that cancer of the human prostate could be influenced in a similar way.

The development of our understanding, albeit imperfect, of the relationship between endocrine status and breast cancer is the result

of a fruitful alliance of clinical practice, biochemical investigation and animal experiment. Some of the most significant contributions in these fields are discussed below.

#### EXPERIMENTAL TUMOURS IN ANIMALS

A great deal of research has been carried out on experimental tumours, particularly in the United States and a voluminous literature has accumulated. Three main lines of investigation have been followed.

##### 1. Induction of tumours by hormones

Only three years after Doisy had isolated the first crystalline oestrogen, Lacassagne (1932) induced mammary cancer in male mice by repeated injections of the hormone. Many workers since have confirmed that oestrogens may promote tumour growth in several species (Noble, 1957).

The breast is not the only organ to be affected. Oestrogen administration has yielded lymphoid tumours in mice, chromophobe tumours of the anterior pituitary, fibromyomata of the uterus in guinea pigs, malignant tumours of the cervix uteri, malignant renal tumours in male golden hamsters and interstitial cell tumours of testes in mice.

Although oestrogens are the most potent, other hormones have been found also to induce tumours. Moon and his colleagues (1950), for example, described lymphosarcomata, adrenal cortical and ovarian tumours in rats receiving injections of pituitary growth hormone.

These examples demonstrate the carcinogenic effects of the administration of exogenous hormones. The secretion of endogenous hormones may be altered by suitable manipulation of the endocrine system. Elegant experiments which demonstrate the interdependence of endocrine organs, and the oncogenic potential of interference with the feed-back mechanisms were reported by Biskind and Biskind (1944). They excised both ovaries from rats and transplanted one of them into the spleen. Ovarian oestrogen was thus liberated directly into the portal circulation and inactivated by the liver. They concluded that the resultant excessive production of anterior pituitary gonadotrophins was responsible for the granulosa-cell tumours and luteomata in the transplanted ovary.

##### 2. The effects of hormones on spontaneous mammary tumours

Spontaneous fibroadenomata occur in about fifty per cent of elderly female rats of the

Sprague-Dawley strain. These tumours are readily transplanted into young rats and their experimental value depends upon their responsiveness to alterations in the animal's endocrine environment.

A biphasic effect on the growth of the tumour has been observed during the administration of oestrogen both in intact (Miller and Noble, 1954) and ovariectomised rats (Huggins, et al., 1956). Small doses of oestrogen promote, and large doses inhibit, the growth of the tumours. The effects of androgenic steroids have also been intensively investigated by Huggins and Mainzer (1957) and in general, they are inhibitory.

##### 3. Endocrine factors influencing hydrocarbon-induced mammary cancers

The two most useful mammary carcinogens are 3-Methylcholanthrene and 9, 10-Dimethyl-1, 2-Benzanthracene (DMBA). The tumours appear within a few weeks in response to a single intragastric instillation or intravenous injection (Huggins, Briziarelli and Sutton, 1959). They are adenocarcinomas histologically similar to human tumours. They are also hormone-dependent, and regression or disappearance of the tumours occurs after oophorectomy, after hypophysectomy and in response to the exhibition of exogenous steroids.

On the basis of their growth characteristics the tumours can be classified into three biological types. Some grow to a certain size, then regress spontaneously; some remain static after an initial period of growth; and others continue to enlarge throughout their life-history (Young, et al, 1963).

Many of these features are characteristic of the human disease, and the hydrocarbon-induced mammary tumour is, therefore, a unique experimental model for intensive investigation of the endocrine factors concerned in the induction and maintenance of breast cancer.

#### CLINICAL OBSERVATIONS

In clinical practice, alteration of the endocrine state of patients has been achieved either by the administration of steroid hormones or by ablation of endocrine organs. Such measures have generally been limited to the treatment of advanced malignant disease.

##### Endocrine Ablative Procedures

###### 1. Oophorectomy

Since Beatson's original observations there have been many confirmatory reports of the value in certain cases of removal of the ovaries.

Elimination of ovarian function has also been achieved by radiotherapy, and Douglas (1952) reported a favourable response in 20 per cent of patients with advanced disease. A major debate has now centred on the timing of castration, which may be done either as a prophylactic measure at an early stage in the disease or deferred until metastases have appeared. From an extensive review of the relevant literature Lewison (1962) concluded that therapeutic oophorectomy is an effective palliative procedure in about 25 per cent of patients and that there is a well defined trend towards prolonged life expectancy and improved survival rate from prophylactic castration whether achieved by surgery or by irradiation.

Oophorectomy is occasionally necessary in young women for the treatment of gynaecological disorders. Careful follow-up studies (Lilienfield, 1956; Hirayama and Wynder, 1962) indicate that in these women there is a reduced incidence of breast cancer in later years, particularly if the operation was done before the age of 37 years. Bilateral oophorectomy offers the greater protection, but even women who have had one ovary excised are significantly less prone to the subsequent development of cancer. These reports suggest that the ovary and its secretions are important in the induction as well as the maintenance of human breast cancer.

## 2. Adrenalectomy

Removal of the adrenal glands is designed to remove the main source of extra-ovarian sex hormones. It is usually combined with oophorectomy even in post-menopausal women in whom secretion of ovarian hormones continues although the uterus atrophies.

In 1945 Huggins and Scott obtained tumour remission following bilateral adrenalectomy in a man with advanced prostatic cancer. Survival lasted only four months in spite of the administration of deoxycorticosterone and a high salt intake. By 1952 cortisone was readily available and Huggins and Bergenstal successfully operated on seven patients with breast cancer of whom three, including one man, responded favourably. Since this time, many reports have indicated a variable degree of success, but remission occurs in about one-third of patients who are submitted to adrenalectomy and oophorectomy.

## 3. Hypophysectomy

This operation was introduced by Luft and Olivecrona in 1953. They reported (1958) a total remission rate of 44 per cent — regression of tumour in 29 per cent, and arrest of disease in 15 per cent of patients. A comprehensive survey of the value of adrenalectomy and hypophysectomy has been conducted by the Joint Committee of the American Medical Association (1961). The results from twelve American Clinics (representing a total of 673 patients) demonstrate no difference between the two methods; there was a 31 per cent response in each.

## Administration of Hormones

### 1. Oestrogens

The isolation of a crystalline oestrogenic hormone by Doisy in 1929 heralded an explosive development of steroid biochemistry, leading eventually to the elaboration of synthetic oestrogens. The value of these compounds in the treatment of advanced malignant disease was demonstrated by Haddow, Watkinson and Paterson (1944). Perhaps the most significant feature of these studies for the clinician is that for the first time, they enabled him to write a prescription for the treatment of cancer. This marks the origin of chemotherapy in malignant disease.

Oestrogen therapy is of greatest value in post-menopausal women in whom tumour regression occurs in about 35 per cent with a mean survival time of 27 months compared with 10 months in non-responsive patients (Council on Drugs of the American Medical Association, 1960).

### 2. Androgens

Loesser first demonstrated in 1939 that between 20 per cent and 25 per cent of patients respond to androgen administration, irrespective of menopausal state. Survival times recorded by the Council on Drugs (1960) were 19 months and less than 10 months in responsive and non-responsive patients respectively. Hirsutism, acne, deepening of the voice and increase in libido are displeasing side-effects which have dissuaded many clinicians, and patients from continuing treatment. Numerous steroid derivatives have been investigated by the Co-operative Breast Cancer Group (1964) in an attempt to find compounds which are non-virilising and yet retain their therapeutic effectiveness. Although some success has been achieved it is doubtful whether these compounds are as effective as esters of the naturally occurring androgens.



**Common Symptoms of Disease in Children**

R. S. ILLINGWORTH, M.D., F.R.C.P., D.P.H., D.C.H. 1967. 280 pages. 4 illustrations. 40s.

**Practical Management of the Elderly**

W. FERGUSON ANDERSON, O.B.E., M.D., F.R.C.P. (Edin., Glasg. & Lond.). 1967. 312 pages, 18 illustrations. 50s.

**The Principles of Medical Computing**

THOMAS R. TAYLOR, M.B., Ch.B., D.P.M., M.R.C.P.G., M.R.C.P.E. July 1967. 168 pages. 39 illustrations. About 27s. 6d.

**Instruments in Clinical Medicine**

F. D. STOTT, M.A., D. Phil. 1967. 152 pages, 132 illustrations. 35s.

**Principles of Resuscitation**

STANLEY FELDMAN, B.Sc., M.B., F.F.A.R.C.S. and HAROLD ELLIS, D.M., M.Ch., F.R.C.S. 1967. 138 pages, 32 illustrations. 30s.

**Textbook of Dermatology**

Edited by ARTHUR ROOK, M.D., F.R.C.P., D. S. WILKINSON, M.D., F.R.C.P. and F. J. EBLING, M.Sc., Ph.D. Sept. 1967. 2000 pages, 920 illustrations. Two volumes, about £18

**Handbook of Experimental Immunology**

Edited by D. M. WEIR, M.D. August 1967. 1264 pages, 297 illustrations. £8

BLACKWELL SCIENTIFIC PUBLICATIONS

5 ALFRED STREET, OXFORD

FORREST ROAD, EDINBURGH

HOUSE  
PURCHASE

FINANCE  
INSURANCE

PRACTICE  
PURCHASE

**We Offer Dental Surgeons the Lowest  
Interest Rates in the British Isles**

**PRACTICE LOANS — 100% ADVANCE.** Interest rate  $1\frac{1}{2}$ % above Bank Rate. Minimum 6% SIMPLE. Repayment up to 15 years.

**HOUSE PURCHASE — 100% ADVANCE.** Repayment 25-30 years.

**EDUCATIONAL FEES PLAN — IMMEDIATE DRAWINGS.** Repayments over 15 years. Supported by all leading Banks.

**LIFE ASSURANCE** to provide Tax Free Income for your family — cover for a loan — partnership — estate duty etc.

**CONTINUOUS DISABILITY INSURANCE — 15% DISCOUNT TO THE PROFESSION.**

*IF YOU NEED FINANCE OR INSURANCE — YOU NEED*

**J. W. SLEATH & CO. LTD.**

INCORPORATED INSURANCE BROKERS

58 THEOBALD'S ROAD, W.C.1.

Telephone: CHAncery 4375

### 3. Other Hormones

High doses of corticosteroids are beneficial in castrated patients and are believed to act by inhibition of the adrenal cortex and consequent reduced production of oestrogen. Prednisolone, a synthetic corticosteroid, is more effective than cortisone and causes less water retention.

Progesterone appears to have little effect but a synthetic progestational compound, 9  $\alpha$ -bromo-11-ketoprogesterone, studied by Goldenberg and Hayes (1959) produced a 20 per cent remission. Combinations of oestrogen and progesterone may be more effective. Stimulated by the observation that hydrocarbon-induced experimental tumours responded to administration of high doses of oestradiol and progesterone, Landau and his colleagues (1962) tried the combination in 15 patients, of whom 9 responded though only for a short time. Recently, Stoll (1967) has reported a 20 per cent response in patients receiving the oral contraceptive, Lyndiol, in which an oestrogen and progestin are combined.

#### Effectiveness of Treatment

It is evident from this brief outline that about one-third of patients respond to the administration of hormones or to endocrine ablative procedures. Adverse reactions to treatment do occur, however. Wilson, Jessiman and Moore (1958) have noted exacerbation of metastatic disease following oophorectomy and adrenalectomy, and Cade (1958) has reported similar effects from the administration of androgens and oestrogens. The results in human patients prompt comparison with the biphasic effects of oestrogens and androgens observed in experimental tumours, and emphasise our present ignorance of the fundamental relationships between hormones and growth.

Much has been written and many opinions have been expressed on the value of certain clinical criteria for the selection of patients with metastatic disease for major endocrine surgery. In his comprehensive review of this subject Fairgrieve (1966) concludes that two categories of patient are most likely to benefit; those with a long "free-interval", that is, in whom more than a year has elapsed between primary treatment and first recurrence, and those with skeletal or skin metastases. He emphasises the importance of assessing the extent and type of metastases. Slowly growing cutaneous or lymph node recurrences are perhaps best treated by local surgery or radiotherapy. Major surgery is inappropriate in pre-terminal states when life expectancy is limited.

Between these two extremes are patients with metastatic disease which is progressive and/or symptomatic for whom endocrine ablative procedures should be reserved.

The main problem which besets the clinician is his inability to forecast for the individual patient whether or not a favourable response will be obtained. It is towards this end that the greatest efforts have been made in the last decade.

#### BIOCHEMICAL INVESTIGATIONS

One of the most rewarding features of medical practice in recent years has been an awareness of the need for collaborative efforts by members of different disciplines, especially in assessing complex biological problems. Not least successful among the alliances so established has been the team comprising endocrinologist, biochemist, surgeon and radiotherapist. Much pioneer work along these lines has been actively pursued in Edinburgh.

The principal approach of the steroid biochemist has been the determination of steroid metabolites in urine and their relationship to clinical observations.

#### Urinary Oestrogens

Animal experiment and clinical observation indicated that oestrogen played a major role in the induction and maintenance of breast cancer. The elaboration of reliable methods for the analysis of urinary oestrogens (Brown, 1955 and Bauld, 1956) provided the means for intensive collaborative activity in Edinburgh. Strong and his colleagues (1956) found no correlation between pre-treatment oestrogen levels and subsequent response to the administration of stilboestrol or endocrine ablative operations. Subsequent reports from other centres have confirmed these observations.

Attempts to correlate the clinical result with changes in urinary oestrogen levels occurring after ablative procedures similarly have been disappointing. Some patients improve in spite of continuing high levels of urinary oestrogen and others deteriorate when oestrogen excretion has fallen to negligible amounts (Brown, *et al.*, 1959).

Several studies have indicated, however, that post-menopausal women with breast cancer differ from the normal population by an increased excretion of oestrogen. The physiological significance of this finding remains obscure, and more detailed study is required to establish its possible relationship to the development of breast cancer.

Overall, the efforts to relate oestrogen excretion to the course and prognosis of human breast cancer have been inconclusive.

#### Urinary Androgens and Corticosteroids

The estimation of urinary androgen and corticosteroid metabolites has proved the most hopeful approach so far. A major contribution in this field has resulted from the collaborative studies in London by Guy's Hospital and the Imperial Cancer Research Fund. Workers there have investigated patients with advanced disease, patients with early breast cancer and normal women.

##### 1. Advanced breast cancer

Urine was collected before operation from patients treated by adrenalectomy or hypophysectomy and estimations were made of gonadotrophins, androgen, oestrogen, corticosteroids and progesterone metabolites. By retrospective analysis of the data it was found that patients who responded satisfactorily to the operation were characterised by a relatively low excretion of corticosteroids and relatively high levels of urinary androgens. A reasonable distinction between the responsive and unresponsive clinical groups was obtained by expressing 17-hydroxy corticosteroids (17-OHCS) and 11-deoxy-17-oxosteroids as a simple ratio.

A more sophisticated statistical approach led to the formulation of a discriminant function which takes the form

$$80-80 [17\text{-OHCS (mgm/24 hrs.)}] + \text{aetiocholanolone}^* (\mu\text{gs/24 hrs.})$$

The design of the formula is such that a negative or positive number is obtained depending on the relative values of the steroids. By this means a clearer distinction between the clinical groups was obtained. A significant majority of patients with a "positive discriminant" responded to adrenalectomy or hypophysectomy whereas the results of treatment in the "negative discriminant" category were generally poor (Bulbrook, *et al.*, 1962).

When the discriminant function is considered in association with clinical observations a group of poor-risk patients with advanced disease is revealed. Remission is obtained in only 2 per cent of "discriminant-negative" patients in whom the primary tumour was noted within six years after the menopause and in whom recurrence had appeared within two years of primary treatment.

##### 2. Early breast cancer

There are indications that the relationships originally demonstrated in advanced breast

\*Aetiocholanolone is one of the urinary androgen excretion products.

cancer also obtain at an early stage of the disease. A negative discriminant function is a rare finding in normal women under the age of 60 years but has been observed in about 50 per cent of patients with early breast cancer. In these patients the incidence of recurrence is four times higher and the death rate is eight times greater than those with a positive discriminant (Bulbrook, *et al.*, 1964).

##### 3. Prospective studies on normal women

The preceding observations suggest that in some women with breast cancer there is an abnormality in the secretion of androgens and corticosteroids. Prognosis is poor in these patients, perhaps because the tumour has become hormone-independent. To determine whether the abnormality precedes the development of disease or results from the presence of the tumour a prospective survey was set up in Guernsey in 1961.

Almost 5,000 healthy female volunteers from this relatively closed population have provided one complete collection of urine. To date, breast cancer has developed in nineteen of the women. Analysis of the results suggests that the excretion of androgen and corticosteroid metabolites was abnormal in a significant proportion of the patients prior to the development of the disease (Bulbrook and Hayward, 1967).

#### CONCLUSION

The management of breast cancer presents a formidable challenge to the clinician. Intensive research on the relationship of the endocrine system to the induction and maintenance of mammary tumours has provided some insight into the nature of the disease. Some tumours appear to regress after alteration of the hormonal environment in which they have developed, others do not. It is not yet possible to determine the biological nature of a particular tumour at a sufficiently early stage in the disease to orientate the search for effective counter-measures. There are indications however, that poor-risk patients, and even healthy women who are "susceptible" to the disease, might be identified by abnormalities of secretion of urinary steroids. It should be possible in the future to confirm these suggestions and to simplify the measurements so that they are more generally available. Thereafter, attempts to produce a more favourable endocrine environment might not only be possible, but acceptable in a society in which hormonal modifications for fertility and birth control are now commonplace.

## REFERENCES

- Bauld, W. S. (1956). *Biochem. J.*, **63**, 488.
- Beatson, G. T. (1896). *Lancet*, **2**, 104 and 162.
- Biskind, M. S. and Biskind, G. R. (1944). *Proc. Soc. exp. Biol. (N.Y.)*, **55**, 176.
- Boyd, S. (1900). *Brit. med. J.*, **2**, 116.
- Brown, J. B. (1955). *Biochem. J.*, **60**, 185.
- Brown, J. B., Falconer, C. W. A. and Strong, J. A. (1959). *J. Endocr.*, **19**, 52.
- Bulbrook, R. D. and Hayward, J. L. (1967). *Lancet*, **1**, 519.
- Bulbrook, R. D., Hayward, J. L., Spicer, C. C. and Thomas, B. S. (1962). *Lancet*, **2**, 1238.
- Mulbrook, R. D., Hayward, J. L. and Thomas, B. L. (1964). *Lancet*, **1**, 945.
- Cade, S. (1958). "Endocrine Aspects of Breast Cancer". Ed. A. R. Currie, Livingstone: Edinburgh. p.2.
- Co-operative Breast Cancer Group (1964). *J. Amer. med. Ass.*, **188**, 1069.
- Council of Drugs of the American Medical Association (1960). *J. Amer. med. Ass.*, **172**, 1271.
- Doisy, E. A., Veler, C. D. and Thayer, S. (1929). *Amer. J. Physiol.*, **90**, 329.
- Douglas, M. (1952). *Brit. J. Cancer*, **6**, 32.
- Fairgrieve, J. (1966). *Surg. Gynec. Obstet.*, **122**, 371.
- Goldenberg, L. and Hayes, M. A. (1959). *Cancer*, **12**, 738.
- Haddow, A., Watkinson, J. M. and Paterson, E. (1944). *Brit. med. J.*, **2**, 393.
- Hirayama, T. and Wynder, E. L. (1962). *Cancer*, **15**, 28.
- Huggins, C. and Bergenstal, D. M. (1952). *Cancer Res.*, **12**, 134.
- Huggins, C., Brizziarelli, G. and Sutton, H. J. (1959). *J. exp. Med.*, **109**, 25.
- Huggins, C. and Clark, P. J. (1940). *J. exp. Med.*, **72**, 747.
- Huggins, C. and Mainzer, K. (1957). *J. exp. Med.*, **105**, 485.
- Huggins, C. and Scott, W. W. (1945). *Ann. Surg.*, **122**, 1031.
- Huggins, C., Torralba, Y. and Mainzer, K. (1956). *J. exp. Med.*, **104**, 525.
- Joint Committee Statement on Endocrine Ablative Procedures in Disseminated Mammary Carcinoma. (1961). *J. Amer. med. Ass.*, **175**, 787.
- Lacassagne, A. (1932). *C. R. Acad. Sci. (Paris)*, **195**, 630.
- Landau, R. L., Ehrlich, E. N. and Huggins, C. (1962). *J. Amer. med. Ass.*, **182**, 136.
- Lett, H. (1905). *Lancet*, **1**, 227.
- Lewison, E. F. (1962). *Obstet. and Gynaec. Survey*, **17**, 769.
- Lilienfield, A. M. (1956). *Cancer*, **9**, 927.
- Loesser, A. A. (1939). *C. R. Soc. franc. Gynec.*, **9**, 77.
- Luft, R., Olivecrona, H., Ikkos, D., Nilsson, L. B. and Mossberg, H. (1958). "Endocrine Aspects of Breast Cancer". Ed. A. R. Currie, Livingstone: Edinburgh p.27.
- Millar, M. J. and Noble, R. L. (1954). *Brit. J. Cancer*, **8**, 495.
- Moon, H. D., Simpson, M. E., Li, C. H. and Evans, H. M. (1950). *Cancer Res.*, **10**, 247, 362 and 549.
- Noble, R. L. (1957). *Pharmacol. Rev.*, **9**, 367.
- Stoll, Basil, A. (1967). *Brit. med. J.*, **1**, 150.
- Strong, J. A., Brown, J. B., Bruce, J., Douglas, M., Klopper, A. I. and Lorraine, J. A. (1956). *Lancet*, **2**, 955.
- Taylor, S. G. (1962). *Surg. Gynec. Obstet.*, **115**, 443.
- Wilson, R. E., Jessiman, A. G. and Moore, F. D. (1958). *New Engl. J. Med.*, **258**, 312.
- Young, S., Cowan, D. M. and Sutherland, L. E. (1963). *J. Path. Bact.*, **85**, 331.

## A Case For Dissection

In an anonymous monograph in the Library entitled "An Answer to the Several Attacks which have appeared against the University of Edinburgh" the author includes in his refutation of the "calumnies which have been circulated against this University, particularly that lately published in the city of Dublin" an interesting little snippet on Edinburgh dissecting habits in the early 19th century:

"Let us figure to ourselves a group of students assembled round a subject. One is cutting out an eye, another is making a prize of the heart, which he is proceeding to examine at his leisure, a third is grubbing in the entrails, and a fourth practising the insertion of the female catheter; the whole party brandishing their scalpels, singing and laughing, as merry as coblers (sic) over their awls. Suppose that the lecturer were to come in and to recognise in this one-eyed, mangled, heartless creature, the frail remains of the wife of his bosom, the sister, or daughter, whom he had cherished with the tenderest affection! How would he be able to bear such a sight? Would he not start back with horror? Would it not put all his philosophy at once to flight?"

Perhaps they weren't calumnies after all . . .

# THE SOCIETY

## IN RETROSPECT

The 230th Session has passed extremely well, the Society having now settled down in its new surroundings and come to grips with the problems revealed by its first year in Hill Square. But the upheaval is by no means over, and the problems now facing the Royal Medical Society are perhaps the most pressing in its whole history — where to go from here? The Society's future must be reassessed in the light of the recent valuation of the Library and a comprehensive policy of management worked out once and for all.

The traditional business of the Society's session has this year been supplemented by a new departure — the Symposia. In November the Society, in conjunction with the MSC (our old partners in the management of the Faculty Ball) organised a Symposium on ABORTION, with Sir Dugald Baird and Prof. Carstairs among the speakers; the evening was a great success — once a large enough lecture theatre could be found for the masses that arrived. Unfortunately, it was not possible to join with MSC for a second Symposium, this time on DRUG ADDICTION, to be held early in the Summer term, but the Society looks forward to more co-operation with the Council in the future.

One of the reasons why we could not undertake to help with a second joint symposium was that the Society itself held a Symposium in the first week of the Summer term, on ANGINA PECTORIS, celebrating the centenary of the first use of Amyl Nitrite in the treatment of Angina by Thomas Lauder Brunton while Senior President of the Society, in 1867. By the generosity of the various drug firms the Society was able to invite the leading authorities on the various aspects of research into Angina, from as far apart as Harvard and Oslo; but none of this would have been possible without the invaluable assistance of Dr. Michael Oliver and Dr. Desmond Julian in the planning of the programme, and Dr. C. Dale Falconer of BMA in the appeals for funds. A full report of the Symposium will be run in the next edition of *Res Medica*, and in

“World Medicine”, and the proceedings are to be published by Geigy.

Of the rest of the Session's business, perhaps mention should be made of two most interesting Addresses, the Inaugural Address by Sir James Learmonth on “The Wound in Literature and Myth” and the final Address by Dr. Macdonald Critchley on “Some Aspects of the Life and Death of Oscar Wilde”. Both Addresses were memorable for their high literary standard and for their excellent deliveries.

The President's Annual Dinner in the Hall of the Royal College of Physicians of Edinburgh was the most successful for some time, both the catering and the speeches reaching a high standard. And again, the Faculty Ball was better than ever, and a credit to its organisers.

Because the Society's official Business is completed it does not mean that the work is finished; the President's Dinner for the 231st Session is about to be organised; Addresses and Talks are in the process of arrangement; and the new Faculty Ball Committee will be appointed by the time this edition of the Journal is off the presses.

Finally, it should be mentioned that the Society is co-sponsor of a new medical-ethical group now being formed in Edinburgh, along the lines of the London Medical Group. The other sponsors are Profs. Duncan, Girdwood and Carstairs of the Faculty of Medicine, Profs. Blackie and Macintyre of the Faculty of Divinity, and, naturally, MSC and SCM. The Group, probably to be called The Edinburgh Medical Group, will arrange periodic lectures and seminars on various ethical and moral aspects of Medicine, and the first lecture and follow-up seminar should take place in the autumn term on the subject of Clinical Experimentation.

From the foregoing it is plain to see that the Society continues to be forward looking, with the health of the Edinburgh Medical School very much at heart.

ROGER SMITH, B.Sc., *Scriba*

## THE LIBRARY

The evaluation of the Society's library by Sotheby & Co. towards the end of 1966 revealed that the library (not including the Dissertations, Minute books or Consultation Press) possessed an insurance value of just under £70,000. This thrust into the limelight the need to adopt a positive attitude towards the collection which continues to face the ravages of time on an absurdly small budget.

Immediate action has been taken to safeguard a number of volumes, each worth several hundreds of pounds, and a more realistic insurance policy secured to safeguard the library in the meantime. But there yet remains the question of library policy, linking, as it must, with the future of the whole Society.

To consider the problem more extensively a special Advisory Committee has met several times already; the committee includes Sir Derrick Dunlop (chairman), Dr. Robin Thin (honorary librarian), Dr. Malcolm Low (treasurer), Dr. David Simpson and Dr. Jack Cormack. The Society is most grateful to them for their assistance.

This committee has worked co-operatively with the Library Committee and Council, and four possible courses of action have presented themselves:

1. the retaining of all or a major part of the

collection; this will involve considerable expenditure on renovation and maintenance and must be weighed against the use to which the books are put.

2. the retaining of part of the collection chosen by:
  - (a) reason of relevance of any book to the history of the R.M.S. and the Edinburgh Medical School.
  - (b) rarity and fame of the book, and hence its financial value.
  - (c) authorship and value of autographed inscription.

Acting on this brief Dr. Jack Cormack and the librarian sifted through the collection in its entirety and have subsequently proposed that a list of approximately five hundred volumes be retained.

3. disposal of the collection by sale; the money realised would broaden considerably the future activity of the Society. In 2. above, those books not retained would likewise be sold.
4. loan of the collection to a University or other academic body.

It will now be necessary to debate the intriguing possibilities of the Library's future. This is the concern of all those responsive to the Society.

MALCOLM MACNICOL, B.Sc., Librarian

## OFFICE-BEARERS FOR THE 231st SESSION

Senior President .....	ROGER H. SMITH, B.Sc.
1st Junior President .....	MISS FRANCES MARR
2nd Junior President .....	CLIFFORD J. EASTMOND
3rd Junior President .....	DAVID McLEOD, B.Sc.
Senior Secretary .....	ROBERT D. HUNTER, B.Sc.
Junior Secretary .....	JOHN B. IRVING, B.Sc.
Convener of Business Committee ..	JOHN R. MACHIN, B.Sc.
"    "    Publicity .....	MISS JANICE M. DUNCAN
"    "    House .....	JOHN WALLWORK
"    "    Library .....	WILLIAM L. CAULFIELD
"    "    Museum .....	ANDREW D. DAVIES
"    "    Dinner Committee ..	MISS CATRIONA REID
Editor of RES MEDICA .....	MALCOLM F. MACNICOL, B.Sc.

## LAUDER BRUNTON

"As I believed the relief produced by the bleeding to be due to the diminution it occasioned in the arterial tension, it occurred to me that a substance which possesses the power of lessening it in such an eminent degree as nitrite of amyl would probably produce the same effect, and might be repeated as often as necessary without detriment to the patient's health."

The "bleeding" referred to in this historic sentence was induced by "cupping or venesection" and the quotation comes from Brunton's article written in the "Lancet" a hundred years ago.

The Symposium celebrating the centenary of his announcement about the treatment of angina pectoris was a considerable success. All those concerned with the enterprise are to be congratulated and it is only regrettable that a fuller account of the proceedings will have to wait until our next number.

# COMPUTERS IN MEDICINE

**Richard D. Turner**

From a dissertation read before the Society on Friday, 4th November, 1966

The subject of this dissertation is Computers in Medicine and even those who have had nothing to do with these machines will be unable to ignore them in the very near future. A brief account of how they work is given here, followed by the description of a few of their applications in Medicine. In fact, learning to programme the machine is very simple, and the University Computer unit runs a special course three times a year for this purpose. Many people think of the computer as something between a glorified adding machine and a sort of god that can do anything, whereas in fact the truth lies somewhere in between.

## PROGRAMMING

It should be emphasised that usually the programmer need know very little mathematics. The programming language is a standard one, and the person who has a particular skill, say in mathematics, can write out a programme for carrying out any particular procedure. He might, for instance, devise an ingenious programme for evaluating the square roots of complex numbers. He could publish this programme in a magazine, and then anyone else wishing to do the same thing as part of another programme could copy this out word for word without having any understanding of the method involved. These "little programmes"

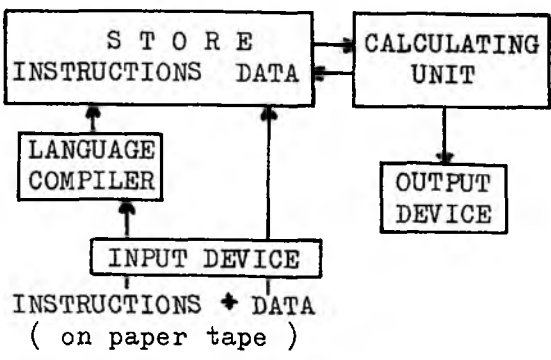
are termed Algorithms, and the index of these is by now very extensive.

There are several features of any computer which make it an extremely versatile machine, but three should be stressed in particular —

- (1) it can carry out simple operations exceedingly fast; for instance, the machine can add two digits together in about a millionth of a second, and all multiplication is done by repeated addition.
- (2) it can follow a chain of instructions. Thus to work out the equation:  
$$x = (a \times b) + (c - d)$$
it is necessary to do the following:  
multiply a by b  
subtract d from c  
add the first result to the second  
print the result and call this x  
and the computer can follow these instructions in that order.
- (3) it can "choose" between following one set of instructions or another according to the result of some intermediate calculation. Thus if one were trying to find whether a number were divisible by 3, 5, or 9 one could tell the computer:— if the result = a whole number then print the result, otherwise try the next one. If there is no "next one" then print 0.

These properties look simple, but enable a very wide range of problems to be tackled. The programme often looks long winded on paper, but the machine is extremely fast.

The following diagram shows the essential features of any digital computer.



The instructions and data are usually coded in the form of punched paper tape. Each key depressed on a special typewriter produces a different combination of holes across the tape, and in the machine these holes can be "read" by means of a light shining through them onto a row of photo-electric cells (the input device). Most machines will accept magnetic tape and punched cards as well.

All instructions for the machine are written in a special programming language (usually Atlas Autocode in Edinburgh) and this is very like English; but when the language compiler receives a word such as "add" a + b it will in turn switch on the various devices inside the computer required to add these two digits together.

The store is the memory of the machine, performing a function similar to that of a tape-recorder, and can be considered as a large number of boxes holding numbers, which can be transferred to and from the calculating unit or printed out as directed by the instructions. The output device is usually a "Line Printer" although paper tape is sometimes used and this can be fed back through the special typewriter to produce a printed result.

**USE OF THE COMPUTER**

To illustrate the use of the machine a programme can be considered. For instance, it might be required to find the number of times a letter occurs in a sentence. Regarding the store as a series of boxes, a Flow Diagram for this programme would appear as follows:—

- (1) Begin
- (2) put the letter to be counted into box 1
- (3) start reading the letters of the sentence, one at a time, into box 2
- (4) if the contents of box 1 = box 2 then add 1 to box 3, otherwise go on to the next letter
- (5) if the last letter of the sentence has been reached print out the total in box 3
- (6) stop.

These instructions can easily be written out in Atlas Autocode, followed by the data which in this case would be the letter to be counted, and the letters in the sentence.

Now this programme needs very little alteration to count the number of times a particular word, or particular phrase, occurs in an entire book, and it was this method which was used to determine whether in fact Paul wrote all the chapters attributed to him in the Bible since any writer characteristically uses particular phrases with a particular frequency. Another possible use of this programme might be to search through vast amounts of literature for a particular reference such as, say, "Acute Tubular Necrosis". This idea could be extended to make the machine print out a list of references of articles which contained both the phrase "Acute Tubular Necrosis" and the phrase "Hypertension" thus providing an interesting method for extracting any desired information from any amount of literature. Others have tried to apply similar programmes to the automatic translation of language, but so far without very much success.

Another idea which has been put forward is the Automatic Library Facility (ALF). Suppose Dr. A. has certain items of information  $1_1, 1_2, 1_3$  and  $1_4$  (which may be symptoms, signs, or results of tests, etc.) concerning a patient, but that he requires more information on the differential diagnosis than his own knowledge or experience affords. Normally he would consult his own colleagues and the available literature but it is now proposed that in addition he consult ALF. Asked for the very first time by Dr. A. what diseases are associated with  $1_1, 1_2, 1_3$ , and  $1_4$ , ALF will answer none, which of course is no great help to Dr. A. who can himself think of two such diseases  $D_1$  and  $D_2$ . ALF stores these two. When next asked a similar question by Dr. B., ALF obviously produces  $D_1$  and  $D_2$ , one of which is news to Dr. B., but who notes that ALF has omitted a third possibility,  $D_3$ . In effect, ALF now "knows" the associations of Drs. A. and B. and clearly after 100 doctors have made their enquiries, ALF's



suggestions will be of use to any doctor who does not know as much as all the previous enquiries put together.

Furthermore, as knowledge about individual diseases accumulates, ALF could also indicate an exhaustive set of other differentiating signs, tests, etc., and if told of the methods of treatment used together with the results obtained, the computer will be able to compare these and offer advice to others on the best treatment available to date.

Yet another important use of the computer organisation described is in drug testing. If it was mandatory to report the prescription of any new drug, together with any symptoms appearing which were not present before the drug was prescribed, then it would be surprising if side-effects were not recognised very soon. In this context it is worth remembering that even after thalidomide, the problem of congenital abnormality remains, and a systematic, statistical analysis of all relevant data could be a powerful research tool.

There is a continual search for tests which are absolutely diagnostic of specific diseases, and the computer can be of value in this field also. For instance, although there may be no single test available, it is often the case that a certain set of symptoms, signs, etc., may be absolutely diagnostic, and statistical analysis of all the factors relevant to each disease may indicate cases where this is so. The principle can be extended to include assessment of the significance of the various waves produced by ECG or EEG machines. Then in certain acute disease, such as myocardial infarction, measurements of B.P., pulse rate, or blood chemistry may be carried out by automatic equipment already available, and the resultant data analysed by the machine which would indicate the treatment required, or might even initiate such treatment in some cases. The advantage of the machine when prescribing a routine of treatment is that the needs of the individual patient are catered for, which should be better than using a standard routine.

There are many other uses for the computer within the hospital and an example is as an aid to the bacteriologist.

Bacteriological identification proceeds by submitting a specimen to a number of tests, deciding on the basis of the results which are the most likely possibilities, then carrying out further tests to differentiate between these, and so on until identification is established to the bacteriologist's satisfaction. A computer procedure has been developed to assist the process

as follows: the results 'phoned in to the computer centre may be as in Fig. 1.

Fig. 1

Computer Input	}	lactose = acid
		sucrose = acid
		indole = negative
		motility = negative
		H <sub>2</sub> S = negative
		Urea = negative

At the centre these are typed out, and the resulting piece of punched tape entered into the computer. Within a few minutes it will print out the most likely bacteria in order of preference, and also the next set of tests which will most efficiently discriminate between these. (See Fig 2).

Fig. 2.

Sh. Sonnei	100	} relative likelihood
Klebs. Rhino scleroma	50	
Sh. Dysenteriae type 1	1.32	
Alk./Dispar group	1.32	
Sh. Flexneri	.69	
further tests:—		
Xylose	1.00	} relative discriminating power
Sorbitol	.90	
K.C.N.	.86	
Dulcitol	.79	

In actual cases it has been found that the computer has agreed with the bacteriologist in all important respects, and has generally established the diagnosis using fewer tests. Of even greater benefit to the patient, however, is the fact that the computer keeps up to date with all the latest developments in the field.

#### COMPUTER CENTRES

It should be noted that in most cases, the machine spends far less time calculating than the operator takes in deciding what to do with the results. A Time Sharing technique is usually used so that data is fed in to small machines, perhaps one in each hospital eventually one day, and a large central computer turns its attention to these to suit itself, thus saving time and money. The central machines are being set up at various places in the country for general University use, by the government, and methods are being developed by which these machines can communicate with one another also, which will have vast potential one day. As far as Medicine is concerned the same device which can communicate with world diagnostic or information networks could be used to calculate nursing schedules or teach-

ing timetable, or may compare the vital statistics of one hospital with another to indicate how an epidemic is spreading.

The next difficulty is that as the requirements get more complicated, so programming the machine takes longer, and several centres are trying to devise systems in which the machine programmes itself. As an example, various attempts have been made to write a programme for the computer to play chess. For a man to tell the machine what to do in every possible situation in advance would take a very long time. However the machine can survey the positions of all the men on the board and then try a move at random. If this results in immediate gain, or if it eventually wins the

game, it will try the same moves for each time the particular combination of men recurs in future games. If it loses, it will remember what its opponent did, and will use his moves in future instead. Analysis of game theory in this way has led to important advances in other sciences, and may well be of use in the medical field in the future.

Altogether the computer may well provide the spectacular changes in Medicine in our generation that antibiotics and bacteriology provided for our forefathers, and time spent acquiring some knowledge of how it works while at University is most unlikely to be time wasted.

## DIAGNOSTIC PROBLEM

Set by Robin B. L. Ewart, M.B., Ch.B., B.Sc.

(answer on page 44)

### Subject :

C.S., married, female, aged 33. Housewife.

### Past History :

1. Usual childhood illnesses.
2. Pneumonia on three occasions between the ages of 3 and 5 years.
3. Rheumatic fever, aged 9 years.
4. Tonsillectomy, aged 10 years.
5. Appendicectomy, aged 16 years.
6. The patient had two normal pregnancies, aged 23 and 24 years.
7. Perforation of duodenal ulcer, aged 25 years. — Gastroenterostomy.
8. Gradually progressive exertional dyspnoea began, aged 27.
9. Two miscarriages, aged 28, followed by tubal ligation on the grounds of rheumatic heart disease.
10. Mitral valvulotomy successfully carried out, aged 29, with relief of symptoms.
11. Recurrence of classical acute rheumatism, aged 30.

Following discharge from hospital, the patient seemed initially to be well but 2½ years later was readmitted with the following complaints —

1. Tendency to bruise on minor trauma, — 1 year.
2. Marked emotional lability — 1 year.
3. Progressive increase in weight amounting to 9 lbs. in the previous six months.
4. Increasing lethargy — 3 months.

### Social and Family History :

Not relevant.

### Examination :

Plump, plethoric woman, looking older than her 33 years.

Marked bruising of all four limbs was evident.

C.V.S. Pulse 102. Regular in time and force. B.P. 180/110. Auscultation of the heart revealed the classical signs of mitral stenosis and incompetence. There was no sign of cardiac failure.

All other systems essentially negative to full examination.

### Findings:

1. History of bruising, emotional lability, increasing weight and lethargy.
2. Plethora.
3. Diastolic hypertension.

What is the diagnosis? How would you confirm it?



**G**en. (daily) pract., v. highly recc.,  
**U**nlimit.poss. for joy,  
**I**mmed. opp. for doc. (or spec.),  
**N**o drawbacks to annoy....  
**N**o general practice, you might think,  
**E**xists of such a class---  
**S**tay, yes there does! As daily drink,  
**S**ome Guinness, in a glass!

# THE HAND IN CLINICAL MEDICINE

**Edward B. French, B.A., M.B., B.CL., B.Ch.,  
F.R.C.P.E., F.R.C.P.**

*Physician, Western General Hospital*

It is no wonder that the diagnostic value of the facies has often been emphasised, for expression, form, colour, condition of the skin and hair and many other features can be studied from the beginning of the interview. In clinical practice it is common, after examination of the face, to take up the hand and feel the pulse. The experienced clinician may gain almost as much information from the hand as from the face, for the hands also show expression and character. Furthermore the hands are so highly developed that the blind and the dumb may use them as effective substitutes for reading and for speech, and many of us gesticulate for emphasis. Indeed, gestures made by patients to indicate the site and character of symptoms can be most helpful. Thus the flat of the hand is pressed upon the vertex of the head with psychogenic headache, both hands squeezing across the front of the chest commonly indicates ischaemic heart pain, or the tips of two or three fingers pressed into the epigastrium suggest the pain of peptic ulcer.

A study of all the conditions in which examination of the hand may contribute substantially to diagnosis would result in a long, dull catalogue. It is proposed therefore first to consider variations in form and function and then to give a sufficient number of illustrations to indicate the diversity of the specialties which may be concerned.

## GENERAL OBSERVATIONS

The firm determined grip or the soft flabby handshake so often reflect the personality. The manicured or the careworn hand, the tobacco stains, the bitten nails, the nervous tremor, the the ring on the finger and the foreign tattoo each tell their story. The circular tattoo in the first left interdigital space made by pen and ink at school can be distinguished from injuries contaminated by coal dust. This may well provide an essential clue to the cause of breathlessness in a patient, previously a miner, who has not divulged that he has changed his job. Conversely the occupation may indicate the cause of many hand lesions such as the pilonidal sinus of barbers, erysipeloid of butchers or anthrax of tanners. A transverse ridge at the same level on each of the nails may date a forgotten illness by the fact that the nails take about six months to grow.

## Movements

In addition to gesticulation and the nervous tremor already mentioned, there may be a familial tremor so easily and unkindly mistaken for the shaky hand of the chronic alcoholic. The hyperkinetic hand of the thyrotoxic patient plucks and twines a handkerchief or nearly tears off the buttons in haste to undo the vest. The flapping, darting movements of the outstretched hand are characteristic of renal or

hepatic or respiratory failure and may be bad enough to cause articles to be flung to the ground. The jerky movement of rheumatic chorea may be exaggerated by picking up an object, while the rhythmic pill rolling of paralysis agitans will cease during a purposeful movement. The finger-nose test and dysidiadochokinesis are among the standard tests for demonstrating sensory and cerebellar ataxias, made worse in the former by closing the eyes.



Figure 1

#### Size and Shape

A disproportionately broad hand and fingers may be helpful confirmation of acromegaly. The long thin fingers (arachnodactyly) of Marfan's syndrome (Fig. 1) could be useful corroboratory evidence of dissection of the aorta in a young person. A great variety of other inherited disorders such as polydactyly, a bent little finger, or a stumpy, broad-nailed, terminal phalanx of the thumb are useful genetic markers. Symphalangism is rare but evidently persistent as shown by the famous Talbot family whose illustrious ancestor from the 14th century is alleged to have shown fusion of the phalanges when the skeleton was disinterred in Salisbury Cathedral. It is a pity that this story has recently been doubted and the family tree pruned by a few hundred years.

#### Colour

Pallor of the hands, especially of the nails and the palms, is a useful clinical check for anaemia. Cyanosis indicates an unusual degree of oxygen desaturation of the blood. Only if

the hand is warm in a temperate climate can it be deduced that the cyanosis is central in origin. Even then there is the rare exception of polycythaemia rubra in which it is the density of colour that gives the cyanotic appearance. It is well to remember in assessing colour that any dark pigment deep to the skin looks blue due to the rearrangement of light as it passes through a turbid medium. The light which is transmitted contains a greater proportion of the longer wavelengths (red), while that which is scattered to the sides and back to the surface contains a correspondingly large proportion of shorter wavelength (blue). For example, the dark blue of a tattoo is made by lampblack (Indian ink) while the blue colour of the veins is due to the dark red blood within them. If the skin of the back of the hand becomes very thin in the elderly or in sufferers from rheumatoid arthritis then the veins may be red. Brown pigmentation due to an abnormal amount of melanin is a feature of a number of local and systemic disorders; it is characteristically seen, especially over the knuckles and in the palmar creases, in many cases of Addison's disease.

#### Temperature

The examiner's hand is a superb thermometer and it is usually easy to observe by palpation that a patient is febrile. In a temperate climate the temperature of the patient's hand is a good guide to the mean blood flow through it, and in appropriate circumstances it may be a helpful indication of peripheral blood flow in general. Hot moist palms often indicate hyperthyroidism, while cold and clammy ones may be due to nervousness. It is a remarkable fact, not always appreciated, that thermal sweating does not affect the palms.



Figure 2



Figure 3

#### Structure of the Hand

Any of the structures of the hand may be affected by a variety of local and systemic disorders, all of which must be recognised in order that the importance of each may be assessed. Sex and age changes may occur. Thus the smooth hairless hands of the child should change to a more lined and hairy hand in the adult male unless hypogonadism is present. In the elderly an atrophy of the collagenous supporting tissue leads to wrinkling, to a characteristic type of purpura and a mottled brown and white pigmentation. The nails, joints, bones, muscles, tendons, nerves, and arteries may be affected by systemic disorder and as examples of each are koilonychia (due to iron deficiency), gout, sarcoidosis, motor neurone disease, xanthomatosis, leprosy and disorders of the pulse.

#### THE DIFFERENT SPECIALITIES

It is not too fanciful to suggest that in cardiology a diagnosis of subacute bacterial endocarditis could be made from the hand alone. No doubt a well taken clinical history should be leading in the right direction, but a pale hand, a waterhammer pulse, clubbing of

the fingers, with several splinter haemorrhages beneath the nails and small tender lumps on the palmar aspect of the fingers (Osler's nodes) would provide the full house.

Reference has already been made to acromegaly, hypogonadism and hyperthyroidism and there are other endocrine changes such as hypopituitarism, myxoedema, tetany and hyperparathyroidism. Before the days of P.B.I. estimations and radioiodine studies some surgeons judged the severity of thyrotoxicosis with greater confidence by shaking hands with the patient than by accepting a figure derived from a dubiously performed B.M.R. estimation. The tachycardia, the bounding pulse, irregular perhaps due to atrial fibrillation, the hot sweaty palms and the fine tremor are still very useful signs. In hyperparathyroidism, absorption of bone may sometimes be sufficient to shorten the terminal phalanx. The soft tissues are then redundant, the end of the finger becomes bulbous and the nail curved. Spotting this pseudoclubbing of the hand led to the diagnosis in a matter of seconds in the case of a woman who previously had been investigated in three hospitals, without success. (Fig. 2)

The dermatologist could have a field day with the hand alone. The amateur suspecting scabies will find that the hand is helpful in providing lesions between the fingers where the characteristic burrows may be seen as thin sinuous lines, from the active end of which the mites may be obtained.

The forensic expert, in league with the C.I.D., may be able to identify a body or a crime from the fingerprints. Indeed, it was this fact that led Dr. Ruxton to attempt to get away with murder by removing, among other things, the terminal phalanges of his victims.

spleen would be comforting confirmation to the clinician.

The geneticist has good reason to be interested in the hand, for inherited abnormalities are so easily seen. Reference has already been made to some of them, but there are many others such as webbed fingers (Fig 3) or the nail-patella syndrome. The latter is a quaint complex of dystrophic or absent nails, small patellae and bony outgrowths on each ilium, which is transmitted as a dominant syndrome.

Finger nails which are concave on the upper surface, thin and brittle (koilonychia)



Figure 4

Flapping tremor, central cyanosis, finger clubbing, leuconychia, spider telangiectases, erythematous palms and Dupuytren's contracture may alert the gastroenterologist to the cause of haematemesis, for any or all of these signs may be present in conjunction with hepatic cirrhosis. Dilated veins on the abdominal wall, some ascites and a palpable

indicate to the clinician that iron deficiency is present before the haematologist comes to the rescue. The reason for the iron deficiency must then of course be sought, but when koilonychia is present the condition is of long standing and is usually due to dietetic deficiency.

Industrial and occupational medicine is commonly concerned with a great variety of

causes of dermatitis, and in the case of tar workers this may lead on to the formation of an epithelioma. Injuries to the hands are extremely common, especially in miners and sawyers, and there are other local hazards such as chrome ulcers and the occupational diseases mentioned under the general inspection.

The *nephrologist* must at present be satisfied with the pale, brownish, dry hand with uraemic twitching as a minor contribution to diagnosis. However, chronic renal disease, which was considered to be due to tuberosc sclerosis, was first suspected in a woman in her sixties by noting the characteristic periungual fibromata: minor lesions present on the face had not been observed.

The *neurologist* has plenty of observations available including, among others, the spontaneous movements already mentioned, sensory and motor changes, muscle wasting and fasciculation, or the very rare azure blue lunulae of hepato-lenticular degeneration.

The *obstetrician* may be consulted about sterility and may observe the short metacarpal and receding knuckle of Turner's syndrome (Fig. 4) while the *ophthalmologist* may notice the long spider-like fingers of Marfan's syndrome in association with dislocated lenses. It might seem too far fetched to include *otorhinolaryngology*, but a woman who was first referred to that specialty for deafness, the cause of which was overlooked, had myxoedema with very little to see in the face; her speech and thought seemed unimpaired though she admitted that her singing voice had deterior-

ated for two years. The hands were slightly swollen in appearance, the skin was dry, and paraesthesiae were present in the fingers due to compression of the median nerve in the carpal tunnel. All these symptoms disappeared on treatment with thyroxine.

The *paediatrician* has interests in common with the geneticist, but has pink disease all to himself for it occurs only in babies and young children. The hands and the feet are so strikingly red, cold and later peeling as to be responsible for the name of the disease.

The *psychiatrist* may find interest in nervous tremor, bitten nails, dermatitis artefacta or barbiturate blisters. In *respiratory* disorders the combination of cyanosis and clubbing with multiple telangiectasia on the fingers as well as around the mouth and face may direct attention to an associated pulmonary arteriovenous fistula. The *rheumatologist* and the *orthopaedic surgeon* have common ground in the various forms of arthritis.

The list is long and could be lengthened both with regard to the number of specialists and the variety of lesions in the hand which is of interest to them. However, more than enough has already been written to draw attention to the diagnostic value which may be found in a careful examination of the hand. It is a part which deserves special consideration for among the major evolutionary features, it is one that has enabled man to control his environment and to rise above all other living creatures.

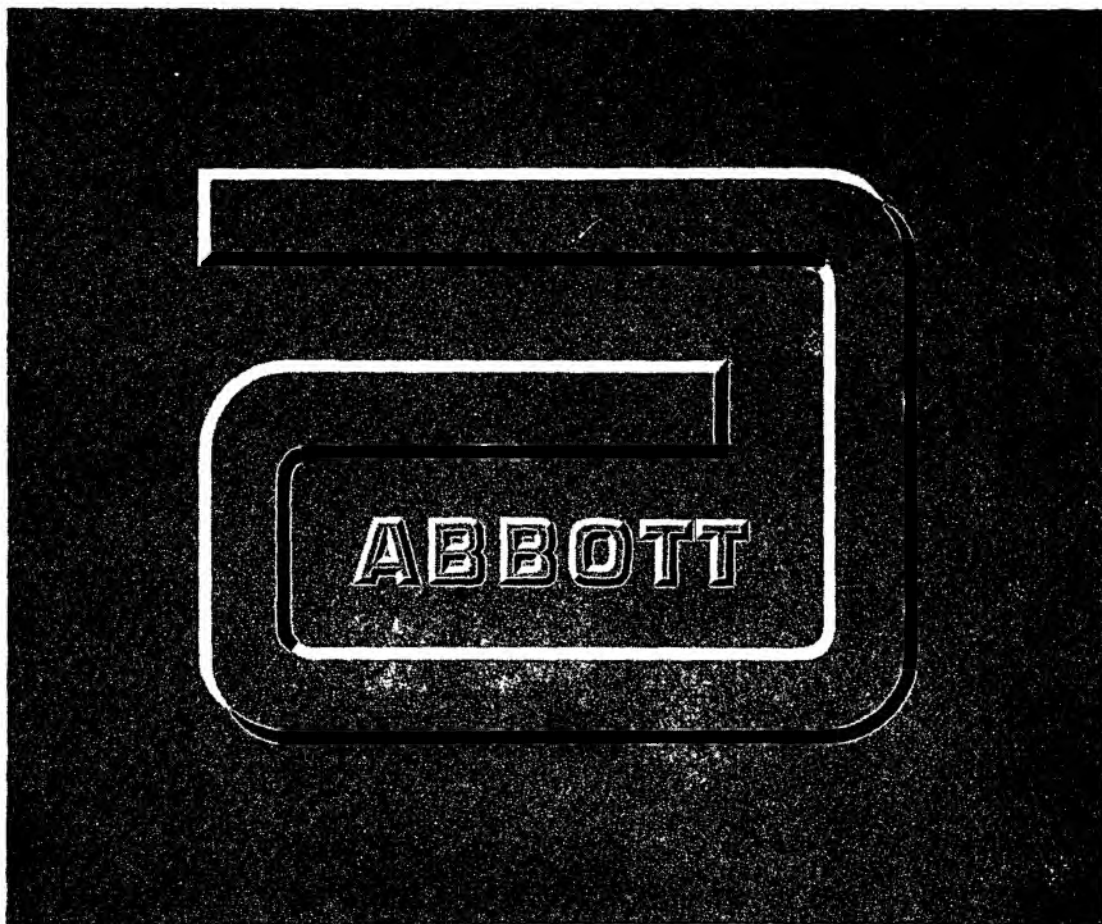
---

## Mesmerism

"The first night I attended to witness a Frenchman, Mr. Lafontaine, perform magnetic experiments; as it was quite possible that the whole of the phenomena exhibited by his patients might have been the result of collusion or illusion, I set the whole down as such. A week thereafter I had another opportunity of watching his performance, when I saw an effect produced upon a stranger, which I believed to be a genuine phenomenon — viz. the inability of the patient to open his eyelids after they had closed. I could not then comprehend the cause of this. Next night I watched very closely whilst he mesmerised this same patient, and before the end of the experiment, I thought that I had discovered the cause of this curious phenomenon."

This paragraph is taken from the opening section of James Braid's "Essay on Hypnotic and Mesmeric Phenomena", a manuscript copy written by the author and presented to the Society in 1853. Braid became renowned in this field and the original article was "read and discussed by them (the members) during three nights of session, 1853."





## The symbol of better health

Just as a patient needs to have complete confidence in the doctor, so the doctor needs to have confidence in the products he prescribes. Ultimately, this means confidence in the manufacturer of pharmaceuticals. Such confidence can only be built up over the years, by the profession as a whole, when it has used the products and found them not only effective, but also convenient and consistent in use. Confidence is a complex phenomenon, but easy to recognise—like the Abbott symbol.

**Abbott pharmaceutical products include:** Aerotrol · Calcidrine · C.V.K. · Dayamin · Desbutal · Di-Paralene  
Enduron · Enduronyl · Erythrocin · Erythroped · Eutonyl · Ferro-Gradumet · Ferrograd C · Harmonyl · Iberol · Nembudeine  
Nembu-Donnal · Nembutal · Norisodrine · Paradione · Peganone · Penthrane · Pentothal · Phenurone · Selsun  
Serenesil · Tridione · Vi-Daylin

**ABBOTT LABORATORIES LIMITED QUEENBOROUGH KENT**

# THE CHOCOLATE COATED PILL

**Roger H. Smith, B.Sc.**

From a dissertation on the side effects of Oral Contraceptives, read before the Society on  
Friday, 2nd December, 1966

The great increase in the world birth rate that is presently taking place, and which increases the population by 165,000 people per day, has been estimated to double the total human population by the turn of the century. The problems set by such a rise in numbers is not confined to the East or to the "under-developed" countries of Africa, but is calculated to increase the population of Britain by 50% in those same thirty-odd years.

Clearly, something has to be done to check this growth which far outstrips the foreseeable increase in food resources, and even more clearly the answer is birth control, in one way or another. In Britain at present the control is largely by two methods, the oral contraceptive and the intrauterine device (IUD), so that in 1965 over 500,000 women in this country were taking one or other form of pill at some time, and 400,000 took pills over a 12 month period without a break. But at the same time, the Pill has come in for much adverse criticism for its possible or actual side effects in both the lay and the scientific press, and as a result, there has grown suspicion and fear in many women and not a few doctors whose job it is to prescribe the Pill.

## THE PILLS

In Britain the main drugs in use are com-

bined progestin/oestrogen preparations, taken between days five and twenty-five of the menstrual cycle. Nine such preparations are approved by the Council for the Investigation of Fertility Control (CIFC), the research branch of the FPA. This paper will consider the evidence regarding the side effects of this type of pill alone.

Another type of Pill has recently been developed and marketed, known as the Sequential Therapy type, where pure progestin is given between days 5 - 20 followed by five days of combined pills. But a certain failure rate does not allow as much confidence in these as in the combined forms, and for this reason only the combined form will be considered.

## POSSIBLE SIDE EFFECTS

There are well established side effects to the Pill, such as initial nausea and vomiting in some women, but there are other effects not so well established, like liver damage, increased risk of thrombo-embolic disease, weight gain and other metabolic changes; this paper seeks to correlate the evidence available regarding these doubtful effects.

## WEIGHT GAIN

It has been said that the weight gain during oral contraceptive therapy presents no problem. It was a man who said it, and not a woman,

Progestin	mg.	Oestrogen additive		Trade Name
		Mestranol mg.	Ethyinyl Oestra- diol mg.	
Lynestranol .....	5.0	0.15	—	Lyndiol
Megestrol .....	4.0	—	0.05	Volidan
Norethisterone .....	2.0	0.10	—	Orthonovin
Norethisterone ac .....	2.5	—	0.05	Norlestrin
Norethisterone ac .....	4.0	—	0.05	Anovlar
Norethynodrel .....	2.5	0.10	—	Conovid E
Norethynodrel .....	5.0	0.075	—	& Previson
Ethynodiol diac .....	1.0	0.1	—	Conovid
				Ovulen

Fig. 1. Combined Therapy Pills approved by C.I.F.C.

and it was in a medical rather than a philosophical context that it was said. When we talk about a weight gain we must consider the age group and sex of the subjects involved, and here we are dealing with women between the ages of 16 and 50, the very people to whom any weight gain seems important. So that, far from presenting no problem, weight gain could prove to be a deciding factor to any woman considering whether to take the Pill for the first time, or whether to continue taking it having once started therapy. Before we pass this off as of minor importance, we should at least examine the incidence and extent of weight gains during therapy, and investigate the cause and nature of the gain.

In a recent study, the C.I.F.C. found that treatment with Anovlar is associated with a high incidence of weight gain; of 156 patients studied, 46% put on more than 3lbs. and 22% gained more than 7 lbs. Liggins, using larger doses of Anovlar in the treatment of dysfunctional uterine bleeding, found general increases of weight of up to 9 lbs., and one case of a gain of 20 lbs., all over similar periods of time. But Wiseman has found that treatment with compounds other than Anovlar, such as Conovid or Ovulen, give equivocal results, weight gains over 3 lbs. being matched by a similar incidence of weight loss greater than 3 lbs.

While comparing their actions in a different context, Jackson found that Anovlar had a predominately progesterone-like influence on the reproductive organs but Conovid gave a more oestrogenic picture. Thus, in those women on Anovlar there was a dormant, hypoplastic endometrium, with thick, scanty cervical mucus, while women on Conovid had cornified vaginal epithelium and proliferative endometrium.

It is conceivable that weight gain in Anovlar therapy, then, is the expression of progesterone-like properties of its progestin, Norethisterone, while the progestin of Conovid, or of Ovulen, having less progesterone-like activity and more oestrogenic properties, would not be expected to stimulate a gain in weight. Such a hypothesis is supported by evidence which suggests that Progesterone itself is an anabolic agent.

Dewar has shown conclusively that the maintenance of the weight gain of pregnancy in mice is dependent upon circulating Progesterone; furthermore, Progesterone administered to male and non-pregnant female mice produced weight gain, and this gain was uninfluenced by coincident oestrogen administration. Such gains were associated with increased appetite, and were the "manifestations" of the accumulation of body fat and body water, regardless of diet. On unrestricted diets there were also increases in body protein.

During human pregnancy, the mother's weight gain is associated with rising blood Progesterone levels; not all of this weight gain is due to increased body water for there is a considerable increase in body nitrogen. The weight gain of oral contraceptive therapy would likewise seem to be anabolic, at least in part, for the fall in weight which follows the cessation of therapy in such cases is slow, spread over several weeks or months, and its rate of fall is not affected to any significant degree by the application of diuretics.

These lines of evidence suggest that progesterone-like therapy, including some oral contraceptives, can be expected to carry with it the possibility of weight gain of an anabolic nature. But a further factor may act in addition to anabolic influence, per se.; that is, increased appetite. The increased appetite might be

seen as part of the anabolic effect, but it might be preferable to think of it rather as a manifestation of the general "new lease of life" so widely reported by patients introduced to oral contraception. If this is so, then dieting may often be a necessary accompaniment of therapy.

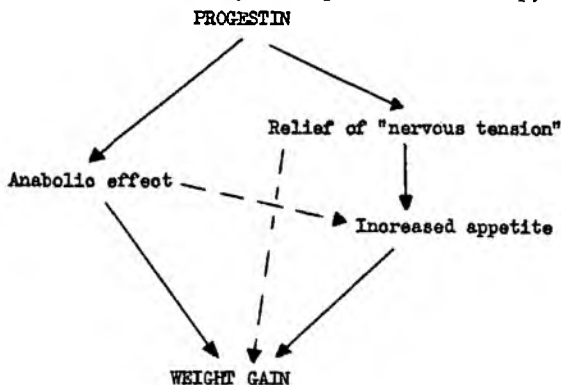


Fig. 2

The effect on appetite would also help explain why other studies, such as that by Flowers, have found weight gains with Ovulen and other products other than Anovlar; indeed, one woman out of 200 on Ovulen gained 20 lbs. in three months.

The conclusion, then, must be that weight gain can be a medical problem, and hence women or oral contraceptive therapy should be followed up; and usually the problem is a psychological one to the patient, which might call for advice. In order to give advice where it is needed we must be presented with more hard facts from large scale studies of weight and appetite in treated women, and, where gains occur, of the nature of this gain.

#### BLOOD COAGULABILITY

Much has been made of the assertion that synthetic steroids might increase blood coagulability. While reporting in the medical journals has stimulated a proper study of the problem, the reaction to the advertising in the newspapers has bred a fear of oral contraceptives in many women. Two lines of study have been pursued:

- (1) a large scale statistical comparison of the incidence of thrombo-embolic disease in women taking oral contraceptives and those of the same age-group not undergoing therapy.
- (2) haematological investigations in the treated and non-treated groups.

#### (1) Haematology

Behind the word "coagulability" there are

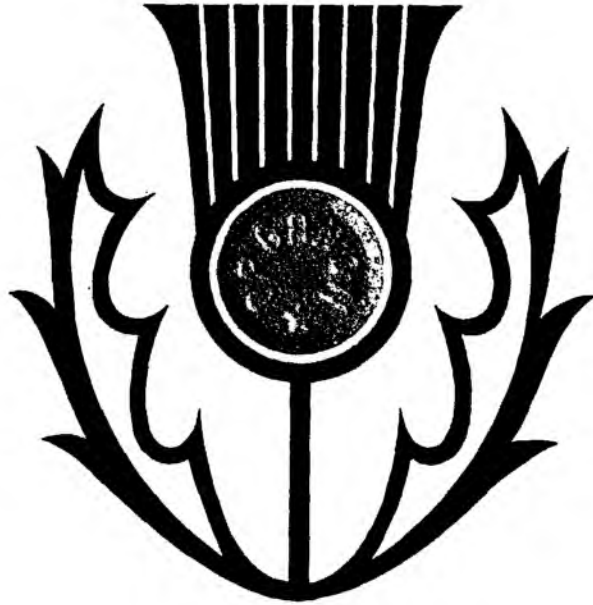
two primary processes of remarkably similar complexity, coagulation and fibrinolysis. Each comprises of a system of precursors and activators; each depends upon successive steps of activation; in each there is a number of negative systems tending to antagonise the various activation steps and products. The two processes are currently thought to be in dynamic equilibrium in the circulating blood, pivoting round the fibrin molecule: the one process forms the clot, the other destroys it. Any change in blood coagulability is the result of an upset of this normal equilibrium. In assessing the effect of an increased activity of any one part of either system, one must consider whether there is not also a change in the activity of a factor or factors in the opposing system. In any event, the interpretation of such a rise within its own system is a very difficult task.

The only factor which has consistently been shown to change is factor VII of the coagulation system; its blood concentration increases. No other coagulating factor has been demonstrated to change in any reproducible manner. Factor VII also increases in pregnancy, and is increased in patients with recent DVT ("Deep Venous Thrombosis"), but only in these latter cases has there been demonstrated a shortening of the heparin clotting time. If an increase in factor VII, per se, is contributory to greater clotting tendencies, such increases as have been shown still cannot be said to constitute satisfactory evidence for increased coagulability. There is neither any information regarding the state of the fibrinolytic system during therapy, nor of any influence that the synthetic steroids might have on the antithrombin and other systems.

Therapy	No.	Bleeding time (secs)	Clotting time (secs)
Control .....	26	145 ± 8.21	278.8 ± 10.7
Medication .....	39	116.8 ± 6.31	261.5 ± 7.02
3 - 8 months Post			
Medication ...	10	103.4 ± 12.4	223.9 ± 15.5

Fig. 3. Significant results (bold type) found with 10 mg Conovid Dosage (after Pincus, 1956).

The only information that can safely be accepted as evidence either way is that showing change in clotting or bleeding times. Pincus, in his classical trials using Conovid, did find shortening of bleeding and clotting times, but using 10 mg doses rather than the 5 mg used



**You already know**

Lyndiol 2.5 to be the oral contraceptive  
with the lowest incidence of side-effects,  
the most reasonable price-to-patient  
and the dosage scheme most likely to  
ensure patient reliability

**But did you also know  
that Lyndiol 2.5 is  
MADE IN SCOTLAND!**

lynestrenol 2.5 mg. mestranol 0.075 mg.

*Detailed professional and patient literature gladly sent on request*



Organon Laboratories Limited  
Newhouse · Motherwell · Lanarkshire

in more modern therapy. No such results were found in the studies of Egeberg or of Thompson whose work is referred to above.

**(2) Statistical Surveys**

Agencies of the U.S. Government have carried out large scale statistical surveys, and have concluded that "there is no increase in the incidence of thrombotic disease in women taking oral contraceptives compared with the incidence in non-pregnant women of the same age group who are not treated".

There have been many isolated reports of thrombo-embolic disease in treated women, but it is important to consider that a certain incidence is in any case expected in women of this age group, whether or not they are taking the pill. It is the view of the Dunlop Committee that the incidence in treated women is indeed just that expected on this basis; but the Committee is nevertheless urging that all thrombo-embolic incidents in treated women should be reported. However, by the time statistical analysis is possible and is available, it is likely that the present form of pill will be obsolete.

**HEPATOXICITY**

Many drugs have been shown to be toxic to the liver, a fact that should not be surprising, for the liver is the main site of drug detoxication and excretion, and it is the first port of call for oral drugs once absorbed into the blood. Cholestatic jaundice of a non-sensitive type has been shown to develop in relation to therapy with the general group of steroids alkylated at the C-17 position, to which group belong most of the progestins presently used in oral contraceptive preparations. The general rule is that the C-17 alkylated steroids cause liver damage if given often enough and in sufficient amounts, so that the problem here is whether

the amounts of these compounds in the various pills constitute a risk of hepatotoxicity.

Many studies have been carried out attempting to determine just this one simple fact, only to find that the answer is not so simple.

There seems to be no common plan to the studies, each one having employed a different drug or combination of drugs on different groups of women in different countries and using different criteria for liver damage. But, complicated as this might seem, it is possible to draw certain conclusions on the subject, and to see certain general trends.

Scandinavian workers have been able to demonstrate quite widespread liver damage in treated women, while elsewhere the conclusion has been that there is no danger of associated hepatotoxicity during normal contraceptive therapy. In Finland, abnormally raised serum transaminase levels were found by Eisalo et al in all of seven post-menopausal women treated, and by Palva and Mustala in five. Eisalo gave one or two tabs. per day of Lyndiol; Palva used Anovlar. Eisalo was later able to reproduce his results in a number of cyclical women between the ages of 17 - 52 using Volidan as well as Lyndiol or Lynestranol.

Other isolated reports have come from Scandinavia, so that it has been suggested that the apparent high incidence of liver damage there might be connected with the fact that viral hepatitis takes an unusually virulent form in this geographical area. However, Borglin in Sweden has not been able to demonstrate hepatotoxicity in patients on Lyndiol.

In a British report on liver damage, by Aascher and Cuthbert, five post-menopausal women had been treated with Anovlar; their ages were between 62 - 80. Stoll in Australia produced

**Fig. 4. Abnormal results of liver function tests**  
(Eisalo et al 1965)

DRUG	Total Patients	SGOT		SGPT	
		No. of Abnormals	Units (mean)	No. of Abnormals	Units (mean)
Volidan .....	45	0	-	2	52-73 (62.5)
Lyndiol .....	39	6	43-79 (58)	7	41-115 (68.2)
Lynestranol .....	25	1	42	1	69

liver damage in treating breast cancer with 6 tabs per day of Lyndiol, equal to 30 mg lynestranol + 0.9 mg mestranol; clearly this represents an abnormally massive dose, but it does serve to illustrate that these are potentially very dangerous drugs.

Thus there would seem to be two important factors in the aetiology of liver damage in treated women; one a possible post-menopausal predisposition to drug induced intra-hepatic cholestasis, and the other the possible predisposition due to previous liver disease. A third possibility has been suggested, that Scandinavian women, and post-menopausal women in general, share some common enzyme deficiency.

More reassuring are the results of a large scale study, by Tyler in Los Angeles, which covers eight years of observation. Tyler reports a general incidence of abnormal liver function, but in each case the changes have been of the order expected in normal pregnancy; it seems fair to conclude that these changes, due to a variety of preparation, might not be pathological but attributable rather to the pseudo-pregnant state. More specifically, he studied 6,500 cycles in 435 women on Orthonovin over a period of 3 years, during which time he found no abnormality which could cause alarm, and certainly no indication in any patient that the pill should be discontinued by reason of liver damage. Swyer and Little working in Britain have failed to demonstrate any liver malfunction in a group of 12 women treated

for a minimum period of 3 years. Similarly, workers in other parts of the world outside Scandinavia have failed to find evidence of liver damage in normal treatment.

Thus, apart from incidences in post-menopausal women, or where large doses of drugs have been used, the only reports of hepatic dysfunction have come from Scandinavia, and from Finland in particular. The pill would therefore seem to be safe as a contraceptive except for the one exception of women with a history of liver disease.

#### CONCLUSION

Having investigated the three problems of weight gain, thrombo-embolic disease and liver damage, it is apparent that there is little in the way of definite scientifically based conclusion to be made. While the scanty evidence available at present allows of reasonable generalisation, it also calls for more investigation. Another twenty years of study could clarify the implications of therapy, but by that time the present form of the pill will have been superseded.

Not every woman taking the pill is destined to become obese and yellow, with massive DVT; it would be unrealistic to think so. But it would be equally ill-informed to ignore the real risks. However, the risks that seem to operate are greatly outweighed by the tremendous social therapeutic advantages of oral contraceptive therapy.

#### REFERENCES

- Liggins, Jackson, Mears: "Recent Advances in Ovarian and Synthetic Steroids and the control of ovarian function". Sidney Symposium, 1964. ed. Shearman.
- Dewar. Q. J. Ex. Physiol., 1957, 15, 216-229.
- Dewar. Q. J. Ex. Physiol., 1964, 49, 151.
- Egeberg and Owren. B.M.J., 1963, i, 220.
- Thomson and Poller. B.M.J., 1965, i, 1586.
- Food and Drugs Administration, 1963. Final Report on Enavid.
- Press Releases of the Committee on Safety of Drugs.
- Sherlock. Diseases of Liver and Biliary System, 3rd Ed., Publ. by Blackwell 1963, p.307.
- Eisalo et al. B.M.J., 1964, ii, 426 and 1965, i, 1416.
- Tyler. B.M.J., 1964, ii, 1264.
- Swyer and Little. B.M.J., 1965, i, 1412.
- Pincus et al. Am. J. Obst. Gynaec, 75, 1333.
- Aascher & Cuthbert. B.M.J. 1964, ii, 688.

#### DIAGNOSTIC PROBLEM (from page 31)

##### Diagnosis :

Adrenocortical hyperfunction. Confirmed by the finding of an elevated cortisol secretion rate together with high levels of urinary 17-hydroxycorticosteroids. In addition the diurnal variation of plasma 17-hydroxycorticosteroids was found to be absent although the absolute values were just within the upper range of normal.

To determine the site of the underlying pathological lesion, the full range of available tests was carried out. Space precludes their

discussion here, but in the event the most telling evidence was provided by a presacral aerogram which disclosed the presence of an abnormally enlarged right adrenal gland. Right adrenalectomy was carried out with the removal of a 28 G. cortical adenoma. Some difficulty was subsequently experienced in discontinuing exogenous steroid therapy, but otherwise the patient made an excellent recovery with resolution of all presenting complaints together with restoration of blood pressure to normal levels.

## RESEARCH TOPIC

### A Study Of Fibrinolysis

According to present concepts, the enzyme responsible for the dissolution of fibrin both intra - and extra - vascularly is generated by the action of an "activator" upon the enzyme precursor plasminogen. Plasminogen is a B - globulin, of molecular weight of the order of 143,000, and a normal constituent of human plasma. It is known to possess a high affinity for both fibrin and fibrinogen, a property fundamental to the Sherry hypothesis of the physiological function of plasminogen where any fibrin clot is visualised as having an intrinsic plasminogen content sufficient to ensure its lysis when activated. The activation is achieved by activator either trapped within the clot at the moment of polymerisation, or diffusing subsequently into the clot from the surrounding liquid phase.

Abundant evidence now exists to suggest that plasminogen activator is released locally by blood vessels into the circulation in response to acute vascular changes<sup>(1,2,3)</sup> In a series of straightforward "in vitro" experiments in which tissue slices were placed upon a layer of preformed fibrin and local areas of fibrinolysis related to overlying anatomical structures, Todd<sup>(4)</sup> presented evidence which suggests that the human vascular endothelium serves as a labile pool for this activator. However, so far the majority of studies on fibrinolytic phenomena "in vivo" have been conducted with regard to the general circulation; thus it has been demonstrated that in normal subjects systemic levels of circulating activator will increase substantially in response to various physiological stimuli, notably exercise<sup>(5)</sup> and mental stress.

An intriguing question arises as to the gross anatomical origins of all this activator, and in an attempt to elucidate such a source I embarked, in the summer of 1966, upon an investigation of the human uterus<sup>(6)</sup>.

The subjects were fifteen female patients undergoing surgery involving lower abdominal incisions. Blood samples were taken from the uterine artery, uterine vein, and for control purposes from a vein in the cubital fossa. The

majority of the plasma so obtained was treated with acetic acid to precipitate the euglobulin fraction. This moiety is relatively free from plasmin inhibitors, which "in vivo" are excluded from formed clots, but which are present in plasma. The remainder was used for inhibitor estimations.

A proportion of the euglobulin was clotted and incubated at 37°C., and the time taken for the spontaneous lysis of the euglobulin clot was taken as a measure of activator concentration. Other aliquots were used for the estimations of plasminogen and fibrinogen levels. Parallel measurements of fibrin degradation products (F.D.P.), the result of "in vivo" plasmin activity in the subject, were carried out using a technique in which inhibition of anti-serum agglutination of fibrinogen — coated red blood cells by these F.D.P.'s — bears a quantitative relationship to their concentration.

It was found that the uterine venous samples had a significantly ( $0.001 < P < 0.002$ ) greater content of plasminogen activator than the arterial samples. Plasminogen, fibrinogen and plasmin inhibitor concentrations bore neither qualitative nor quantitative correlation to this fibrinolytic activity, there being no significant difference in these parameters between venous and arterial groups. The arterio - venous comparison of fibrin degradation products showed a significantly ( $P < 0.001$ ) higher concentration in the uterine vein than the artery.

These results show that under the conditions of the study, the uteri were contributing to the fibrinolytic potential of the circulating blood. This contribution must be in the form of activator, since no complementary difference in any of the other parameters could account for the present findings. The discovery of F.D.P.'s coming from the human uterus makes it conceivable that normally a constant consumption of the factors of fibrinolysis is taking place, with the enzymatic breakdown of fibrin, thus necessitating their continual maintenance.

Experiments on human blood by Buluk & Furman<sup>(7)</sup> in which an arterio - venous activator difference was demonstrated across the



kidney suggested to these authors that the kidneys might be the organs responsible for activator maintenance. The evidence presented above must throw doubt upon any assumption that, in females at least, the kidney is the sole candidate for this role.

The fact that no significant reduction in plasminogen or fibrinogen levels was found on passage through the uterus is interesting in that active fibrin disintegration can apparently proceed without detectable consumption of these factors. Such a consumption must be real, but the quantities involved are presumably below the detection threshold of our present techniques, quite apart from being insignificant within their total plasma concentrations.

One could say that it is hardly surprising that

an organ so highly vascular and constantly involved in the process of coagulation and fibrinolysis should be found to have a high activator potential, but when a definite contribution by this organ to systemic activator levels is evident, one must consider not only the local processes involved with menstruation and pregnancy, but also the part played by this, and conceivably a number of other organs in the complex fibrinolytic picture of the body as a whole.

In order to further these existing lines of thought I hope, this coming summer, to carry investigations to dogs, where experimental scope is wider.

ANGUS V. P. MACKAY, B.Sc.

#### REFERENCES

1. Kwaan, H. C. & McFadzean, A. J. S. 1956; "Plasma Fibrinolytic activity induced by Ischaemia"; Clin. Sci., 15, 245.
2. Genton, E., Kern, F. & V., Kaulla, K. 1961; "Fibrinolysis induced by Pressor Amines"; Amer. J. Med., 31, 564.
3. Holemans, 1963; "Enhancing the Fibrinolytic activity of blood by Vasoactive Drugs"; Med. Exp. 9, 5.
4. Todd, A. S. 1958; Nature (London) 181, 495.
5. Cash, J. D.; B.M.J. (1966) 2, 502 - 506.
6. Mackay, A. V. P., Das, P. C., Myerscough, P. R. & Cash, J. D. 1967; J. Clin. Path. (To be published)
7. Buluk, K. & Furman, M. 1962; "The Controlling Function of the Kidneys in Fibrinolysis; Experimentia (Basel) 18, 146.

#### THE CONTRIBUTORS

PROFESSOR JOHN GILLINGHAM, head of the Department of Surgical Neurology, Royal Infirmary of Edinburgh and Western General Hospital, is a world authority on stereotaxic techniques in Parkinsonism. In conjunction with the Department of Medical Physics he is also introducing automatic patient monitoring for the detailed study of head and spinal injuries.

DR. EDWARD FRENCH is a physician at the Western General Hospital and a renowned diagnostician. He has contributed to both Davidson's Textbook of Medicine and Macleod's Clinical Diagnosis and on the wards is a skilled and meticulous teacher.

MR. THOMAS HAMILTON is a Melville Trust Cancer Research Fellow in the Department of Clinical Surgery. His major research interest lies in the endocrine factors associated with human and experimental breast cancer. During 1964 he was engaged in research on hydrocarbon-induced tumours in the Ben May Laboratory for Cancer Research, Chicago, and in 1966 was awarded the Clark Prize for Cancer Research.

DR. IAN WILLIAMS was a member of Council when he gave his dissertation. He is now working in the Royal Infirmary and has completed a spell in the Department of Orthopaedics. He has yet to decide finally which branch of medicine to pursue.

RICHARD TURNER is a final phase student. He sits his Finals this year and is interested in the application of computer techniques in medicine, an approach he may well follow up later.

ROGER SMITH graduated with honours Physiology last year and is at present in his fourth year of medicine. He has been Senior Secretary for two years and has been elected Senior President for next session.

## BOOK REVIEWS

**THE CHRISTIAN PHYSICIAN** in the Advance of the Science and Practise of Medicine. Edited by A. M. Connell and A. J. Orange. publ. G. A. Lindeboom. 142 pp.

This book is a report on the 2nd International Congress of Christian Physicians held at Oxford last year. While not as comprehensive as the book reviewed above, it does reflect a variety of situations created by the advance of medicine. The papers presented include contributions on the medical implications of promiscuity, drug addiction and the population explosion, as well as ones on the role of the Christian doctor in scientific, therapeutic and clinical research.

The contributors are all Christian physicians and believe that Christianity has a basic part to play in the advance of medicine. In a profession such as this it is becoming more obvious each day that the study of medical ethics requires serious recognition of the Christian viewpoint. D.B.

**ETHICAL RESPONSIBILITY: Medicine.** A Christian approach. Edited by Vincent Edmunds, M.D., M.R.C.P. and C. Gordon Scorer, M.D., F.R.C.S. E. & S. Livingstone. publ. 200 pp. 1967. 30s.

The age of the simple doctor/patient relationship and straightforward treatment is passed! As man's power to control the functioning of the human body extends, so his ethical responsibilities increase bringing a complexity of socio-medical problems and moral arguments.

This book sets out the topics of medical conjecture which have recently received widespread publicity, and discusses them from a Christian viewpoint. The articles are clear and well written; the problems are logically discussed and, in the views presented by the authors, the reader becomes aware of the sincerity and Christian faith behind the writing.

As more and more ethical responsibility is required of the doctor it is imperative that he should honestly consider each of these problems. As the Bible has provided us with our moral code since the time of Moses what is more logical than that we should turn to it for guidance in modern day issues?

This book would greatly benefit all doctors and students, and indeed all those who are in any way concerned with the social and moral structure of the world's communities. D.B.

**THE ENIGMA OF CORONARY HEART DISEASE.** By A. H. T. Robb-Smith. 150 pages. Published by Lloyd & Luke Ltd. 1967. 30s. net.

This is an admirable monograph on a subject which is defined by many as an epidemic. And the enigmatic element of this "epidemic" is concisely reviewed.

The author points out that statistics are influenced not simply by the actual incidence of the disease, but by the changing nomenclature in use and by the attitude of doctors to the condition. In fact there is little evidence at present to suggest that the increased prevalence in degenerative heart disease reflects anything more than the survival of an increasing population of an age susceptible to these pathological changes. Consideration is also given to the multifactorial entanglements of the disease — culture, social class, country and sex, for instance.

The book leans perforce on much statistical evidence. While the majority of this is presented clearly, some of the graphs suffer from having been reduced to a smaller page size and this makes their interpretation daunting. Perhaps later editions, which are assuredly deserved, will carry simplified figures of these. In view of the recent symposium on angina pectoris, this book should hold out special interest to the medical profession in Edinburgh. M.F.M.

**THE E.E.G. IN CLINICAL PRACTICE.** Laidlaw & Stanton. E. & S. Livingstone. 40s.

This readable book opens with a brief description of the technique of E.E.G. recording, and this is followed by a chapter dealing very simply with the interpretation of the records.

The main section is concerned with the clinical application of the E.E.G. in various disorders. Typical cases are described and lavishly illustrated with normal and abnormal tracings. The contribution which the E.E.G. can make to diagnosis or management in any given situation is assessed, and its limitations emphasised.

The fourth chapter discusses the future place of electroencephalography in both neurology and general medicine. Finally, there is an appendix designed especially for those wishing to learn the technique of E.E.G. reporting.

Carefully planned, clearly worded and beautifully presented, this book is recommended to all interested in acquiring a basic understanding of the electroencephalogram. C.B.M.G.

LECTURE NOTES ON PSYCHOLOGICAL MEDICINE. Rodger. (Third Edition). E. & S. Livingstone Ltd. 8s 6d.

Concise information on Psychological Medicine in hard to come by. To attempt a course through a subject so beset with theoretical controversies in a little over 100 pages is a remarkable achievement.

The authors temper their stride through this course of lecture notes with aptly chosen references to a number of recognised books on the subject, enabling the reader to break off into areas of greater detail that may catch his fancy (or his prospective examiner's approval!). It is especially pleasing to see recommendation of many of the excellent Penguin series concerned with this topic. The book is headed in neat sections, and includes a basic glossary of terms at its outset.

M.F.M.  
HISTOLOGICAL APPEARANCES OF TUMOURS.  
By R. Winsten Evans. E. & S. Livingstone. Edinburgh, 1966. £10 10s.

This is not a book aimed at the undergraduate reader but he would do well to be aware of it as a reference volume. It is aimed at the clinician and pathologist who want to have in one volume a good account of the most common tumours and some of those rarely seen. Towards this aim it succeeds admirably.

Each chapter of the book is complete in itself giving an embryological account of the tissue or organ, and then going on to describe the various tumours which are formed. This approach leads to a methodical and more understandable exposition. It also gives an insight into the difficulties of tumour classification.

This book is profusely illustrated with photomicrographs of a very high standard. It is however a little disappointing to find no colour reproductions but in a book of this scope the cost would be excessive. It would also have been of use to have occasional photographs of the macroscopic appearance of some of the tumours. Diagrams of the most common sites of origin and metastatic spread would also have been helpful. However these criticisms are small when one considers the excellence of the descriptive text.

Neoplastic disease would appear to be becoming more important to the clinician. This type of reference work is therefore of value no matter what is the chosen field. To the undergraduate it affords the opportunity of delving deeper into aspects of tumour pathology and coming to a better understanding of neoplasia.

A.M.D.

THE EYE IN GENERAL PRACTICE. C. R. S. Jackson. E. & S. Livingstone 1967.

The scant amount of time devoted to ophthalmology in Edinburgh's new curriculum allows but the shallowest study of the subject. For this Dr. Jackson's little book is admirably suited. For the student whose interest in the subject is not limited to passing the necessary examination, the book has several frustrating omissions. Little attention is paid to aetiology and pathology; as with all Livingstone publications the quality of the illustrations is excellent but there are simply not enough; description and illustration of operative technique is negligible. As the book is tailored to meet the needs of the general practitioner these omissions are perhaps understandable. For the average student and G.P. the book remains adequate — with a little appropriate revision it could be excellent.

I.C.M.  
CLINICAL EXAMINATION. Edited by John McLeod. 2nd Edition. E. & S. Livingstone 1967. Pp. 567. 45s.

The enthusiasm which greeted the first edition of this text was a well-deserved tribute to the teachers of the Edinburgh Medical School. For the first time many of their bedside diagnostic hints were set down in print in an easily-assimilated form. The second edition has been expanded to include chapters by Sir James Fraser on examination of the Surgical patient and by Dr. J. S. Robson on simple laboratory tests. Examples of methods of examination discussed have now been added to most chapters and the illustrations increased by some 50 line drawings and plates.

At 45/- "McLeod" seems destined to join "Davidson" as a must for medical students throughout the Commonwealth.

I.C.M.  
DEMONSTRATIONS OF OPERATIVE SURGERY.  
Hamilton Bailey. 3rd Edition. E. & S. Livingstone 1967. Pp. 422. 50s.

This, the smallest volume from the Hamilton Bailey surgical stable, is a useful introduction to operative surgery for the clinical student. Written throughout in the first person, the text reads as a commentary on twenty major and minor procedures by 22 leading surgeons. Early chapters deal with theatre organisation and technique. The most common operations in general, orthopaedic, gynaecological and neurosurgery are then described in turn. A glossary of surgical instruments is included in the appendix. Unfortunately anatomical detail has been kept at nursing level throughout, limiting the book to a basic but not unhelpful introduction for the junior clinical student.

I.C.M.

THE STORY OF WILLIAM HUNTER. By Sir Charles Illingworth. E. & S. Livingstone. Pp. 130. 35s.

William Hunter may not have been so well remembered by succeeding generations of medical students as his younger brother, John, but during his own lifetime he had no peer as a teacher.

The boy of thirteen who left Kilbride in 1731 to begin his studies for the Ministry soon tired of the church, and turned to medicine. After studying in Edinburgh under Professor Munro, and in London, he became a teacher of Anatomy himself, in that city, in 1740. He went on to found London's first medical school, and in those days when the care of women in childbirth was left to incompetent midwives and physicians, and surgeons hesitated to risk their reputations by practising the art, he became Queen Charlotte's Obstetrician.

But this sensitive, scholarly man, who showed such compassion for his patients and concern for his pupils, had interests that ranged far outside medicine.

The book is written in the first person, and if this suggests that some historical accuracy has been sacrificed, it has also made it easier for the author to construct a fascinating narrative.

N.B.T.

EMERGENCY SURGERY OF THE HAND. Eric Moberg. E. & S. Livingstone Ltd. 10s 6d net.

Primary management of the acute hand injury is the responsibility of the general practitioner, the casualty officer and the surgeon. This comprehensive little monograph is for those who cannot afford the time to consult a larger text on the subject. Let it be said however that Professor Moberg is an internationally known figure in this field and condenses into 70 pages information he considers essential from his experience. He stresses the importance of preventing infection, of Bunnell's atraumatic operative technique, of immobilising the hand in its functional position, and of quantitative assessment of the sensory function (tactile gnosis) of the hand; he includes a test for sensory loss based on the Ninhydrin reaction.

The book reads easily and has been translated from the original Swedish, via German, by Mr. McQuillan, Senior Lecturer in Orthopaedic Surgery at this university. It is well worth the financial outlay.

M.F.M.

## THE MEDICAL and DENTAL DEFENCE UNION OF SCOTLAND LTD.

### BENEFITS OFFERED BY THE UNION:

Defence of claims for alleged negligence in professional work and of actions for slander arising out of professional acts and relations, and indemnity for damages and legal costs arising from such claims.

Defence of claims against a principal in respect of acts by an assistant or locum.

Advice on difficulties arising out of professional practice.

All benefits available to members in Scotland, England, Wales, Northern Ireland, Isle of Man, and Channel Islands, and to Short Service Officers with H.M. Forces in any part of the world, provided the Total Commissioned Service does not exceed five years.

Benefits of Membership for new graduates available from date of application provided duly registered at that date.

The subscription for new graduates is £3 per annum, for the first three years after qualifying thereafter normal subscription of £6 for members practising medicine and £4 for members practising dentistry.

An entrance fee is not payable by those who are elected to membership within twelve months of their first registration.

Full particulars and Forms of Application for Membership can be obtained from the Secretary.

**C. C. MILLAR, T.D., C.A.**

105 ST. VINCENT STREET, GLASGOW, C.2

DONALD FERRIER LTD.

## Emergencies in Medical Practice

Edited by C. ALLAN BIRCH, F.R.C.P.

8th Edition (June, 1967) 866 Pages. 150 illus. 60/- (Post 4/6d)  
'The fact that the book has now reached its eighth edition is some measure of its popularity.'

## Bailey's Physical Signs in Clinical Surgery

Edited by ALLAN CLAIN, F.R.C.S.

14th Edition (May, 1967) 640 Pages. 940 illus. (206 in colour) 75/- (Post 4/6d)  
'Drastically revised in a new format . . . intended primarily for the medical student commencing clinical studies, this book is also indispensable to the qualified practitioner.'

## Outline of Orthopaedics

By J. CRAWFORD ADAMS, F.R.C.S.

6th Edition (July, 1967) 484 Pages. 381 illus. 40/- (Post 4/6d)  
'A thoroughly revised edition of this well known and very popular textbook.'

CECIL and LOEB'S

## Textbook of Medicine

Edited by PAUL B. BEESON and WALSH McDERMOTT.

12th Edition (June, 1967) About 1800 Pages. 210 illus. £7.3.6d (Post 6/-)  
Two Volume Set £8.11.6d (Post 6/-). De Luxe Edition £10.10.0.  
'This new edition brilliantly upholds the highest standards of its predecessors.'

### MEDICAL, DENTAL and SCIENTIFIC LENDING LIBRARY

The Library service GUARANTEES subscribers with the supply of books priced up to seven guineas — providing they are still currently in print and available from the publishers. ALL BOOKS are the LATEST EDITIONS!

Annual subscription from 45/- . . . Prosepectus sent post free.

SPECIAL REDUCED TERMS FOR UNDERGRADUATES

PAUL WOOD'S

## Diseases of the Heart and Circulation

3rd Edition (August, 1967) About 1,100 Pages. illus. Approx. £7.7.0 (Post 4/6d)  
'Announcing the long-awaited, thoroughly revised new edition of this well-known British reference work — a classic in its field.'

## Practical Paediatric Problems

By JAMES H. HUTCHISON

2nd Edition (July, 1967) About 525 Pages. 90 illus. About 50/- (Post 4/6d)  
'A revised edition of this popular textbook — suitable for undergraduates, postgraduates preparing for senior diplomas and also practising paediatricians.'

## Clinical Virology

By R. H. A. SWAIN and T. C. DODDS

New Book (July, 1967) Pages. illus. 75/- (Post 4/6d)  
'An entirely new book which should prove an invaluable addition to the literature in this particular field — well illustrated and produced.'

## The Medical Annual 1967

Edited by SIR R. BODLEY SCOTT and R. MILNES WALKER

Ready Summer, 1967. About 700 Pages. 160 illus. 52/6d (Post 4/6d)  
(Special Subscription Price 47/6d plus post 4/6d)

OBTAINABLE FROM

# DONALD FERRIER LTD.

MEDICAL AND SCIENTIFIC BOOKSELLERS

5, 8, 9, 10 and 18 Teviot Place, Edinburgh 1.

(Telephones—CAL 5325 and 5689)