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THE
ULSTER MEDICAL JOURNAL

PUBLISHED ON BEHALF OF THE ULSTER MEDICAL SOCIETY

VOLUME 41 SUMMER 1972 No. 2

HISTORY AND THE HALF-DEAD DISEASE

Campbell Oration 1972

by **G. F. ADAMS, M.D., F.R.C.P.,**

Professor of Geriatric Medicine, Queen's University, Belfast, and
Consultant Physician, Wakehurst House, Belfast City Hospital.

"It will be difficult for the kindliest temper to give a friendly welcome to the medical philosophy of Saxon days" (Cockayne 1864)

IT is a very great honour, especially for a Queensman, to be invited to give this lecture, and I am most grateful to the Committee of the Robert Campbell Trust for the invitation. It came to me as a complete surprise because I have never had any reason to suppose that I might be privileged to join the distinguished company of former orators. They comprise a star-studded honours list of a league unfamiliar to me, and I know only too well that I cannot bring to this occasion the academic attainment or the erudition of those who have entertained this Society since 1922 with descriptions of brilliant original work. Most of my tale concerns the deeds, sometimes the misdeeds, of other people.

Robert Campbell died ten years before I became a medical student, but his name is legendary in Ulster's medical history, and I have sometimes wondered what exceptional virtues, combined in him, urged his colleagues to endow this memorial. A colleague has been defined as a person utterly devoid of talent who in some unaccountable way is successful in doing the same job as one's own. Obviously there was no such cynicism in the minds of Robert Campbell's contemporaries, but to inspire the affection and regard underlying this Trust he must have been much more to them than just a talented teacher and pioneer of paediatric surgery. The explanation given by another member of that great family, the late W. S. Campbell, is that although he was a man of few words, he was capable of warm-hearted eloquence when he chose, and evidently he inherited the honesty, clear vision and integrity of moral purpose characteristic of his great-uncle, the first Reverend Robert Campbell. This remarkable man, known countrywide around Templepatrick as "honest Bob", was willing to defy the wrath of Henry Cooke

and even the General Synod to maintain his freedom of thought. (Campbell, 1963).

We who knew W. S. can appreciate the impact of these Campbell personal attributes, and it is appropriate on this occasion to recall Bill's own brilliant undergraduate record. A fellow student, Professor D. H. Smyth, who gave this oration six years ago, said of him that he won every prize, every medal and every scholarship the medical school had to offer from his second year onward, always with such characteristic modesty and absence of consciousness of his own great abilities that the rest of his year were content to compete amongst each other to be second to him (Smyth, 1967).

The object of this Memorial Trust was "to perpetuate the memory of the said Robert Campbell, and to advance the cause of medical and surgical science". My attempt to fulfil the second obligation is a review of the past, and the more recent, history of treatment of strokes. This will not include the progress in emergency care which has done so much to ensure survival at the onset of strokes; we are concerned here with the management of residual disability in the heavily handicapped patients who sometimes seem unlucky to have survived.

All medical progress leaves wreckage in its wake, but advances which ensure survival are not always matched by equally effective means to treat residual disability. Perhaps this is most true of the brain-damaged victims of cerebrovascular disease, and apart from its growing incidence, my reason for choosing this as the topic for the Campbell Oration is the feeling that although at least as deserving as other disability groups of all the support we can give them and their families, it seems to me that little has been forthcoming for them from professional, voluntary or other agencies in our society. The size of the problem is indicated by estimates that 130,000 people in Great Britain are significantly disabled by strokes (Harris *et al*, 1971), and new victims accrue every year at a rate just short of 2 per 1000 population. If similar proportions apply to the population of Northern Ireland we may have 3,500 disabled hemiplegics in our community, about 2,500 more strokes occur each year, and about 750 of the survivors will need a lot of help (Table I).

TABLE I

Strokes in Northern Ireland

Prevalence possibly	3,500
Incidence new victims/annum	2,500
Fate – early deaths	1,250
– continued nursing	250
– moderate disability	750
– slight disability	250

History does not relate how primitive man coped with a stroke, but descriptions of traditional forms of treatment, some sounding remarkably "modern", date from long before the Christian era. Prior to the time of Hippocrates only scattered references to the nervous system are available (McHenry, 1969), but it is clear

from the Edwin Smith Surgical Papyrus (Circa 3500 B.C.) that the ancient Egyptian may have known quite a lot about strokes. The first use of the word "brain" appears in this papyrus and there is a description of the neurological sequelae of head injury, referring particularly to aphasia, emotional instability, and the danger that residual paresis of arm and leg may cause a contracted hand "with nails in the middle of his palm", and a dropped foot. In treatment, however, the Egyptians seem to have thought more of magical rituals, amulets and exotic medicines than of physical practices, but there are references to the treatment of the paralysed in the library established in Nineveh in 650 B.C. by Assurbanipal, King of the Assyrians.

According to Dr. Edwin Clarke, Hippocrates wrote the first adequate account of apoplexy (apoplexia—"being struck with violence"). He observed that paralysis or convulsions followed brain injury and that they appeared on the opposite side of the body to the head wound, and that the loss of speech was related to paralysis of the right side. His Greek contemporaries between 500–400 B.C. appear to have shared his pessimistic view of the value of treatment expressed in the oft-repeated aphorism that "it is impossible to cure a severe attack and difficult to cure a mild one". (Clarke, 1963).

The next two or three centuries must have brought advances and enlightenment, because the treatment recommended to Greek and Roman physicians in the first century A.D. compares favourably with the better standards of care available to hemiplegic patients today. It has been described in detail by Caelius Aurelianus (Drabkin, 1950).

Not much is known about this man except that he was African by birth and owes his fame to his Latin translations of the system of medicine devised by the physicians of the Methodist School of Greek medicine. He was particularly attracted to the prolific writings of Soranus of Ephesus, a leading member of the School, who had studied in Alexandria and later practised in Rome in the reigns of Trajan and Hadrian between 98 and 138 A.D. Only two of his original treatises exist, but the Latin translations of others on acute and chronic diseases made by Aurelianus four hundred years later influenced the teaching and practice of Galen's medicine, and this in turn, was to dominate medical science for centuries in Europe.

The Methodists believed in three basic disease states:

1. An excessively dry, tense stringent state.
2. An excessivly fluid, relaxed atonic state.
3. A state involving some aspects of each.

Methodist physicians were far in advance of their predecessors (and some contemporaries) in the study of precise symptoms and in differential diagnosis, and they made clear distinctions between acute and chronic diseases.

In Caelius Aurelianus' Second Book on Chronic Diseases, paralysis is discussed at length. He notes that it is common in old age, occurs seldom in youth, and comes on most often in winter, at times for no apparent reason, at others from clear causes such as injury, indulgence or association with other conditions. The types of onset and symptoms are described in detail and then the treatment. He states that while always a serious disorder and hard to cure, prospects were

always worse if the paralysis was complete, or complicated by sensory loss, or by some other disease affecting parts essential to life, anticipating our modern concern about respiratory, cardiovascular or renal insufficiency complicating stroke. Soranus seems to have anticpated also the modern concept of transient cerebral ischaemia by his observation that paralysis is a chronic disease characterised by attacks, remissions, active phases and periods of quiescence.

Sound advice was given on general management of strokes including details of the environment the patient should be nursed in, and of food, washing, and toilet techniques (including the use of catheters). The use of medicines was precisely defined, and included small quantities of wine to reduce spasm.

The essentials of physical treatment were heat, massage and passive exercise. The paralysed limbs were warmed and relaxed by an imaginative variety of methods outlined in the following lists:

Warmth	*Baths*	*Applications*
Wax	Cold or hot	Sulphur
Pitch plasters	Sea-water or weak brine	Wild cucumber
Hot sand	Cold packs	Gum ammoniac
Sun-baths	Showers, douches, sponge baths	Squill
		Nettle seed
Charcoal fire	Vapour, hot air	Pellitory
Heated walls	Gaseous baths	Pepper
Heated pavement stones or bricks	Mud baths	White hellebore
		Black cumin
Sun-warmed hides	Turkish baths	All-heal
	Needle baths	Illyrian iris
		Lemnian earth
		Adarce

After massage with aromatic vegetable oils or with ointments composed of medicaments with real or imagined virtues, the limbs were warmed and and exercised, perhaps in the waters of a hot spring, or wrapped in a calf-skin rug by rolling on sun-warmed sand.

Paralysed fingers were softened for manipulation in wax, and weights drawn over pulleys were used to extend contractures and exercise relaxed limbs, the patient being encouraged to join in the effort himself. Instruction was given in rising from a chair, standing, and walking, making use when necessary of "a carriage which is easily moved by hand, a device of the kind often built for babies learning to walk". (Fig. 1 illustrates a medieval contraption such as this). Other walking aids were wooden handles to step over, or ditches providing variable inclines to walk into. Weights were added a few ounces at a time to the patients' shoes and the pace of walking was gradually stepped up. Bathing in the warm springs of Padua or Vesuvius, or in the sea, was assisted by inflated bladders attached to the paralysed parts to reduce the effort required in swimming.

Soranus criticised old-fashioned remedies which seemed likely to cause further injury, such as "subjecting the paralysed parts to the cutting blows of a whip", toxic fomentations, or anything "which weakens the body and is beyond our

power to control". Some treatments now outdated were recommended—cupping, leeches, and emetics, but these have only dropped out of use within the memory of senior doctors living now, and if all hemiplegics today were as well cared for as Soranus advised, there might be fewer bedfast chronic invalids left amongst them.

I have given rather a lot of time to these details because it is clear that what may be considered "modern" in our treatment of the hemiplegic today incorporates many basic principles of rest, warmth, relaxation and promotion of movement which were known and used effectively two thousand years ago by physicians whose intelligence and profound good sense laid the foundations of our best traditions of medical care.

The principles of Greek and Roman medicine spread, with other aspects of Roman culture, across Europe, but they deteriorated or were discarded with the disintegration of Roman civilization in the Dark Ages. "After the fall of the Roman Empire practically nothing of merit was contributed to medicine during the next eight hundred years" (McHenry, 1969). In Britain the decline was accelerated by the ruin of learning and education brought about by successive Viking invasions. The Danes picked out monasteries, the centres of learning, for specially destructive attention, and by the time Alfred became King in 871 knowledge of Latin had almost vanished in England, even among the clergy.

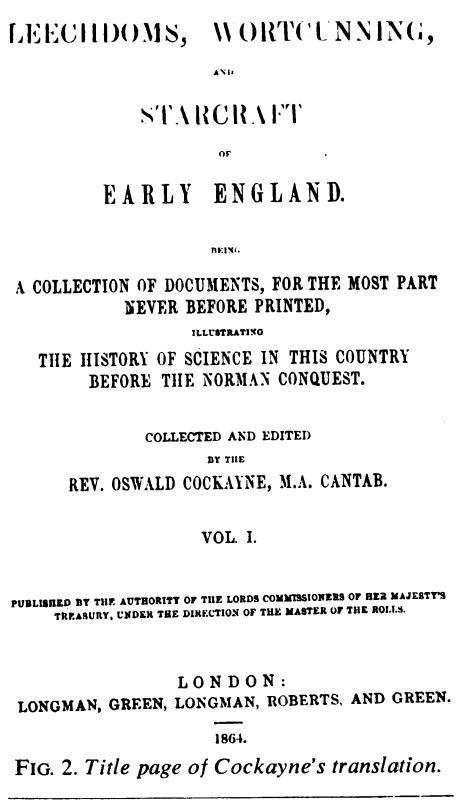
FIG. 1. *Medieval Walking Aid.*

King Alfred owes his legendary greatness not only to success in battle against the Vikings, but also to his success in the revival of education. He imported scholars to establish court schools and even made his own translations of standard works which still survive. The chronicles which grew out of his activity include three books of leechdoms, or the art of healing, written in Winchester by the monks Bald, Oxa and Dun, soon after Alfred's death in 900 A.D. These books were translated by Cockayne (1864) under the delightful title of "Leechdoms, Wortcunning and Starcraft in Early England", meaning of course, "Medical remedies, Herbals and Astrology" (Fig. 2). In the second book there is a description of the treatment of strokes in Anglo-Saxon England, a mixture of superstitious ritual and remnants of Greek and Roman medical practice.

Hemiplegia is referred to as "the half dead disease" which did not come to man before 40–50 years of age, but when it did, involved the right or left half of the body, paralysing sinews owing to the "thick viscid humour" affecting them. This had to be removed by bleeding, drinks or leechdoms. The drinks included water in which peas or beans had been boiled, or a potion called oxumelli containing

one part vinegar, two of honey, one of water, with a radish added and allowed to stand overnight. This is described as a "Southern acid drink" suggesting that it was derived from Greek medicine. The only physical treatment advised was the application of goats' droppings mixed with honey, or sodden in vinegar, to the paralysed sinews.* It is a sober thought that these scripts were written almost five hundred years after the time of Caelius Aurelianus and a thousand years after Soranus.

Compare the fate of the hemiplegic Saxon with the prospects of his Greek counterpart a millenium earlier: the one lying on a sunlit bank overlooking the Aegean, enfolded in the soft comfort of a warm calf-skin, drowsing in the fragrance of oils used to massage away his spasticity, relaxed from a hot bath, awaiting his morning stint of exercise; the other languishing in the dark damp cold of his rush-floored hovel, sickened by ineffective medication, with his useless arm and leg contracting in a case of honied goat-droppings.



LEECHDOMS, WORTCUNNING,

AND

STARCRAFT

OF

EARLY ENGLAND.

BEING

A COLLECTION OF DOCUMENTS, FOR THE MOST PART NEVER BEFORE PRINTED,

ILLUSTRATING

THE HISTORY OF SCIENCE IN THIS COUNTRY BEFORE THE NORMAN CONQUEST.

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BY THE

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VOL. I.

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LONDON:
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1864.

FIG. 2. *Title page of Cockayne's translation.*

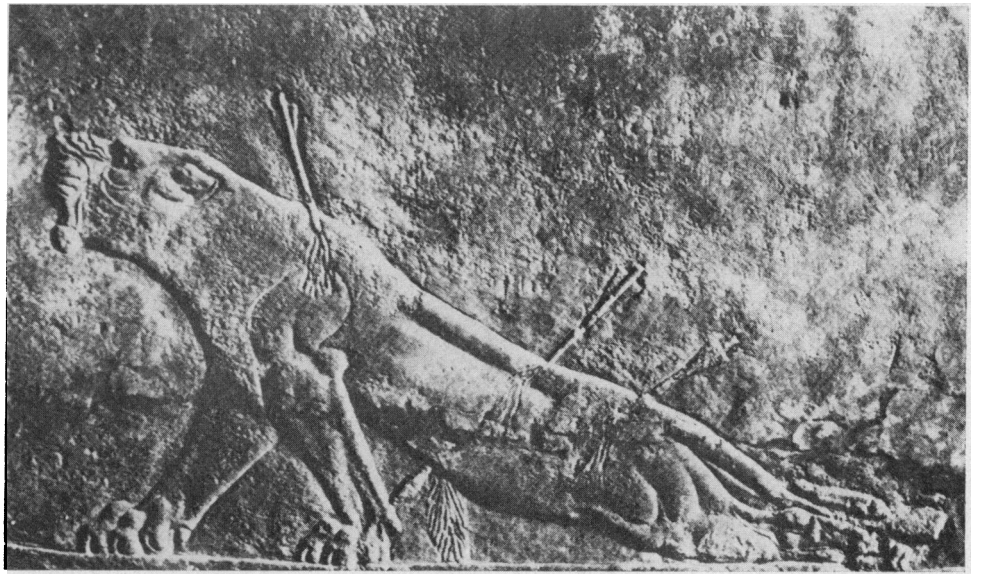
It is a pity that no illustration of this contrast is available but for some reason artists down the ages have neglected hemiplegia, although attracted to many other striking presentations of illness.

Paralysis is illustrated in ancient art in various forms. For example, there is a well-known Egyptian stele believed to portray a limb shortened and wasted owing to poliomyelitis (Fig. 3), and in a frieze at Assurbanipal's palace there is a lioness paraplegic from spinal cord injury (Fig. 4). Appreciation of facial paralysis appears in masks designed for magical rituals by native communities from different parts of the world (Fig. 5). Medieval woodcuts show many varieties of the halt, the lame and the blind. There is a well-known group of amputees, "Les Estropies" painted by Pieter Breughel about 1550 (Fig. 6), and a cripple described as hemiplegic from a French woodcut by Callot (Fig. 7) (although ability to use a crutch in the hemiplegic hand casts doubt on the diagnosis). In the famous

*(This is in keeping with the treatment the manuscript recommended for foreign bodies in the eye—"If anything to cause annoyance get into a man's eye, with 5 fingers of the same side as the eye run the eye over and fumble at it saying 3 times TETUNE RESONCO BREGAN GRESSO—and spit thrice!")

FIG. 3. (*left*)—*Egyptian stele believed to portray a victim of poliomyelitis.*

FIG. 4. (*below*) — *The dying lioness from the Palace of Assurbanipal.*



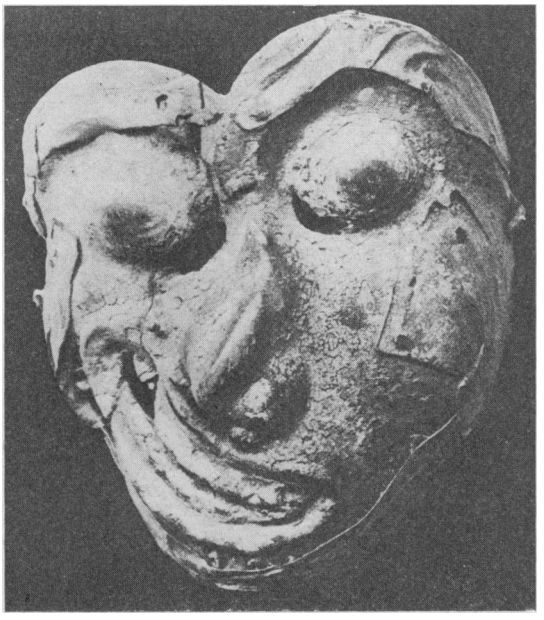


FIG. 5. *Native mask used in magic ritual.*

FIG. 7.
"Un Infirme"
by the French artist Jean Callot.

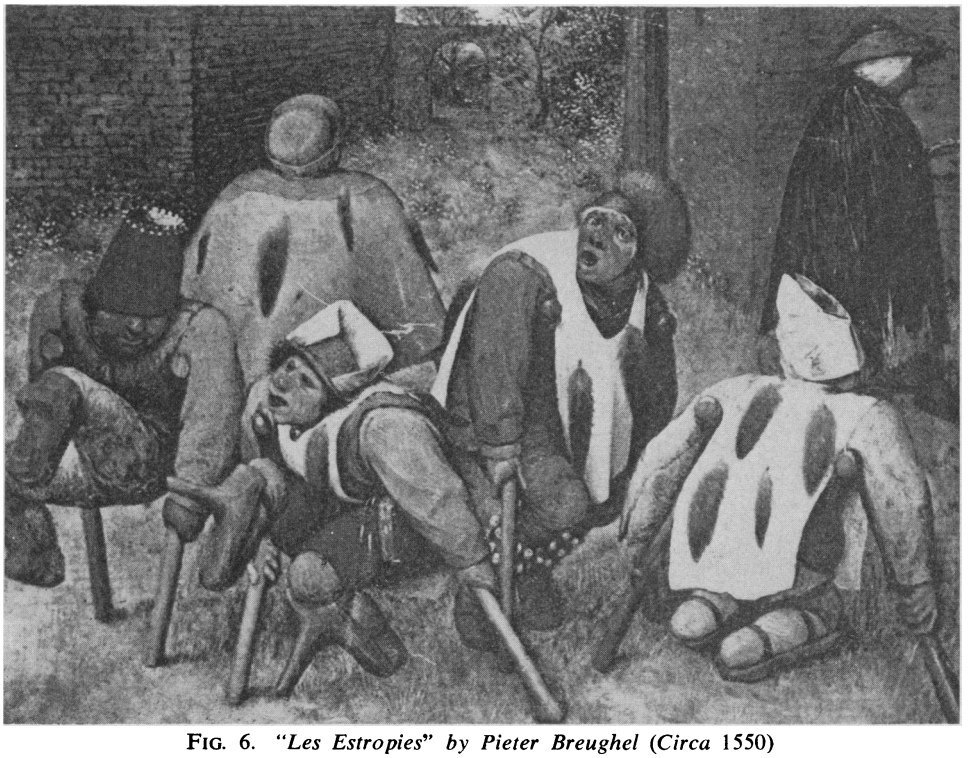


FIG. 6. *"Les Estropies" by Pieter Breughel (Circa* 1550)

Kruppleprozession by Hieronymus Bosch (Fig. 8) not more than three of the illustrations appear possibly to represent strokes, only a small and uncertain proportion of the thirty-two beautifully etched little figures, complete with clearly depicted walking and crawling aids.

It is strange that deformity resulting from such a commonplace disorder as a stroke has not attracted more attention from artists and sculptors down the ages, but Dr. Clarke (1971) suggests that the deficiency may be more apparent than real. Owing to weathering and other causes of destruction, only a fraction of ancient art remains, and of this only the more striking and unusual fragments have been recorded in photographic collections. In one of these (Fig. 9—Von Hollander, 1912) there is a photograph of three 17th century figures from the Boboli gardens in Florence which are described as clowns. It seems to me that the postures of the two figures on either side resemble the characteristics of residual hemiplegic paralysis (Fig. 10), and perhaps they represent the nearest approach there is to statutes of strokes. I do not know of any illustrations of treatment unless one can include a woodcut of Les bains de Plombières dated 1553 (Fig. 11) illustrating the famous baths surrounded by cripples crowding to them from neighbouring hotels in search of "the cure".

In spite of this lack of artistic evidence, progress was being made in medieval times at least towards a better understanding of strokes. Thirteenth century surgeon-anatomists were interested in neurological investigation and Willliam of Saliceto suggested that voluntary action was controlled by the brain, and involuntary movements by the cerebellum (McHenry, 1969). However, in spite of much diligent neuro-anatomical study including brilliant artistic work by da Vinci and by Kalkar, who illustrated Vesalius' dissections, the Rennaissance added little or nothing to knowledge of the physiology of the nervous system.

Clinical neurology, at least in relation to the origin and presentation of strokes, might be said to have begun in the seventeenth century with Willis who wrote one of the earliest textbooks on nervous diseases and coined the word neurology. He was not, as many believe, the first to describe the circle of collateral vessels by which he is so well known. McHenry gives credit for this to Fallopius (1561) but Willis, and his contemporary Wepfer (1658) were first to explain the clinical importance of the Circle. Willis described two patients whose escape from apoplexy in spite of cartoid and vertebral artery occlusions he attributed to the efficiency of this anastomotic circle at the base of the brain. Another advance made at this time (and attributed by McHenry to Mistichelli, a professor of medicine at Pisa) was the description of the decussation of the pyramids to explain why hemiplegic paralysis occurred on the opposite side to the cerebral lesion. Mistichelli seems to have been a more distinguished neuroanatomist than therapist; apparently the treatment he recommended for paralysis included a hot cautery applied to the sole of the foot.

The treatment of strokes during the Renaissance at best was probably a Galencial interpretation of the principles described earlier, at worst a hangover of medieval or even earlier rituals and superstition. However, even then there were those whose views were remarkably advanced, even by our early twentieth century standards.

FIG. 8.

Kruppleprozession by Hieronymus Bosch

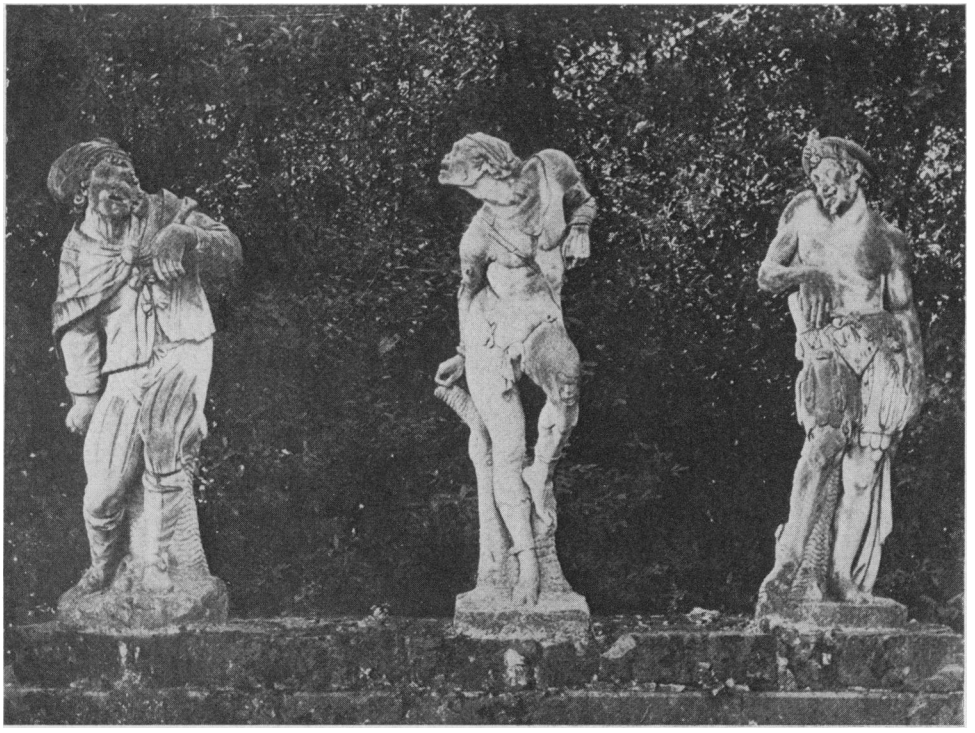


FIG. 9. (*above*)—*Statues described as three clowns from Boboli Gardens, Florence.*

FIG. 10. (*left*)—*Postural disorder in residual hemiplegic paralysis.*

FIG. 11. *The famous baths of Plombières* (*Circa* 1553).

The eighteenth century brought electrotherapy, a highlight perhaps in the history of treatment of hemiplegia, not because of its efficacy, because it had little or none, but because of the excitement and argument that raged around it. A pioneer in its use as a form of medical treatment was Krotzenstein who, around 1747, was Professor of Physic at Halle and later in Copenhagen. He is described as a resourceful and brilliant scientist, but there were those who regarded him as a vulgar pushing fellow with a sharp tongue which is said to have "procured him more enemies than his ability procured him professorships".

A contemporary of Krotzenstein was Richard Lovett, a lay clerk of Worcester, who gave an account of the uses of electrical treatment which, he claimed, would seldom fail to cure rigidities or wasting of the muscles, and had cured one case of hemiplegia in his care. He has been described as an old man (though only aged 58) pottering about Worcester administering electric shocks where he thought they

would be useful. Others who were applying them in much the same empirical way in those days were John Wesley and Benjamin Franklin.

Franklin was much less optimistic about the value of treatment by electricity than others at that time, and commented that although patients with paralysis seemed to improve at first he "never saw amendment after the fifth day". He attributed the benefit his patients derived to the exercise of coming to his house, and the spirit given by hope of success. Imaginative paintings from a French treatise on hemiplegia of those days indicate the fanciful concept of electrotherapy prevalent in the eighteenth century.

By 1765 a critic wrote that although it was the fashion in all Europe eighteen years earlier to "electrise" all paralytic patients, medical fashions, like others, go out of use and this was no exception having only lasted nine or ten years. But, like other fashions, it was showing signs of a return and, indeed, towards the end of the eighteenth century it did become a popular attribute of the quacks, notably James Graham (circa 1780).

Graham "the Emperor of Quacks" studied medicine in Edinburgh but did not qualify. He probably picked up some knowledge of electricity from Franklin while he was studying eye and ear surgery in Philadelphia. He returned to England and is supposed to have spent thousands of pounds installing electrical apparatus and a Magnetic Throne in the Great Apollo Apartment of his Temple of Health at Adelphi House in London. In another room he had a Celestial Bed which, at a price, assured the occupants that "children of the most perfect beauty could be begotten". Apparently he solicited as one of his assistants Emma Lyon, the celebrated Lady Hamilton, who is said to have been exhibited as Goddess of Beauty and to have acted as a nude model for his lectures on health.

At the beginning of the 19th century little had been added to existing knowledge of the treatment of strokes and much that was recommended was still biased by ritual nonsense. In a treatise on Pathological and Practical Researches on Diseases of the Brain and Spinal Cord in 1828, John Abercrombie, an Edinburgh physician, referred to recoveries induced by tickling the paralysed parts with a feather, or by stinging with nettles, commenting that Celsus had employed the same practices. However, much of the rest of his advice was essentially sound, and his outlook was optimistic concluding that "in general we can employ nothing better than much dry friction and particularly persevering exercise of the limbs themselves, as soon as they have recovered the slightest degree of motion which shall make them capable of it".

Electricity became fashionable again as predicted, and the first physician in charge of a hospital electrical department in England was Dr. Golding Bird of Guy's. His lectures, published as a book in 1847, were a well-informed advance in electrotherapy, but perhaps the most distinguished exponent of electrophysiology at this time was Duchenne, who applied faradic stimulation to the study of muscle responses in health and disease, and published his pioneer work in electro-diagnosis and electrotherapy (De l'electrisation localisée) in 1855.

About this time another physician, Julius Althaus, was becoming interested electrotherapy. A German by birth, he studied medicine in Gottingen, Heidelberg and Berlin, where he graduated in 1855. His postgraduate interest seems to have been attracted to nervous diseases and he evidently studied with Romberg in Berlin and in Paris with Charcot, before emigrating to London. Here he continued to pursue his neurological work and was attracted to the possibilities of electrotherapy while working with Dr. Todd in King's College Hospital. In 1866 he founded a hospital for epilepsy and paralysis in Regent's Park which was the forerunner of the present Maida Vale Hospital, which retains a bust of its founder (Fig. 12). Evidently neither his work nor his book were well-received by the "establishment". His obituary states that "he held somewhat extreme views as to the value of electricity in the treatment of diseases of the nervous system, views which have not altogether been justified by experience". He was a Member of the Royal College of Physicians for many years but was never elected a Fellow. However, ten years after his treatise on electrotherapy he published a textbook on nervous diseases which reads extremely well and nowhere better than in his description of hemiplegia, (Althaus, 1877).

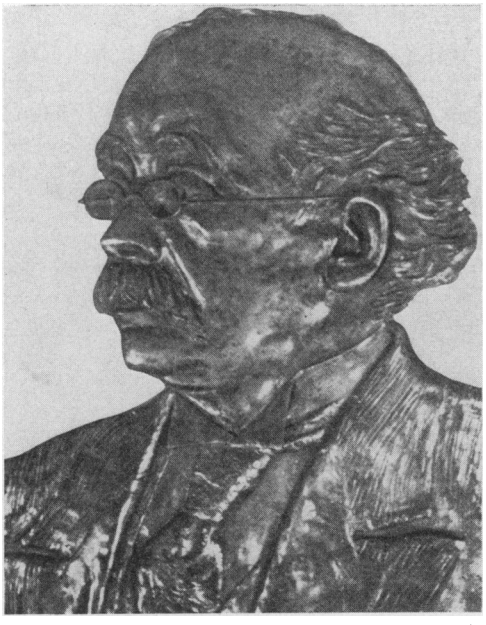


FIG. 12. *The bust of Julius Althaus from Maida Vale Hospital.*

Althaus clearly appreciated the burden imposed by cerebrovascular disease on society, and quoted statistics from America and from England to support his belief that "apoplexy must be ranked with the most important diseases we are called upon to treat in practice". He laid particular stress on the added disability imposed by sensory deficit in hemiplegia: "A limb which has been deprived of tactile sensation becomes really inanimate, although there may be no motor paralysis. It may still be moved, but only under the guidance of the eye; and as soon as this is withdrawn, the condition of limb for the time being drops out of consciousness". Even in textbooks today loss of sensory awareness is seldom high-lighted so well as a handicap to the management of hemiplegia. Evidently Althaus was alive to the advanced views of the physiologists whose researches were then founding an understanding of integration in the nervous system. He was familiar too with the miliary aneurysms described by Virchow and recognised by Charcot and Bouchard as a cause of cerebral haemorrhage. They dropped into the shadows of pathology of the nervous system for a century until brought into prominence again recently.

There has always been conflict of opinion about the value of treatment and the prognosis of strokes. Some were optimistic and encouraging, as was the description written by John Smith in King Solomon's Portraiture of Old Age in 1666, the year of the Great Fire of London. He distinguished between apoplexies which progressed to coma and death, and those which degenerated into a "Palsie which might not immediately kill and "of which there might possibly be a removal, at least for a season, that there might some space be given him to recover a little strength, before he go home and be no more seen". Physicians were always forthcoming to support this view and carry on a tradition of hopeful and expectant treatment. Early enthusiasts were Kirkland (1792) and Copland (1850), but a defeatist note is evident in the writings of the great Charcot (1881) who taught that if not followed by speedily fatal symptoms, in "the immense majority of cases (the patient) only retains life at the expense of deplorable infirmities most frequently rendering him incapable, and even condemning him to perpetual confinement to bed". Charcot seems to have been influenced by the high proportion of hemiplegics he found amongst the inmates of la Salpetrière—200 of the 1,000 chronic invalids there.

In contrast to this were the more optimistic and encouraging views expressed by various physicians in our own country before and during Charcot's time. Perhaps the best of these is in Gowers' textbook of neurology (1888) in which he gave a description of the different presentations and the management of strokes which was probably better than anything previously written about them. Some of his aphorisms should be known to everyone concerned with hemiplegic patients.

> "The tendency to improvement, by cerebral compensation, and by spontaneous disappearance of indirect symptoms, is very marked and makes it difficult to estimate the actual influence of treatment that is employed; at the same time it renders these cases a tempting field for the assumptions of the quasi-therapeautist".
>
> ". . . friends of the patient, if not the patient himself, should be made aware of the hopelessness of a search after a cure on the one hand, and, on the other, of the slow improvement that time will bring".
>
> "In few diseases does more harm result indirectly from the mistaken kindness which conceals unpleasant truths".
>
> "A contracted dropped foot can be more readily prevented than cured".
>
> "Practice should not be continued long enough to fatigue the brain, but should be repeated several times a day".
>
> "Great patience and perseverance are required, but these will be rewarded by progress far more rapid than is possible if the patient is left alone".

Gowers recommended rest for two weeks in slight strokes, and four to six weeks if more severe, employing gentle rubbing to lessen rigidity and athetoid spasm. He observed that little could be expected from electricity and it should not be applied at all in the first six weeks. He believed that hand splints should be applied for a few hours daily following relaxation obtained by immersion in

warm water, and made use of a hollow rubber ball which could be inflated to *extend* the fingers and encourage use of the hemiplegic hand. He emphasized the importance of perseverance with speech re-education because recovery is to be thought of in terms of months rather than weeks.

So we come to twentieth century treatment of hemiplegia. In the first half of the century cerebrovascular disease attracted little attention compared with the striking advances which were giving such dramatic and successful results in the treatment of many other medical and surgical conditions. Clinicians were concerned with aetiology and differential diagnosis of strokes, and one was given careful teaching in these, but in the thirties as student, houseman, and later as registrar in the Royal Victoria Hospital, I cannot remember ever having impressed on me the insight or the scope of common-sense practical ideas which Gowers evidently brought to the management of residual disability fifty years earlier. Most textbooks dismissed it in a brief paragraph, perhaps with some reference to passive movements and frictions, but there was a lack of well-informed opinion on prognosis. This probably reflected changing hospital practice, whereby the hope of long-term recovery for many of the more severely disabled hemiplegics was often lost in the early weeks when they were cast out as "chronic sick". Indeed, because of this, much of the progress made in the treatment of hemiplegia in recent years is a by-product of geriatric medicine. Most strokes occur in old people, and modern geriatric practice began from experience in the "chronic" wards of the old infirmaries where the proportions of hemiplegics were high.

Progress in the treatment of strokes recently has advanced along two lines—better understanding of the *physical* and of the *mental* disabilities of patients with strokes.

Much credit for revived interest in the treatment of hemiplegic physical handicaps is due to the late Dr. Majory Warren of the West Middlesex Hospital (Fig. 13) who gave an address to this Society in 1949. Her contribution was that, even within the stringent economy and repressive conditions of a municipal institution during the ninenteen thirties, her clear vision, practical good sense and ability to make the best use of what came to hand, enabled her to anticipate the more sophisticated methods used today to restore control of posture, of balance, and of moving equipoise to hemiplegic patients.

Dr. Warren added another dimension to hemiplegic care by recognising the physician's responsibility for every aspect of their need—insistence on proper clothing, down to socks and shoes, in days before "dressing practice" was heard of; on a thorough study of environmental handicaps—lights, steps, taps, latches, and proper levels for shelves, long before occupational therapy was generally available in hospitals; and on detailed medical-social study, taking account of the patient's well-being, present and future, at bedside conferences on ward rounds.

Dr. Purdon Martin and the late Dr. Louis Hurwitz, both Queensmen, made distinguished contributions to the care of the brain-damaged patient by their well-known studies of postural fixation and the mechanisms of balance and postural control; physiotherapy techniques in the management of hemiplegia have improved on a foundation of better knowledge and application of basic physiological principles

FIG. 13. *The late Dr. Marjory W. Warren of the West Middlesex Hospital.*

concerned with the integrative action of the brain; but Marjory Warren's intuitive principles of hemiplegic care are not out of character in the company of these advances.

Besides this contribution from Queensmen towards the management of hemiplegic physical disability, the Belfast Medical School may also claim to have helped towards the betterment of those with mental disabilities by devising a pattern of assessment and a practical approach to the treatment of what we have called *mental barriers* to recovery from strokes (Adams and Hurwitz, 1963). Although the importance of intellectual, as opposed to physical, impairment in delaying recovery has been recognised by physicians down the centuries, no attempt was made until quite recently to analyse the specific disorders of intellectual functions involved, or to take proper account of them in treatment. We may not have a claim to originality in this, but in sifting and correlating some of the tangled skein of knowledge about disordered mental function relating to cerebrovascular disease we have brought some order into a somewhat bewildering field of opportunity. The credit for this belongs to another of our distinguished neurologists, a former President of this Society, Dr. Sydney Allison, and this is how it happened.

As you know, Dr. Allison has an international name as an authority on organic mental states, and these present frequent problems in geriatric neurology. I am indebted to him for the help and advice he gave so willingly on many occasions on visits to our geriatric wards and I learned from him, amongst other things, to appreciate that patients seldom fail to recover from strokes owing to paralysis alone, and to look for the more obscure causes of failure. Applying this in a search for these causes in 45 hemiplegics in long-stay wards it transpired that the physical disability of paralysis combined with severe sensory loss or limited exercise tolerance, accounted for failure in only half of these patients; the others had defects caused by local brain disease resulting in handicaps which could be classified in four groups—impaired learning ability; disturbed awareness of self or space; disordered integrative action; and emotional disorders.

I was trying to analyse the results of this survey when Louis Hurwitz, returning from his years in Queen Square and the United States, came as neurologist to the Belfast City Hospital. He was fired by Dr. Allison with the same interest in the neglected problems of hemiplegia as mine, but, of course, in neurology he was so much more accomplished and better informed. With his help the list of mental barriers was extended, better defined and polished to include:

(a) *inability to learn* (clouded consciousness, asphasia, memory defects, dementia).
(b) *disturbed awareness* with attitudes towards illness disordered by separation from reality (anosognosia, neglect or denial of hemiplegic limbs, disordered spatial orientation).
(c) *disordered integrative action* (impaired postural function, apraxia, agnosia, perseveration, synkinesia).
(d) *disturbances of emotional behaviour* (emotional instability, apathy, loss of confidence, fear, unwillingness to try, catastrophic reactions, depression).

It became clear that we usually have to depend on the observations of interested attendants (nurses, therapists or relatives) to draw attention to these barriers because the patient himself seldom identifies or complains of them, and that their recognition is of practical not academic importance, being necessary so that appropriate treatment to get over or around them may begin as soon as possible.

Investigation of mental capacity in hemiplegic patients and assessment of the outlook for them—their "rehabilitation potential" have been discussed elsewhere (Hurwitz and Adams, 1972), and it seems that since we began to pay more attention to mental barriers, the recovery rate of our hemiplegic patients is at least 30 per cent better than it was.

The next step forward may be the national, or even the international, application of standard rating scales to compare the results of treatment. Ullman (1962) said that the victims of strokes present unique challenges which too often go unrecognised and therefore unheeded. Even if the arterial disease responsible for most strokes could be prevented tomorrow, so much is established already that strokes will continue to offer these challenges for many years to come. However, the future for these patients is much brighter than it has ever been. I have no doubt, for example, that before long much more will be done for the hemiplegic arm than we know how to do now, and, as always, most progress will derive from revision of old ideas.

Our contribution is only a small part of the wide-ranging activities of neurologists and psychiatrists attracted to these problems on both sides of the Atlantic. Indeed, distinguished lay contributions also have been made from, and about, famous people such as E. Hodgins (who wrote "Mr. Blandings builds his Dream House"), and Valerie Griffith, who did so much for Patricia Neal and Alan Moorehead. What was unusual here was the opportunity we had to integrate this proficiency in rehabilitation of brain-damaged patients, and the exceptionally well-united neurological, neurosurgical and neuropathological facilities available to our medical school. Once we hoped for an institute of Neurological or Cerebrovascular Diseases. Some day it will be founded, but it is sad to think that it will not enjoy the benefits of the unique contribution Louis Hurwitz would have made to its work.

In conclusion, it seems that there have always been wide variations in professional interest in patients with strokes. This is to be expected, but it is surprising that there is so little community interest in their well-being and that we have no Stroke Society active on their behalf. Multiple sclerosis, mental health, muscular dystrophy and many other conditions have busy associations promoting the welfare of patients no worse crippled, and of families no worse demoralized than those afflicted by strokes.

Failing such organized professional and community support perhaps we should just hope to avoid such disastrous disability at the end, and to live on like Bernard Darwin's Uncle Lenny "without having lost any one of his tastes, with a mind really and truly as good as new", until his last hours. As Darwin (1955) said "there could be no more serene sundown".

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AN AUTOGRAPH LETTER OF DR. RENE LAENNEC

by **J. S. LOGAN,**
The Royal Victoria Hospital, Belfast

THE Deputy Keeper of the Public Records of Northern Ireland has kindly allowed us to reproduce this attendance or class certificate issued by Doctor Laennec in 1826 to John Creery Ferguson (Figure 1). John Ferguson was a native of Tandragee, County Armagh. Born in 1802, he received the degree of M.B. from Trinity College, Dublin, in 1827, and became eventually the second professor of medicine in the Belfast medical school. He was appointed to the chair of medicine in the new Queen's College at Belfast on its foundation in 1849, and occupied it until 1865. He was attending physician at the Belfast General Hospital from 1853 (Moody and Beckett 1959).

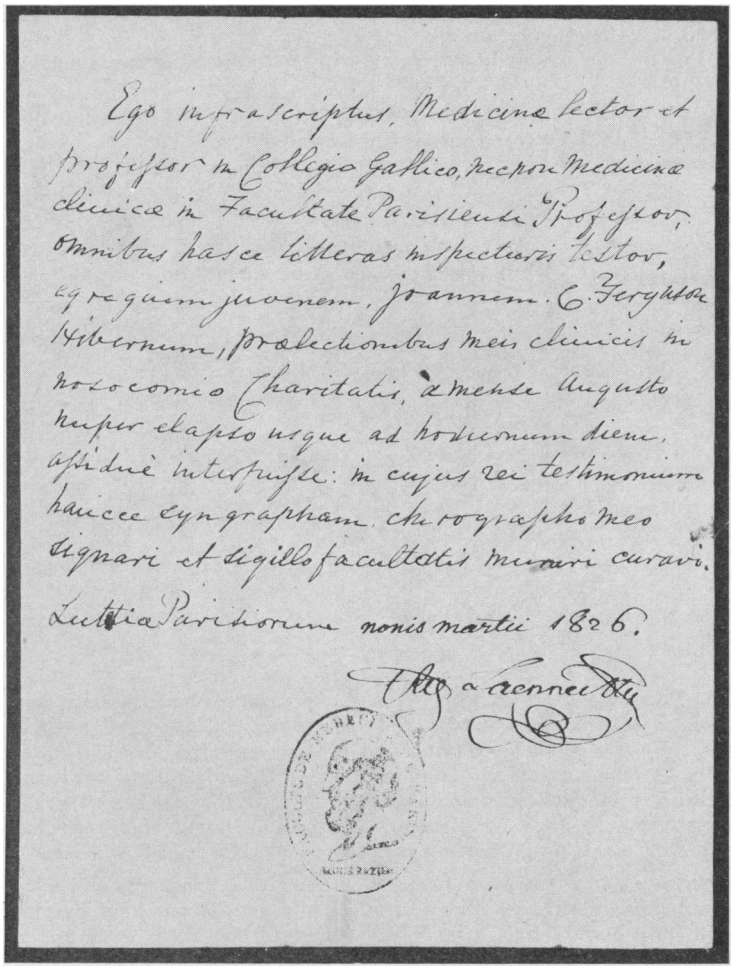
Ego infrascriptus, Medicinæ lector et
professor in Collegio Gallico, necnon Medicinæ
clinicæ in Facultate Parisiensi Professor,
omnibus has ce litteras inspecturis lectoris,
et quam juvenem, Joannem C. Ferguson
Hibernum, prælectionibus meis clinicis in
nosocomio Charitatis, a mense Augusto
nuper elapso usque ad hodiernum diem,
assidue interfuisse: in cujus rei testimonium
hanc ce cyrographam chirographo meo
signari et sigillo facultatis muniri curavi.
Lutetiæ Parisiorum nonis martii 1826.

FIG. 1.
Autograph letter of Doctor René Laennec.

Of the physicians of the Paris school of medicine in the early nineteenth century, in the days of its pre-eminence, René Laennec, the Breton, is best remembered. His invention of the stethoscope in 1816 (the year after Waterloo), his development of the physical examination of the chest, and his correlation of auscultation and pathological anatomy began a method in chest medicine, which, reinforced and not superseded by radiology and thoracotomy, is still ours. Laennec died at his home at Kerlouarnec in Finistère on the 13th August, 1826, only five months after writing this certificate. It is interesting to see the similarity of the signature on the certificate to that reproduced on the portrait of Laennec (Figure 2).

FIG. 2.
Portrait of Doctor René Théophile Laennec.

The certificate may be translated as follows. "I the undersigned, reader and professor of medicine in the Collège de France, and professor of clinical medicine in the Faculty of Paris, bear witness to all readers of this letter that that excellent young man John C. Ferguson, from Ireland, has been present constantly at my

clinical lectures in the Charité hospital from the month of August last until today. In witness whereof I have been at pains to write this note in my own hand and to have it furnished with the seal of the Faculty. At Paris, on the 7th March, 1826."

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Acknowledgements

The photograph of the letter (Figure 1) is by the Public Record Office of Northern Ireland, and that of the portrait of Laennec (Figure 2) is by the Royal Victoria Hospital department of photography.

DRUG SURVEILLANCE:
The Role of the Committee on Safety of Medicines

A Lecture given in the Department of Pharmacy
at The Queen's University of Belfast in December, 1971

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IT should be emphasised that it is not only new drugs that can give rise to adverse reactions. In a recent survey in Belfast (Hurwitz and Wade, 1969) it was found that 19.8 per cent of patients treated with digoxin suffered adverse reactions to it, and that adverse reactions to digitalis accounted for one third of all drug reactions monitored. Withering in 1785 was aware of the fact that the drug he had pioneered was not without hazard and wrote "it is better the world should derive some instruction, however imperfect from my experience than that the lives of men should be hazarded by its unguarded exhibition, or that medicine of so much efficacy should be condemned and rejected as dangerous and unmanageable."

I. THE NEED FOR DRUG CONTROL AUTHORITIES

(i) *The beginning of monitoring of drug hazards*

The objective assessment and measurement of the efficacy of drug therapy is a recent discipline. Attempts to measure and assess the ill effects of drug therapy are recent and as yet can hardy be called a discipline. Yet it was in 1877 at a meeting in Manchester that the British Medical Association initiated the first collaborative study of the adverse reactions of a drug. A committee was set up to investigate the sudden unexpected deaths which sometimes occurred during the induction of chloroform anaesthesia (McKendrick Coats & Newman 1880). Since that time there has always been some concern amongst doctors about adverse reactions to drugs; and reactions to smallpox vaccine, typhoid vaccine and more recently poliomyelitis vaccines have been a continual source of anxiety not only to doctors but also to the public, whose fears have sometimes been fanned to great emotional heights by anti-vivisectionists and anti-vaccinationists. At the end of the First World War, an epidemic of jaundice and fatal hepatic necrosis amongst soldiers treated for syphilis with organic arsenicals was so serious that it was the subject of a special report by the Medical Research Committee predecessor of the present Medical Research Council (Medical Research Council, 1922). And a few years later it was recognised that fatal jaundice could be caused by cinchophen, a remedy used in the treatment of gout (Worster-Drought, 1923; Short & Bauer, 1933), and agranulocytosis by the analgesic drug amidopyrine (aminophenazone; aminopyrine; Pyramidon) (Madison & Squier, 1933; Kracke & Parker, 1934).

The introduction of the sulphonamides to medicine in the late 1930's brought familiarity with adverse reactions to all doctors. But these drugs, penicillin, strepto-

mycin and the corticosteroids led to such advances in the efficacy of medical treatment that the adverse reactions although recognised, caused no great anxiety. This state of affairs was changed in 1961 by the thalidomide catastrophe (Mellin & Katzenstein, 1962). This tragedy left its mark not only on the unfortunate children but also on the medical profession, the pharmaceutical industry, the public and on governments. Now it is recognised that there is an urgent need to determine not only the adverse reactions that a drug may cause but the incidence of those reactions in relation to the use of the drug, and to determine sections of the population at greater than average risk (D'Arcy and Griffin, 1972).

(ii) *The Thalidomide disaster*

In view of the historic importance in terms of legislation it might well be desirable to spend some time describing the spectrum of thalidomide toxicity.

(a) *Thyroid dysfunction*

The first adverse reaction reported caused by thalidomide, oddly enough was the least important and that was the development of myxoedema. This report was made in 1959.

(b) *Neuropathy*

Early in 1960 isolated reports were received by Burley of Distillers Company (Biochemicals) Limited, from various parts of Great Britain describing symptoms and signs suggestive of peripheral neuritis occurring in patients receiving thalidomide regularly for periods of six months or more. Florence, however, recorded the first report in the literature in December 1960. In four patients polyneuritis had developed while they were taking thalidomide, and he thought that the symptoms could possibly be a toxic effect of the drug. Kuenssberg *et al* soon added five similar cases in January 1961. It was not till the more detailed report of Fullerton and Kremer in September 1961 that the association of thalidomide and resulting neuropathy became fully realised in Great Britain.

(c) *Teratogenicity*

In December 1959 Weidenbach presented the case history of a girl born on November 10, 1958, to a twenty-four-year-old primigravida. The upper and lower limbs were missing. The hands and feet originated directly from the shoulder and pelvic girdle respectively. There were also deformities of the digits. No additional abnormalities were noted. The infant progressed very well in the nursery and continued to develop in accordance with her age. The history of the gestation yielded nothing unusual. Neither parent could recall a family history of malformation. Although it was recognised that no conclusion regarding the ætiology of the malformation could be drawn it was thought that, owing to the symmetry and involvement of all extremities, a hereditary factor was most likely.

Kosenow and Pfeiffer, at the September 1960 meeting of the German Society of Paediatrics in Kassel, had a scientific exhibit describing two infants with similar malformations and also micromelia, hemangioma of the midline of the face and duodenal stenosis.

In September 1961, Wiedemann presented a paper calling attention to the current

increase in the incidence of hypoplastic and aplastic malformations of the extremities. Over a period of ten months he had seen thirteen patients. He was aware of twenty-seven similar cases in his area. Since no hereditary signs appeared in the histories of any of his thirteen patients he considered an exogenous cause that must have come into effect around the beginning of 1959. He questioned whether a drug among the constant flow of new drugs entering the market, might have been involved.

Pfeiffer and Kosenow presented a paper on the question of exogenous causes of severe malformations of the extremities to the North Rhein-Westphalia Paediatric Meeting in Dusseldorf on November 18, 1961. They mentioned thirty-four newborn infants with defects of the long bones seen at the Children's Hospital at Muenster from January 1, 1960 to November 18, 1961. After their presentations Lenz, of Hamburg, raised the question of thalidomide consumption by the mothers. This was later reviewed, and it was found that a large number of the mothers involved had taken thalidomide.

The Fetal Life Study received an inquiry in 1962 concerning the incidence of phocomelia in relation to a recent increase that had been observed in West Germany. The Fetal Life Study was established in 1946 in a selected population at the Columbia-Presbyterian Medical Center as a long-term prospective epidemiologic investigation of human reproduction, to determine the incidence of foetal deaths, neonatal deaths and congenital malformations and to delineate associated factors. From more than 10,000 pregnancies prospectively followed in the years 1946 to 1960 and more than 2,000 followed in 1961 the group was unable to find any causes of phocomelia similar to the pictures appearing in the literature. A possible explanation of this discrepancy became apparent at a Rhein-Westphalia paediatric meeting in Dusseldorf, Germany on November 18, 1961. Dr. Lenz of Hamburg, suggested that this malformation was related to the ingestion early in pregnancy of the drug thalidomide (alpha-(N-phthalimido)glutarimide).

It was not long, however, before individual case reports began to appear. These cases also illustrated the problem of retrospective epidemiology. In one situation the drug had to be retrieved from a former neighbour. In another case, in which the mother had been included in a hospital-study prospective survey, the fact that she was given thalidomide was not known by her family doctor. In retrospect studies two out of three family doctors could not remember whether thalidomide had been taken.

Several communications indicated that small doses might be devastating. One patient who was a week overdue for a menstrual period took 50 mg of thalidomide a day for one week only; her premature baby had phocomelia. In another report the mother apparently received 100 mg of thalidomide for three nights and 50 mg for two nights in the second week of pregnancy; the baby was born with phocomelia. If the dates in these situations were correct these may illustrate the earliest stages of pregnancy in which teratogenic effects should be sought in the assessment of teratogenicity. It is even more worrying that in these cases the drug was exerting its teratogenic effect in women who did not even know for certain that they were pregnant.

(iii) *The continual appearance of new hazards and new dimensions of adverse reactions*

The first confirmed reports of the transplacental transmission of cancer in man by means of a hormone, stilboestrol have recently been published. The evidence provided by this extremely important research and its significance need immediate and careful assessment.

Recently Herbst and Scully (1970) reported seven cases of adenocarcinoma of the vagina in adolescent girls in the New England area during a period of four years. The patients' ages ranged from 15 to 22 years. They had symptoms of irregular vaginal bleeding for up to one year. Five were treated by radical surgery and one by wide excision. All were alive one to four years after operation. The seventh, in whom the disease was too far advanced at surgical exploration, died within six months. The authors were puzzled about the causation of this apparent clustering of cases, as carcinoma of the vagina is uncommon and usually occurs at a much older age.

An eighth case was added in a retrospective study of factors that might have been associated with the appearance of these tumours. Herbst and colleagues (1971) noticed that maternal bleeding when the girl's mother was pregnant with the patient and in previous pregnancies was more common than in a control group. But of greater significance than that was the finding that seven of the eight mothers had been treated with diethylstilboestrol during the first trimester of the material pregnancy, while none of the control group was so treated. A separate study by P. Greenwald and colleagues has now confirmed this association, adding five more cases in which the actual dosage of synthetic oestrogen used has been obtained.

All 13 patients were born between 1946 and 1953, a period when stilboestrol was being given for repeated or threatened abortion. All the mothers who took stilboestrol began treatment in the first two months of pregnancy. They received either a constant dose administered throughout pregnancy or a continually increasing dose given almost to term. The actual dosage varied but followed roughly that suggested by A. W. Smith beginning at 5 mg by mouth during the sixth or seventh week of pregnancy and increasing by 5 mg at two-weekly intervals to the 15th week, when 25 mg daily was being given. The dose then increased by 5 mg at weekly intervals until the 35th week, at which time as much as 125 mg of stilboestrol was being taken by mouth daily.

The original series of seven cases exceeded the number of cases in the entire world literature for a tumour of this type in adolescent girls born before 1945. Indeed, adenocarcinoma of the vagina was thought to have some relationship to vaginal remnants. Moreover, if these neoplasms were the result simply of high-risk pregnancies, this should have become apparent before 1945. It was therefore suspected that exposure to stilboestrol and vagina carcinoma in the offspring might have a cause-and-effect relationship. The suggestion is reinforced by the fact that stilboestrol was used only infrequently in general obstetric practice. Even at the Boston Hospital for Women, where a special high-risk pregnancy clinic was being conducted only about one in twenty-one patients delivered in the wards had received stilboestrol during the five year period 1946 to 1951. Thus when the expectancy of a chance association is less than 5 per cent, the occurrence of

maternal stilboestrol therapy in 12 out of 13 cases of vaginal adenocarcinoma in young women cannot be considered coincidental.

II. Background to Drug Control in the United Kingdom

The role of the Medicines Act 1968 can probably best be understood against the historical perspective of attempts by the government to control the use of potent pharmacologically active agents in terms of quality and efficiency.

The Gin Acts of the 18th century introduced the concept of control over sales and supply, recognised the necessity of protecting the community and pioneered later efforts to overcome the misuse and abuse of drugs.

The British Pharmacopoeia was first published in the 19th century. Successive editions and addenda up to the present day have produced standards of quality control, which have justly enjoyed international prestige. Unfortunately, there has never been an adequate machinery for the enforcement of these high standards.

The Dangerous Drugs Acts recognised the risks of drug addiction, and introduced the idea of control of manufacture under licence, together with strict recording of sale and supply.

The Pharmacy and Poisons Acts and the introduction of the Poisons Rules, elaborated the theme of control over sale and supply. Though designed primarily to deal with poisons; medicines were later included. The control of poisons and medicines by similar rules has been cumbersome and fraught with difficulties, but it has helped to maintain some control in a long process of transition.

The Therapeutic Substances Acts added new concepts to control. The design was the control of substances such as vaccines or sera, the purity and potency of which could not be controlled by chemical means. Such control was difficult to contain within a pharmacopoeial monograph, for it demanded the use of biological standardisation, requiring standard materials, against which the products could be assayed. Many of these standard materials are now international.

The Therapeutic Substances Acts (T.S.A.) further recognised that the personnel and the conditions of the premises in which such products were manufactured were as important in control as the tests which could be applied to the end-product. Thus factory inspection and in-process control played an integral part in the considerations for the issue of a licence under the Acts and their regulations, either to manufacture or to import. For the first time primary considerations of safety began to emerge for these Acts envisaged not only the purity and potency of preparations, but allowed the restriction by prescription to any medicines, which would be a hazard to the community if freely available.

The Cancer and Veneral Diseases Acts were enacted to prevent the public advertisement and promotion of medicines for these serious conditions, thus preventing not only fraudulent claims but protecting the sufferers from inadequate and unsuitable treatment. In this way the control of advertisement and promotional literature for medicines was begun.

It was in this multiplicity of legislation that even before the establishment of the Committee on Safety of Drugs in 1963 that concepts of quality control, restrictions

over sale and supply, of in-process control, and control over promotion and advertisement and of manufacture under licence were born. However, there was considerable complexity of control under the different acts. Although such statutes and regulations as the Pharmacy and Poisons Acts, the Dangerous Drugs Act and the Poisons Rules controlled the sale and supply of some medicines, others came under the control of the Therapeutic Substances Act, and no central agency existed that gave consideration to all medicines, so far as their safety for use in man was concerned. Although everything pointed to the need to consolidate the legislation on medicines, the old machinery seemed to work and for decades no great problem had arisen. The task of preparing consolidating legislation was formidable and disentangling the complex machine was a daunting venture.

Lulled into security by the quiet years, both public and Government were unprepared for the therapeutic explosion of the last thirty years. This complacency was rudely shattered by the thalidomide tragedy. The conscience of the public was troubled and the Government galvanised into activity. No existing legislation was available to take care of this new consideration, and to consider these new concepts of safety and at the same time to produce comprehensive and consolidating legislation was bound to be lengthy and time-consuming. In the meantime, something had to be done, for any product could be marketed, with a few exceptions under the Therapeutic Substances Acts, however dangerous or ill tested it might be. As an interim measure in 1963 the Minister of Health, on advice, established the Committee on Safety of Drugs. The Committee consisted of a panel of independent experts from various fields of Pharmacy, Pathology, etc .and served under the chairmanship of firstly Sir Derrick Dunlop and more recently Professor Scowen. The Committee was serviced by a professional secretariat of pharmacists and medical officers who under took the assessment of the submissions and presented these to the Committee and various sub-committees.

The Committee on Safety of Drugs was set up in June 1963 by the Health Minister, in consultation with the medical and pharmaceutical professions and the British Pharmaceutical Industry, with the following terms of reference: —

(i) "To invite from the manufacturer or other person developing or proposing to market a drug in the United Kingdom any reports they may think fit on the toxicity tests carried out on it; to consider whether any further tests should be made and whether the drug should be submitted to clinical trials; and to convey their advice to those who submitted reports.

(ii) To obtain reports of clinical trials of drugs submitted thereto.

(iii) Taking into account the safety and efficacy of each drug, and the purposes for which it is to be used, to consider whether it may be released for marketing, with or without precautions or restrictions on its use; and to convey their advice to those who submitted reports.

(iv) To give to manufacturers and others concerned any general advice they may think fit.

(v) To assemble and assess reports about adverse effects of drugs in use and prepare information thereon which may be brought to the notice of doctors and others concerned.

(vi) To advise the appointing Ministers on any of the above matters."

The Committee had no legal powers, but worked with the voluntary agreement of the Association of British Pharmaceutical Industry and the Proprietary Association of Great Britain. They promised that none of their members would put on

clinical trial or release for marketing a new drug against the advice of the Committee, whose advice they would always seek.

An effective drug control authority should have adequate machinery for assessment in three broad functional areas:

(i) scrutiny before clinical trial
(ii) scrutiny before marketing
(iii) surveillance of each drug after marketing so that adverse reactions can be adequately monitored and documented, and if necessary a warning issued to the medical profession.

A strong sub-committee structure was set up, drawing in a wide variety of expertise, which could not be contained within a single committee of workable size. Sub-committees were first formed to advise on toxicity and clinical trials, and in adverse reactions. Later it became necessary to form an advisory group of experts on vaccines and biochemicals.

When an application from a manufacturer was received it could largely be classified into a reformulation or Minor Submission, and a New Drug or Major Submission. These submissions were requesting either permission to market or to conduct clinical trials. The submission was assessed by a pharmacist and then by a senior medical officer of the professional secretariat. A summary was prepared and the submission and summary circulated to members of the appropriate sub-committee before the sub-committee meetings where the data was presented by the Senior Medical Officer dealing with the submission and this was discussed and recommendations were then passed from the sub-committee to the main committee, after which a decision was made and the manufacturer informed.

Clinical Trial

Before clinical trial can be considered full information is required on the chemistry, pharmacodynamics, metabolism, acute and intermediate toxicity, on teratology and in drug interactions. If the pharmacodynamic studies indicate a therapeutic potential and the committee is satisfied with the quality and safety of the drug, no objection is raised to clinical trial. The nature of the trial is the responsibility of the applicant, provided always that the committee can be satised that the staff responsible for the trial and facilities available to them are appropriate.

Although a pamphlet, "Notes for the guidance of manufacturers and other persons developing or proposing to market a drug in the United Kingdom" was available, the Committee did not lay down rigid requirements for the pre-clinical toxicity testing programme of new drugs. This was the responsibility of the manufacturer, although the Committee's staff were always available for consultation on the proposals.

The pharmocodynamic properties and therapeutic potential of the new drug are studied and considered in relationship to its metabolism, the pattern of toxicity and its teratogenic potential. Ideally the toxicological and teratological studies should be performed in species that are known to metabolise the drug in the same way as man. Unfortunately, this information on the metabolism is seldom available at this stage and toxicity testing is most frequently performed in the rat and dog and teratogenicity studies on the rat and rabbit. Both toxicological testing

and teratogenicity studies should be performed at three dose levels by the intended route or routes of administration of the new drug. In the toxicological studies the doses should be so adjusted that the low dose is within the range of the proposed therapeutic dose, the high dose so designed that the toxicity of the drug is manifested and the target organ identified. Intermediate term toxicity studies, defined as studies involving less than half the animal's life-span, are required for two or more species, most commonly the rat and the dog. Detailed haematological and clinical chemistry monitoring is regarded as a pre-requisite of modern toxicology, as are detailed terminal histopathological studies of major organs. If the toxicity tests indicate that one particular organ shows signs of dysfunction, the clinical monitoring of the subsequent trial should involve intensive monitoring of that particular organ, and assurances should be sought that clinical investigation will proceed cautiously. If organ enlargement is a feature of the toxicity studies, histopathological work should be undertaken to find out whether this is a functional hypertrophy or a manifestation of toxicity.

The general recommendations for teratological studies are modest, involving administration of the test drug, during the period of organogenesis, at three dose-levels to two species, usually the rabbit and rat. Evidence should be presented that the strain of animal used produces abnormal offspring following the administration of a known teratogen such as thalidomide. Other investigations such as fertility studies are conducted at the discretion of the applicant.

Marketing

When clinical trials have been completed and a request is received for marketing, the assessment will be based largely on the clinical documentation in relation to the proposed clinical use. In the early clinical studies evidence will have been obtained on the absorption, distribution, metabolism and excretion of the drug. In addition, the clinical pharmacology will have been studied, when appropriate.

The preparations of the drug proposed for marketing must show an adequate stability and uniformity of content. It must be clearly demonstrated that methods of formulation and preparation do not modify the drug action or interfere with its biological availability.

Evidence will be sought in the documentation for any sign of possible organ toxicity which might be revealed from the monitoring by haematological and clinical chemical methods. Problems of possible interactions with other drugs must also be scrutinised. In addition at this stage if the drug is intended for prolonged use additional studies will be required of long-term toxicity in animals.

Finally, the proposed promotional literature is examined to ensure that in the view of the committee no extravagant or misleading claims are made and that the necessary precautions and contra-indications are adequately expressed.

Adverse Reaction Reporting

The surveillance of drugs after marketing is directed by the Sub-Committee on Adverse Reactions. The primary mechanism for monitoring is based on a voluntary and spontaneous reporting system, using a simple, reply-paid 'yellow-card' whereby doctors and dentists are encouraged to report any suspected adverse reactions to

drugs to the Committee. Contact between the Committee and its staff now moved away from the pharmaceutical industry through its medical advisers, to the practising doctor whether in hospital or in general practice. The number of reports of suspected adverse reactions to drugs is a disappointingly low proportion of the total, and the true incidence of even major reactions is as yet not well documented. The fraction reported to the Committee just constitutes the tip of the iceberg, most of which remains submerged beneath the surface of our awareness (Dunlop, 1969).

Collaboration with the World Health Organisation drug monitoring schemes is well established as is also contact with drug regulating authorities in Europe and the F.D.A. in the U.S.A. and Canadian F.D.D.

The Medicines Act 1968

The Medicines Act of 1968 has resulted in the translation of Committee on Safety of Drugs into the newly formed Committee on Safey of Medicines. An identical sub-committee structure exists but with the addition of a sub-committee on Chemistry, Pharmacy and Standards. Its functions and procedures will differ little from that of its predecessor but it will act as the advisory committee to the Licensing Authority.

The Licensing Authority will issue in effect five major groups of licences:

(a) *Licences of Right*
  (i) Product Licences—these are applicable to a product already on sale on the duly appointed day, namely 1st September, 1971.
  (ii) Clinical Trials Certificate—applicable to drugs already undergoing clinical trial with the approval of the Committee on Safety of Drugs on the duly appointed day.

(b) *Clinical Trial Certificates*
Valid for a period of two years for drugs approvad by the Committee on Safety of Medicines for clinical trial.

(c) *Product Licence*
Valid for a period of five years on drugs approved for marketing by the Committee on Safety of Medicines.

Under the Medicines Act new provisions are introduced which control manufacture, distribution, and storage of drugs, and to cover these provisions a medicines inspectorate has been established and manufacturers and wholesale dealers have to hold appropriate licences.

(d) *Manufacturer' Licence.*

(e) *Wholesale Dealers' Licence.*

The Licensing Authority issue "Notes on Application for Clinical Trial Certificates" and "Notes on Application for Product Licences" as a guide to manufacturers of the nature of the data required.However like the previous Committee on Safety of Drugs no firm recommendations are laid down since the assessment of new drugs is a constantly changing scene in the light of new developments and the awareness of new hazards.

Conclusion

"The Committee has thus endeavoured to safeguard the sick by ensuring that new medicines are adequately tested, before they are introduced for trial: by ensuring that the preparations are constant and appropriate before marketing, and that their therapeutic potential outweighs any possible hazards: and that the claims are reasonable, and the precautions outlined. In addition, it maintains

a *close surveillance after marketing,* so that any unexpected or unusual effects may be recognised at the earliest opportunity and the professions informed of them.

The Committee, however, would be failing in its task of safeguarding the sick, if its attention was totally focussed on aspects of safety alone. For absolute safety cannot exist and the more potent the remedy, the more may be the capacity for harm. This is a difficult road to travel for the sick are not safeguarded if undue restriction and caution impedes therapeutic advance, and constant care is required to ensure that no patient shall be deprived of any potential therapeutic advance even at an early stage of development if an urgent need arises." (Scowen 1971).

Quite clearly the standard of safety or freedom from toxicity must be greater for a drug which is used for a trivial indication, e.g., a headache than for a drug that is effective in potentially life threatening condition.

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A CLINICOPATHOLOGICAL STUDY OF MICRONODULAR AND MACRONODULAR CIRRHOSIS IN BELFAST, NORTHERN IRELAND

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THE definition of cirrhosis is essentially anatomical, with an additional clinical concept. This is based on the "Report of the Board for Classification and Nomenclature of Cirrhosis of the Liver" at the Fifth Pan-American Congress of Gastroenterology in Cuba (Gastroenterology 1956). The cases of cirrhosis in the present study conformed to the criteria laid down at this Congress. The pathological classification of cirrhosis is unsatisfactory and various synonyms have been used to describe the same lesion. Broadly, cirrhosis may be classified anatomically as micronodular or macronodular in type. The micronodular type has been variously named portal, nutritional, fine or Laennec's cirrhosis. The features of micronodular or portal cirrhosis were those described by Baggenstoss and Stauffer (1952). The macronodular type of cirrhosis has also been termed coarsely nodular cirrhosis, postnecrotic or posthepatitic in type. Popper (1966) has distinguished two subcategories of macronodular cirrhosis—postnecrotic and posthepatitic (Gall, 1960).

The different anatomical types of cirrhosis are probably points along a continuum and not separate entities. In the later stages of the disease the distinctive features of most aetiological types of cirrhosis tend to disappear, and the end-stage liver is usually coarsely fibrotic, shrunken and macronodular. In the present study, macronodular (postnecrotic and posthepatitic) cirrhosis was diagnosed from both the gross and microscopic appearances as described by Baggenstoss and Stauffer (1952), Steiner (1960) and Gall (1960). Macronodular cirrhosis was not subdivided into two subcategories in the present study. The livers in this study represented mostly the end-stage with a micronodular or macronodular cirrhosis pattern. The incidence of liver cirrhosis was determined and a comparative pathological study of micronodular and macronodular cirrhosis made in Belfast, Northern Ireland.

MATERIALS AND METHODS

Cases of cirrhosis of the liver including micronodular (portal) and macronodular (postnecrotic/posthepatitic) cirrhosis were selected from autopsies performed at the Royal Victoria Hospital, Mater Infirmorum and City Hospitals, Belfast, from January 1, 1938 to December 31, 1966 inclusive. The clinical records were reviewed, and all histological material was re-examined. The sections were stained with haemtoxylin and eosin (H & E) and Perls' reaction for haemosiderin.

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Results

During the years 1938 to 1966 inclusive, 22,050 autopsies were performed. According to the criteria postulated earlier, there were 170 cases of micronodular cirrhosis and 168 cases of macronodular cirrhosis.

Micronodular (Portal) cirrhosis: There were 170 cases in which the morphological and histological data suggested micronodular cirrhosis. The youngest patient was 27 yr. of age and the oldest 97 yr.; the average age was 62 yr. There were 87 males and 83 females with an average age of 60 and 64 respectively.

Macronodular (Postnecrotic/Posthepatitic) cirrhosis: There were 168 cases, of whom 89 were males and 79 females. The youngest was aged 4 yr. and the oldest 87 yr. The average age was 58 yr., and there was no appreciable difference in the age between males and females. Eight cases (4.7 per cent) were under 20 yr. of age. The incidence, sex distribtuion and ages in these groups of cases with liver cirrhosis are shown in Table I.

TABLE I

Incidence, sex distribution and ages in micronodular (portal) cirrhosis and macronodular (postnecrotic/posthepatitic) cirrhosis in 22,050 autopsies.

Observations	*Type of cirrhosis*	
	Micronodular	*Macronodular*
Number of cases	170	168
Incidence relative to 100,000 autopsies	770	761
Distribution Male : Female	1 : 1 (87 : 83)	1.1 : 1.0 (89 : 79)
Average age (in years)	62	58
Range (in years)	27–97	4–87
Number <20 years	0	8 (4.7 per cent)

Incidence of liver cirrhosis

The frequency with which liver cirrhosis is found at autopsy varies from series to series. These figures probably depend on available hospital facilities, the frequency of autopsy and whether there is a particular interest in liver diseases. In this series, there are 640 cases of liver cirrhosis, of which 170 were micronodular cirrhosis, 168 macronodular cirrhosis, 140 biliary cirrhosis, 121 cardiac cirrhosis, and 40 cases that were not classified. Thus the incidence of liver cirrhosis was found to be 2.9 per cent of all autopsies preformed during 1938 to 1966 inclusive. The incidence of liver cirrhosis found at autopsy in different countries is shown in Table II, adapted from Hällén and Krook's (1963) paper on liver cirrhosis. The incidence of liver cirrhosis in European countries varies from 1.8 to 3.3 per cent, but a higher incidence seems to be present in the United States of America. A very high incidence is present in Chile, but the number of

TABLE II

Incidence of liver cirrhosis found at autopsy in different countries (Adapted from Hällén and Krook 1963)

Country	*Authors*	*No. of autopsies*	*Cirrhosis (%)*
Austria	Holtzner et al (1956)	24,008	1.8
Chile	Armas-Cruz et al (1951)	400	8.5
Germany	Langer, Honus (1954)	40,126	2.5
U.S.A.	Hall et al (1953)	16,600	4.4
U.S.A.	Kirshbaum, Shure (1943)	12,267	2.8
Sweden	Hällén, Krook (1963)	8,279	3.3
N. Ireland	Present Study (1972)	22,050	2.9

autopsies performed is small, and there may have been selection of cases for autopsy, giving a high incidence of liver cirrhosis.

Clinical data prior to final admission

The clinical notes of cases with micronodular cirrhosis and macronodular cirrhosis were consulted, but as some of the case records were insufficient with respect to certain clinical data, this aspect of the study may be subject to error. The main clinical findings are shown in Table III.

TABLE III

Clinical Data Prior to Final Admission.

Observations	*Types of Cirrhosis*					
	Micronodular (170 cases)		*Macronodular (168 cases)*		*Extrahepatic Disease 500 cases*	
	No. of cases	*Per cent.*	*No. of cases*	*Per cent.*	*No. of cases*	*Per cent*
Syphilis (+ve W.R.)	20	11.7	8	4.7	6	1.2
Excess alcohol intake	34	20.0	20	11.9		
Diabetes mellitus	20	11.7	5	2.9	13	2.6
History of jaundice or "hepatitis"	6	3.5	24	14.2		
No. diagnosed before autopsy	69	40.4	114	68.0		

Syphilis or a positive Wassermann test had been noted in 11.7 per cent of patients with micronodular cirrhosis, and 4.7 per cent with macronodular cirrhosis. Syphilis was recorded in 1.2 per cent of the autopsies performed in this institute. In none of the cases was the disease regarded as active or as being per se of aetiological importance in liver cirrhosis.

A statement concerning excess intake of alcohol was made in the clinical records of 20 per cent of the patients with micronodular cirrhosis and in 11.9 per cent with macronodular cirrhosis. The alcohol consumed was mainly beer or whisky. Jolliffee and Jellinek (1941) stated that the incidence of cirrhosis in alcoholics was 6.8 times more in inebriates than in the general population. It has been suggested that the cirrhosis is nutritional in alcoholics, as they tend to have a low protein intake, especially choline deficiency, but the cirrhosis has not been clearly established as nutritional.

Diabetes mellitus occurred in 2.9 per cent of cases with macronodular cirrhosis, and in 11.7 per cent with micronodular cirrhosis. Only 2.6 per cent of the patients autopsied in this institute had a clinical diagnosis of diabetes mellitus. Hällén and Krook (1963) found diabetes in 13.0 per cent of their cases of liver cirrhosis, as compared with 5.8 per cent in patients autopsied at their centre during 1957 to 1960. MacDonald (1964) also found that diabetes mellitus was more common in patients with portal cirrhosis than in those without cirrhosis.

Number of patients diagnosed before autopsy

Sixty-eight per cent of patients with macronodular cirrhosis and 40.4 per cent with micronodular cirrhosis were diagnosed before death to have liver cirrhosis. The higher rate of diagnosis was made in patients with macronodular cirrhosis due no doubt to the greater degree of hepatocellular damage than is found in cases with micronodular cirrhosis.

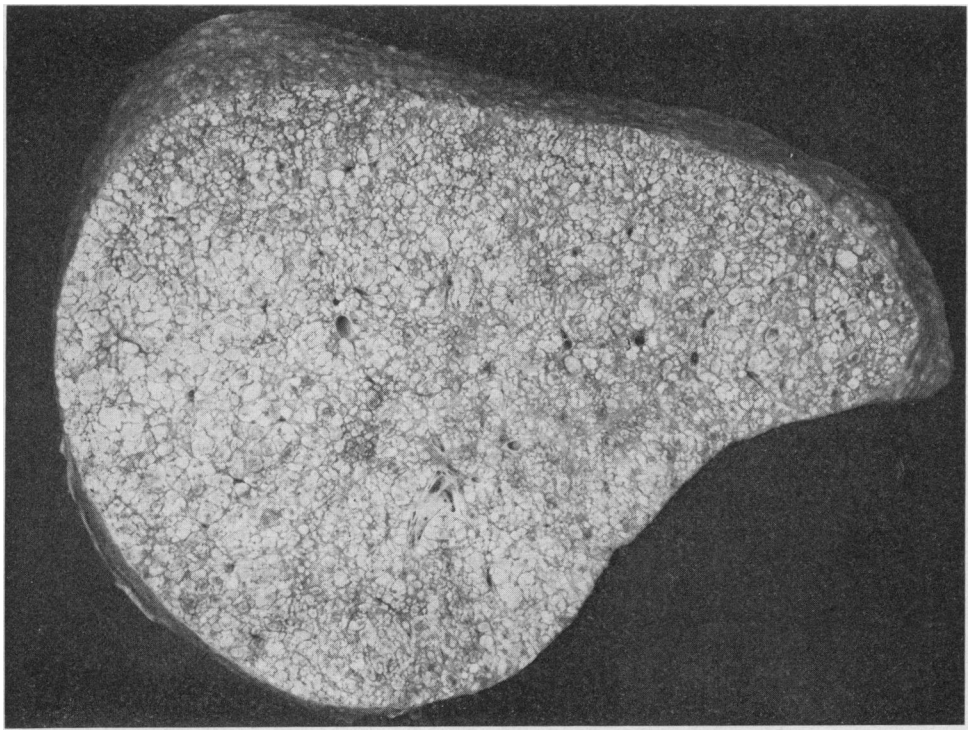
PATHOLOGICAL ASPECTS

Hepatic lesions in micronodular (portal) cirrhosis

The livers weighed between 540g and 3360g, the average weight being 1730g. In 46 per cent (78) of cases, the livers weighed over 1500g, assuming 1500g as the weight of a normal liver. The livers were granular and the regenerative nodules varied in size, but were generally smaller than 5 mm. in diameter. The typical macroscopic appearance of a liver showing micronodular cirrhosis is seen in Fig. 1. In 29.5 per cent of cases infiltration with fat was mild, and moderate to severe in 15 per cent. There was no fat infiltration in 55.5 per cent. There was mild infiltration by lymphocytes in 65.3 per cent (111 cases) and moderate to severe infiltration in 21.2 per cent (36). There was slight bile duct proliferation in 60 per cent (102), and moderate to severe in 7 per cent (12) of the livers. The fibrous bands were narrow and the internodular connective tissue caused extensive distortion of both hepatic and portal venules. These features are shown in Fig. 2.

Hepatic lesions in macronodular (postnecrotic/posthepatitic) cirrhosis

The weight of the livers ranged from 550g to 3500g, with an average weight of 1300g. Thirty-two per cent (54) weighed more than 1500g. The livers were nodular, and the nodules varied from 5 mm. to 2 cm. in size. The bands of fibrous tissue separating the regenerating nodules were thicker than in the livers of micronodular cirrhosis, and the nodules were of varying sizes as shown in Fig. 3. Infiltration with fat was mild in 19 per cent (32) and moderate to severe in 6.5 per cent (11)



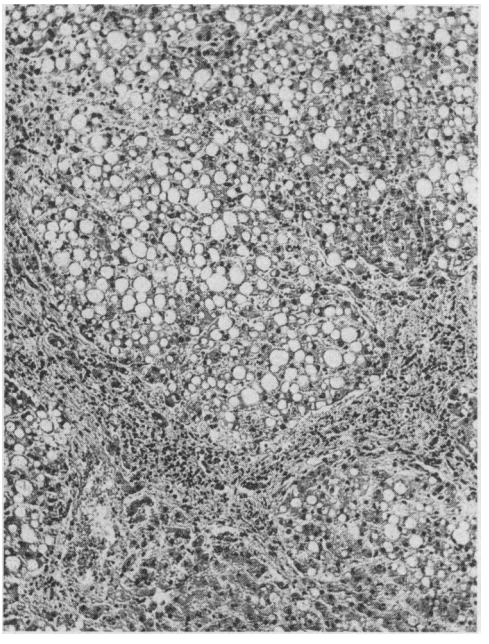


FIG. 1. *Section of liver showing a fine diffuse nodularity as seen in micronodular or portal cirrhosis. The nodules vary in size but are less than 5 mm. in diameter.*

FIG. 2. *Microscopic appearance of micronodular (portal) cirrhosis. There is fatty change and some liver cells are necrotic. Fine fibrous bands dissect the liver. There is lymphocytic infiltration with bile duct proliferation in the fibrous bands* (H. & E. x 110).

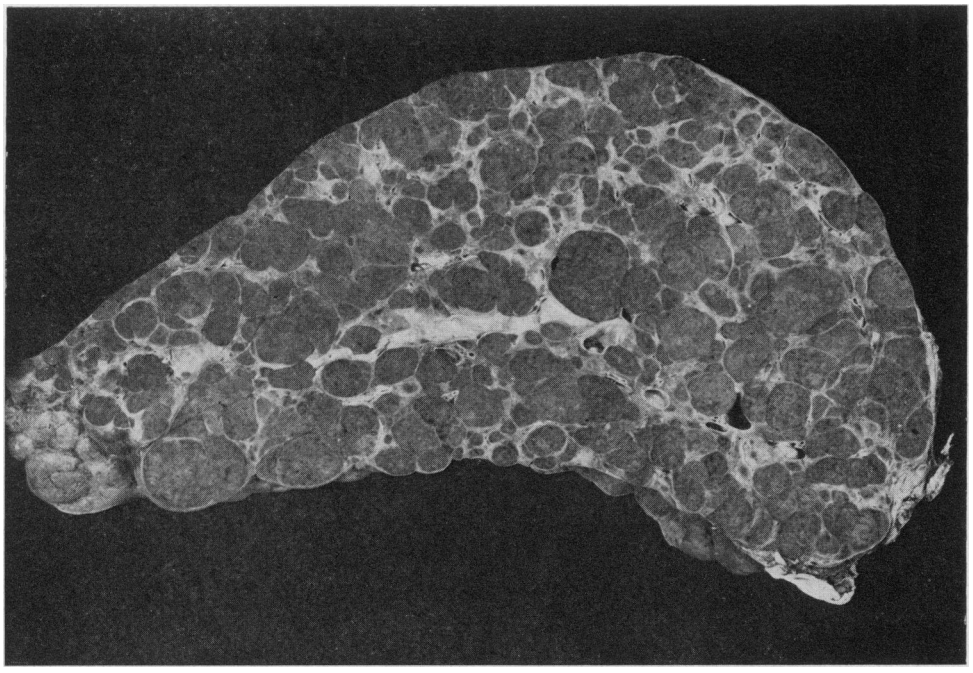


FIG. 3. *Section of the liver showing a coarsely nodular pattern as seen in macronodular cirrhosis. The regenerating nodules measure 5 mm. to 2 cm. or more in diameter and are separated by broad bands of fibrous tissue.*

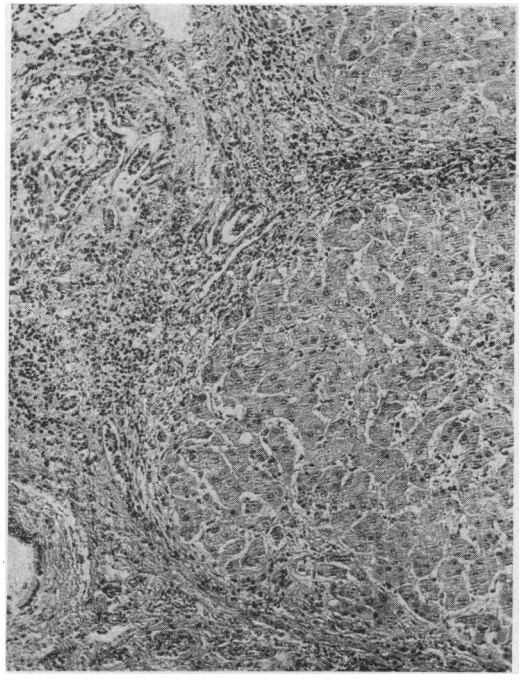


FIG. 4. *Microscopic appearance of macronodular (postnecrotic) cirrhosis of the liver. Broad bands of fibrous tissue containing proliferating bile ducts and lymphocytes, intersect nodules of regenerating liver cells which are larger than in portal cirrhosis. There is no fatty change* (H. & E. x 110).

of cases. There was no fat infiltration in approximately 75 per cent. There was moderate to severe bile duct proliferation in 67.2 per cent (113) and mild proliferation in 13.6 per cent (23) of the cases. There was moderate to severe infiltration by lympocytes and mononuclear cells in about 81.5 per cent (135) of the livers examined. In others there was mild leucocytic infiltration. The histological features are shown in Fig. 4. A summary of the macroscopic and histological features in micrnodular cirrhosis and macronodular cirrhosis is shown in Tables IV and V.

TABLE IV

Findings at autopsy in micronodular cirrhosis and macronodular cirrhosis

Observations	*Type of cirrhosis*			
	Micronodular (170 *cases*)		*Macronodular* (168 *cases*)	
	No. of cases	*Per cent*	*No. of cases*	*Per cent*
Average weight of liver	1730g		1330g	
Liver > 1500g	78	46.0	54	32.0
Average weight of spleen	335g		415g	
Spleen > 250g	83	49.0	117	70.0
Ascites	47	27.6	91	54.1
Oesophageal varices	38	22.3	88	52.3
Rupture of	26	*(68.4)	55	*(62.5)
Peptic ulcer	26	15.2	11	6.5
Primary hepatic carcinoma				
Total	12	7.0	37	22.0
Type: Hepatocellular	11 (9 R. lobe)	**91.6	32 (12 R. lobe)	**86.5
Cholangiocarcinoma	1	** 8.4	4	**10.8
Mixed	0	** —	1	** 2.7
Portal vein thrombosis				
Total	2	1.1	12	7.1
No. associated with liver carcinoma	1	***(50)	10	***(83.3)

*Expressed as a percentage of the total number of oesophageal varices.
**Expressed as a percentage of the total number of cases with primary hepatic carcinoma.
***Expressed as a percentage of the total number of cases with portal vein thrombosis.

TABLE V

Histological features in micronodular (portal) cirrhosis and macronodular (postnecrotic/posthepatitc) cirrhosis.

Observations	*Type of cirrhosis*	
	Micronodular (170 *cases*)	*Macronodular* (168 *cases*)
Morphological appearances	Altered uniformly	Altered: large areas of atrophy
Regenerative nodules	Uniform size < 5 mm.	Greater variations in size > 1 cm.
Infiltration with fat	Moderate to severe 15 per cent	Moderate 6.5 per cent
	Mild 29.5 per cent	Mild 19 per cent
Internodular fibrous tissue	Narrow zones	Wide zones
Bile ducts	Mild to moderate proliferation	Moderate to marked proliferation
Leucocytes	Mild to moderate lymphocytosis	Moderate to marked lymphocytosis

Other findings at autopsy

Evidence of portal hypertension

Splenomegaly (weight above 250g) was present in 70 per cent of patients with macronodular cirrhosis, and in 49 per cent with micronodular cirrhosis. Oesophageal varices were demonstrated in 52.3 per cent of cases with macronodular cirrhosis and in 22.3 per cent with micronodular cirrhosis. Ascites was found in 54.1 per cent of patients with macronodular cirrhosis and in 27.6 per cent with portal cirrhosis. Thus portal hypertension as evidenced by splenomegaly, oesophageal varices and ascites was observed more frequently in macronodular cirrhosis than in micronodular cirrhosis. Sixty to 68.4 per cent of the varices bled in both groups.

Peptic ulcer

This was found in 3.7 per cent of autopsies performed in this institute. Peptic ulceration was observed in 6.5 per cent of cases with macronodular cirrhosis and in 15.2 per cent with micronodular cirrhosis. MacDonald (1964) found that 14 per cent of patients with portal cirrhosis had peptic ulcer. Hällén and Krook (1963) found that 11 per cent of their cases with liver cirrhosis had peptic ulcer. The increased incidence of peptic ulcer in portal or micronodular cirrhosis may be due to the more frequent alcohol intake in these cases causing gastric irritation and faulty nutrition. It has been suggested that in liver cirrhosis there is an increased level of circulating plasma histamine, due to decreased breakdown by the liver cells, and it is this increased circulating level of histamine which causes peptic ulcer by increasing gastric acidity; but the exact mechanism is still obscure.

Primary hepatic carcinoma

This tumour was observed in 7 per cent of the patients with micronodular cirrhosis and in 22 per cent with macronodular cirrhosis. Hepatocellular carcinoma was the most common type (91 per cent), and cholangiocarcinoma was found in 9 per cent (5) of the 54 cases with a primary carcinoma of the liver. The right lobe of the liver was the commonest site for the development of the tumour in micronodular cirrhosis. In macronodular cirrhosis, 54 per cent of the tumours had a diffuse or multicentric origin. Hällén and Krook (1963) observed primary carcinoma of the liver in 11 per cent of autopsy series on liver cirrhosis. They found an equal frequency of carcinoma of the liver in the two aetiological groups studied by them—"alcoholic" and "posthepatitic" cirrhosis. The increased frequency of primary carcinoma of the liver in macronodular cirrhosis is explained by MacDonald (1964) on the basis that these patients represent an end stage of portal cirrhosis; "they have had cirrhosis for a number of years, with a long interval between early liver injury and the development of carcinoma."

Portal vein thrombosis

The incidence of portal vein thrombosis in macronodular cirrhosis was 7.1 per cent, and in the majority (81 per cent) of these patients there was an associated primary liver cell carcinoma. Approximately 1 per cent of patients with micronodular cirrhosis had portal vein thrombosis.

The Pancreas

Twenty per cent of autopsies with extrahepatic disease showed interacinar and inter-lobular pancreatic fibrosis, with minimal lymphocytic or adipose infiltration. Loss of cells in the islets was seen in 7 per cent, and hyalinization in 2 per cent of the control autopsies. No diabetes mellitus was recorded in these cases.

In micronodular (portal) cirrhosis 44.7 per cent of the 170 patients showed some degree of pancreatic fibrosis with atrophy of the acini. In 14 per cent of the cases, there was a mild to moderate leucocytic infiltration, mainly lymphocytic. In six patients, the islets of Langerhans were hyalinized and four of these cases had diabetes mellitus. There was poor cellularity of the islets in 29 patients, of whom six had diabetes mellitus.

In macronodular (postnecrotic/posthepatitic) cirrhosis pancreatic fibrosis with atrophy of the acinar glands was seen in 53 per cent of the 159 patients examined. There was lymphocytic infiltration of the fibrous tissue in 9.4 per cent of the cases. The islets of Langerhans were hyalinized in six cases, and two of these patients had diabetes mellitus. A summary of the findings in the pancreas in the autopsied patients with extrahepatic disease, and micronodular and macronodular cirrhosis is shown in Table VI.

TABLE VI

Findings in the pancreas in control autopsies with extrahepatic disease, micronodular cirrhosis and macronodular cirrhosis.

Observations	*Types of cases*					
	Controls (100 *cases*)		*Micronodular cirrhosis* (170 *cases*)		*Macronodular cirrhosis* (159 *cases*)	
	No. of cases	*Per cent*	*No. of cases*	*Per cent*	*No. of cases*	*Per cent*
Pancreatic fibrosis	20	20	76	44.7	84	53.0
Leucocytic infiltration	1	1	24	14.0	15	9.4
Islets of Langerhans						
Total involved	9	9	35	20.6	17	10.6
Hyalinized	2		6		6	
Decreased cellularity	7		29		11	
No. with clinical diabetes mellitus	0	*0.0	10	*28.5	2	*11.7

*Expressed as a percentage of the total number of islets involved.

MacDonald and Mallory (1960) found that 60 per cent of cases with portal cirrhosis had significant degrees of pancreatic fibrosis. There are errors involved in a study of this kind, because of the subjective element in the evaluation of pancreatic fibrosis. Woldman, Fishman and Segal (1959) found that in 222 cases of cirrhosis or fatty infilration of the liver, 70 per cent had pancreatic fibrosis. The increased incidence of pancreatitis in patients with cirrhosis of the liver has been attributed to acute episodes of alcohol intake, intermittent lack of protein intake, and to passive venous congestion, resulting from portal hypertension in

cases of liver cirrhosis. In the present study, no definite association between hyalinization and decreased cellularity of the islets of Langerhans and diabetes mellitus was found.

Iron deposition in the liver and pancreas

There was haemosiderin deposition in the liver of 30 per cent of the 329 patients with liver cirrhosis, whereas only 5 per cent of the 100 control patients with extrahepatic disease showed haemosiderin. The haemosiderin deposits also appeared to be greater in amount in the patients with liver disease than in the patients with extrahepatic disease. Of the 329 cases of liver cirrhosis, 3.6 per cent showed an excess of iron in the liver cells, internodular fibrous tissue and Kupffer cells, which was indistinguishable from the livers of patients with idiopathic haemochromatosis. Of the 329 patient with liver cirrhosis, 5.4 per cent showed excess iron in the pancreas, present as granules in the acinar cells and connective tissue.

Causes of Death

Although many factors played a role in causing death in each patient, an attempt was made to estimate from the observations at autopsy the most important cause in each case. The chief causes of death are shown in Table VII. The most

Table VII

Most important causes of death in micronodular cirrhosis and macronodular cirrhosis.

Causes of death	*Types of cirrhosis*			
	Micronodular (170 *cases*)		*Macronodular* (168 *cases*)	
	No. of cases	*Per cent*	*No. of cases*	*Per cent*
Hepatic insufficiency	37	21.8	65	38.7
Associated liver carcinoma	12	7.1	37	22.0
Haemorrhage—total	30	17.6	59	35.1
From varices	26	15.3	55	32.7
From peptic ulcer	4		4	
Cardiovascular Disease—total	24	14.1	7	4.1
Hypertensive, rheumatic, bacterial endocarditis	16		3	
Myocardial infarct	8		4	
Pulmonary infection	20	11.9	6	3.5
Abdominal catastrophies—perforations, strangulation, etc	16	9.4	5	2.9
Non-hepatic malignant tumours	14	8.2	8	4.7

frequent causes of death in micronodular cirrhosis and macronodular cirrhosis were hepatic insufficiency and haemorrhage from bleeding oesophageal varices. In macronodular cirrhosis, 38.7 per cent of the patients died from hepatic insufficiency, and 35.1 per cent from haemorrhage. This was seen to a lesser extent in micronodular cirrhosis where 21.8 per cent of patients died from liver insufficiency and

17.6 per cent from gastro-intestinal haemorrhage. Death from cardiovascular disease was observed more frequently in micronodular cirrhosis than in macronodular cirrhosis.

Discussion

Baggenstoss and Stauffer (1952) in their study of cirrhosis of the liver following viral hepatitis found that cases of post-hepatitic cirrhosis could present either as a nodular or granular liver as in macronodular cirrhosis and micronodular cirrhosis. They suggested that the liver may react in a variety of ways to an attack of viral hepatitis. Sheldon and James (1948) and Kunkel and Labby (1950) found that postnecrotic cirrhosis comprised the common type of cirrhosis of the liver produced by viral hepatitis. Baggenstoss and Stauffer (1952) proposed that the broad zones of atrophy in this group were probably expressive of a severe attack of viral hepatitis and the lack of regeneration. The large regenerative nodules characteristic of postnecrotic cirrhosis were probably evidence of extremely vigorous regeneration after the attack of hepatitis. Neefe and others (1955) in their study examined large numbers of soldiers who had hepatitis during World War II; then re-examined a number of them several years later, and found the frequency of liver cirrhosis was no higher than in a control series. MacDonald and Mallory (1958) believe that the risk of cirrhosis following hepatitis is only 0.7 per cent. Perhaps the most characteristic feature of all was the fact that once cirrhosis was established, the disease was progressive and failed to respond to therapy (Kunkel and Labby 1950). Baggenstoss and Stauffer (1952) found that patients who had posthepatitic cirrhosis died at a mean age of 36 years as compared with a mean age of 50 years for the alcoholic group. In the present study, 4.8 per cent of the patients who died from macronodular cirrhosis were under 20 years of age. Sixty-eight per cent of patients with macronodular cirrhosis and 40.4 per cent with micronodular cirrhosis were diagnosed before autopsy. A higher rate of clinical diagnosis was obtained in macronodular cirrhosis due to the greater degree of hepatocellular damage. An increased incidence (11.7 per cent) of diabetes mellitus was also found in patients with micronodular cirrhosis, compared with the incidence (2.6 per cent) in the patients autopsied at this institute.

It appears that the relationship between infectious hepatitis and liver cirrhosis is obscure. Hällén and Krook (1963) found the liver to be coarsely nodular in 36 per cent of cases with posthepatitic cirrhosis, 4 per cent with alcoholic cirrhosis and in 26 per cent of cases of cryptogenic cirrhosis. Dible (1951) and Perkins et al (1950) also found that hepatitis may produce the morphological equivalent of portal cirrhosis or postnecrotic cirrhosis.

The hepatic changes in the alcoholic have been related to nutrition as chronic alcoholics usually eat sparingly and erratically. It has been claimed that lack of lipotropes like choline or methionine cause fat infiltration of the liver, which leads to a portal-type of micronodular cirrhosis. Kimmelstiel, Large and Verner (1952) have shown that alcohol has an effect upon fat metabolism independent of nutritional factors. Thus it seems that alcohol may have direct and indirect effects on hepatic fat metabolism quite independently of nutritional changes. The alcoholic

commonly presents with micronodular, portal cirrhosis, but postnecrotic cirrhosis with a macronodular pattern is also seen (Baggenstoss and Stauffer, 1952). In the present study, a history of excess alcohol intake was noted in 20 per cent of cases with micronodular cirrhosis and 11.9 per cent of cases with macronodular cirrhosis. A history of jaundice or hepatitis was noted in 14.2 per cent of patients with macronodular cirrhosis and in only 3.5 per cent with micronodular cirrhosis.

The patients who had macronodular cirrhosis died at a younger age than patients with micronodular cirrhosis. The average age at death in cases with macronodular cirrohosis was 58 years, and in patients with micronodular cirrhosis 62 years. Baggenstoss and Stauffer (1952) noted after an attack of hepatitis cirrhosis can apparently develop in a relatively short time, even in a matter of weeks. Sherlock (1948) noted the rapidity with which cirrhosis may develop in these patients.

The average weight of the livers in patients with micronodular cirrhosis was much heavier by 400g than in cases with macronodular cirrhosis. Connor (1939) and Hall and Morgan (1939) found the livers in general to be smaller than normal in alcoholic cirrhosis. Fat infiltration was observed more commonly and was more severe in micronodular cirrhosis than in macronodular cirrhosis. There was a heavier lymphocytic infiltration of the fibrous tissue and liver parenchyma in macronodular cirrhosis than in micronodular cirrhosis. In accordance with the findings in the present study, MacSween and Jackson (1966) observed that the commonest cause of death in micronodular cirrhosis and macronodular cirrhosis was hepatic failure. Here 38.7 per cent with macronodular cirrhosis and 21.8 per cent with micronodular cirrhosis died of liver failure. There was an associated primary liver cell carcinoma in many of these patients. A primary hepatocellular carcinoma of the liver was found in 22 per cent with macronodular cirrhosis and in 7 per cent with micronodular cirrhosis. Death from bleeding oesophagael varices was more frequent in patients with macronodular cirrhosis than in micronodular cirrhosis. This suggests that portal hypertension is more severe, and is present more often in macronodular cirrhosis than in micronodular cirrhosis. This is contrary to the findings of Baggenstoss and Stauffer (1952) who found that in alcoholic cirrhosis the regenerative nodules were smaller and more numerous and consequently compressed a greater number of smaller hepatic and portal venules, thus causing a higher incidence of portal hypertension.

Demonstrable haemosiderin pigment was observed in a large proportion of livers from patients with liver cirrhosis, both micronodular and macronodular types. In the control patients without hepatic disease, haemosiderin in the liver was significantly less frequent (5 per cent) and slight in quantity. Thirty per cent of the 329 patients with micronodular cirrhosis and macronodular cirrhosis had haemosiderin in the liver cells, but only 3.6 per cent of the livers contained iron to the same extent as in cases with haemochromatosis. In approximately 60 per cent of these there was a history of multiple blood transfusions, excess alcohol and iron intake to explain the presence of hepatic haemosiderin. Pancreatic siderosis was found in 5.4 per cent of the 329 patients with liver cirrhosis, but the iron deposition was light and not as heavy as in haemochromatosis. There is some degree of overlap between siderosis in liver cirrhosis and haemochromatosis. Thus, cases of liver cirrhosis and haemosiderosis should be classified as pigment

cirrhosis, unless there is a strong genetic evidence for idiopathic haemochromatosis.

The correlation between aetiological factors and postmortem changes is poor, and the further study of morphological features would be of most value in the early stages of the disease. It would appear that a satisfactory classification of liver cirrhosis would be an aetiological one with a morphological description of the pathological features.

Summary

During 1938 to 1966 inclusive, 22,050 autopsies were performed by the Staff of the Institute of Pathology, Belfast. The incidence of liver cirrhosis (640 cases) found at autopsy was 2.9 per cent. There were 170 patients with micronodular cirrhosis and 168 with macronodular (postnecrotic/posthepatitic) cirrhosis. These groups of patients were studied and compared clinically and pathologically. Patients with macronodular cirrhosis died at a younger age than those with micronodular cirrhosis. Approximately 4.8 per cent of the patients with macronodular cirrhosis died before the age of 20 years. There was no sex difference in micronodular cirrhosis and macronodular cirrhosis.

Jaundice and ascites were more frequent in macronodular cirrhosis. Hepatic insufficiency and haemorrhage from oesophageal varices were the most common causes of death in both types of liver cirrhosis. Portal hypertension, as evidenced by ascites, splenomegaly and oesophageal varices was more common in macronodular cirrhosis than in micronodular cirrhosis. The average weight of the liver in micronodular cirrhosis was 400g heavier than in macronodular cirrhosis. The incidence of primary hepatic carcinoma was 22 per cent in macronodular cirrhosis and 7 per cent in micronodular cirrhosis. Portal vein thrombosis was associated with the hepatic carcinoma. Peptic ulcer was found in 15.2 per cent with micronodular cirrhosis, 6.5 per cent with macronodular cirrhosis and in 3.7 per cent with extrahepatic disease. Diabetes mellitus was observed in 11.7 per cent with micronodular cirrhosis, 2.9 per cent with macronodular cirrhosis and in 2.6 per cent of cases with extrahepatic diseases. Approximately 50 per cent of patients with micronodular cirrhosis were not diagnosed until autopsy. Sixty-eight per cent of patients with macronodular cirrhosis were diagnosed before autopsy, presumably because of the greater degree of liver parenchymal damage.

Haemosiderin pigment was present in 30 per cent of the 329 patients with micronodular cirrhosis and macronodular cirrhosis, but only 3.6 per cent of the livers contained iron to the same extent as in patients with haemochromatosis. There was a poor correlation between the aetiological factors and postmortem changes. A satisfactory classification of liver cirrhosis would be an aetiological one with an anatomical or pathological description.

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A REVIEW OF 100 CONSECUTIVE CASES OF JAUNDICE SEEN IN A SURGICAL UNIT

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THE problems presented by the jaundiced patient are many and yet the establishment of an early diagnosis is important. To find the relative frequency of the various causes of jaundice a record of all such patients seen by one of us (H.L.) has been kept since the adult surgical unit was opened three years ago in the Ulster Hospital, Belfast.

SELECTION OF CASES

One hundred consecutive patients who were either clinically jaundiced when seen or who had a serum bilirubin level greater than 1.0 mg. per ml. make up the series. It can be seen from Table I that just over half (52) of the cases were

TABLE I

Final Diagnosis in 100 *Patients with Jaundice*

Hepatitis	10	
Cholecystitis		
Cholelithiasis	52	
Choledocholithiasis		
Previous Cholecystectomy	6	
Tumours	19	
Pancreatitis	7	
Not Diagnosed	1	
Drugs and Transfusion	5	

associated with inflammatory or calculous disease of the gall bladder or common bile duct. Of these 19 were male and 33 female. Their age range was 21 to 91 years. Eight of these patients did not come to operation for various reasons, the diagnosis being established by a combination of liver function tests, x-rays and clinical behaviour. Of the 52 cases, 35 were shown at operation or by x-ray to have cholelithiasis, 17 choledocholithiasis and in six patients no stones were demonstrated in the gall bladder or the common bile duct. In seven patients the presence or absence of calculi was either not recorded at operation or they were not investigated.

In 44 patients the diagnosis was confirmed at operation and 43 of them had cholecystectomies. The other patient was unexpectedly found to have cavernous transformation of the portal vein and as cholecystectomy proved impossible cholecystostomy was performed and several stones removed. Thirty-five of the patients operated upon had stones in the gall bladder; in six cases no stones were found. In the remaining three patients the presence or absence of stones was not recorded. Of the 44 patients who were operated upon 20 had exploration of the

common bile duct and stones were found there in 17. In three cases there were stones in the common bile duct but none in the gall bladder. None of the 24 common bile ducts which were not explored was dilated. In 19 there was no evidence of calculi either on palpation or on cholangiography. In five patients the duct was not explored purely on clinical grounds, these patients having been operated upon before operative cholangiography was available. One case had exploration of the duct on radiological evidence alone but no stones were found.

Six patients presented with jaundice who had previously had a cholecystectomy elsewhere and all had stones in their common bile ducts. Details of these cases and the operative findings are given in Table II.

TABLE II

Sex	*Age*	*Time since Cholecysectomy*	*Diameter of Duct (cms.)*	*Cystic Duct Remnant*	*Operation*
Female	67	14 Years	2.5	None	Choledochoduodenostomy
Male	53	7 Years	0.4	Long	Choledochtomy
Female	76	20 Years	2.0	G.B. Remnant	Choledochoduodenostomy
Female	56	7 Years	1.5	G.B. Remnant	Choledochtomy
Female	66	9 Months	1.5	None	Choledochtomy
Female	72	31 Years	2.5	None found but seen on x-ray	Choledoohoduodenostomy

The sex, age, time since cholecystectomy, diameter of the common bile duct, size of the cystic duct or gall bladder remnant found and operation performed in six patients presenting with jaundice after previous cholecystectomy.

It is surprising that only 19 per cent of patients seen with jaundice in a surgical unit had neoplastic disease. The sites of the tumours are shown in Table III.

TABLE III

Site of Tumour in 19 Patients with Jaundice

Pancreas	14
Bile Duct	1
Gall Bladder	1
Ampulla of Vater	2
Unknown	1

That 10 of the 100 cases seen by a surgeon should ultimately be diagnosed as having hepatocellular disease is not surpising as it is frequently difficult to differentiate hepatitis from cholecystitis. Three of the caes had a laparotomy when the diagnosis of hepatocellular disease was made.

Seven patients had jaundice associated with pancreatitis, presenting with the typical signs and symptoms of the disease and a significantly raised serum amylase level. There were five patients who developed jaundice while in hospital which was

thought to be due to drugs or transfusion. A definite cause for the jaundice in one patient could not be found and further investigation was refused.

Discussion

Tumours

It is well established that carcinoma of the pancreas is the most common tumour to cause jaundice. Many of these are inoperable and even when pancreaticoduodenectomy is possible it carries a high mortality and a poor prognosis. Whether the overall results from pancreatectomy are better than a by-pass operation is questionable. The two patients in this series who had resections had fairly stormy post-operative recoveries and only survived six and eight months. This is not the case with tumours of the ampulla of Vater. These are easily missed but carry a relatively good prognosis, 52.6 per cent of cases operated on primarily in the Lahey Clinic and having pancreaticoduodenectomy survived five years or more (Cattell, Warren and Au (1959). In the two patients in this series the tumours were mobile and easily demarcated from the rest of the pancreas and both were dealt with conservately by local resection. These patients are alive and well 6 and 18 months after their operations. In one of these patients pancreaticoduodenectomy would have been extremely hazardous if not impossible because of obesity yet he returned to work as a labourer three months after his operation. For a surgeon inexperienced in pancreaticoduodenectomy the low mortality and morbidity associated with the more simple operation of local excision may prove to be the better procedure for this relatively rare tumour.

Cholecystitis and cholelithiasis

The high incidence of inflammatory or calculous disease in this series raises the interesting question of the pathological processes which caused the jaundice in these patients. It is obvious that a stone impacted anywhere in the common bile duct will cause jaundice. Of the 44 patients in this group who came to operation only 17 or 39 per cent were shown to have stones in the common bile duct and to which the jaundice could be attributed. Fosburg (1963) found stones in the common bile duct in all patients with chronic cholecystitis and jaundice and Smith *et al* (1963) give a figure of 61 per cent in a similar series. In the present series it is impossible to separate the patients with acute cholecystitis from those in whom the disease was chronic. All had histological evidence of the latter but some were operated upon after an interval to allow the inflammation from the acute episode to resolve and so the results are not comparable with other series.

Why should the remaining 61 per cent of patients have developed jaundice? There seem to be four possible theories: —

(a) Some may have had infective hepatitis which was not evident from the liver function tests. This, of course, could apply to the patients who had choledocholithiasis and Smith *et al* (1963) gave this as a possible explanation for the low incidence (15 per cent) of choledocholithiasis when jaundice was the only indication for choledochotomy in their series.

(b) The jaundice may have been due to undiagnosed pancreatitis The clinical picture of acute pancreatitis and acute cholecystitis may be similar and the

serum amylase may be elevated in both (Hinchey *et al* (1965). Biliary tract disease is found in about two-thirds of patients with acute pancreatitis (Logan (1965) and so if operation is delayed the resolved pancreatitis may not be recognised.

(c) The jaundice of acalculous acute cholecystitis is often attributed to oedema of the common bile duct (Davidson, (1968), Eckel, (1950) yet operative cholangiography performed during the acute episode fails to show obstruction at this level. In these patients the gall bladder is inflamed but the common bile duct is also usually red and thickened and the inflamation of the gall bladder may be the most obvious part of an inflammation of the whole biliary tract. Fish *et al* (1968) find the evidence for this inconclusive while Glenn and Thorbjarnarson (1963) and Sherlock (1968) offer it as a possible explanation.

(d) Stones may have passed from the common bile duct into the duodenum and Fish *et al* (1968) record an incidence of "passed stones" of 13.5 per cent.

The liver function tests available today may be helpful in establishing the difference between hepatitis and biliary tract disease but they do not help in differentiating between those cases in which calculi are present in the common bile duct and those in which there are no stones. In the present series the highest values for the bilirubin before operation was on average higher in cases where stones were later found in the common bile duct (7.8 mgm/100 ml.) than those where no stones were found (4.4 mgm/100 ml.). There was a similar difference in the corresponding figures for the alkaline phosphatase (44 and 32 K.A. units) but the ranges for both of these showed considerable overlap and consequently were not helpful in indicating the presence or absence of choledocholithiasis. Smith *et al* (1963) also found bilirubin levels of little help but a raised alkaline phosphatase was a better indication of the presence of a duct stone. Hinchey *et al* (1965) believe that the bilirubin is more elevated in the presence of a common duct stone while Watkin and Thomas (1971) found that above 2 mgm/100 ml. there is no level at which choledocholithiasis becomes more probable and we would agree with this conclusion.

Jaundice following cholecystectomy

The contention that complete removal of the gall bladder and cystic duct at cholecystectomy is essential for the prevention of choledocholithiasis at a later date is supported by the fact that three of the six patients in this group had had incomplete operations. In all of these the remnant was over three centimetres in length. In two there were remnants of the gall bladder which contained stones and in the third a long cystic duct was found which passed behind the common hepatic duct and joined it on the left side. In another case a large remnant appeared to be present in the x-rays but none was found at operation due to the size of the dilated common bile duct and the distorted anatomy in the region. Garlock and Hurwitt (1951) state that the cystic duct stump can become in effect a diseased gall bladder undergoing inflammatory changes of varying degrees. Second operations in the region of the common bile duct can not only be difficult but dangerous and therefore the surgeon carrying out cholecystectomy must ensure that the cystic duct is tied off flush at its junction with the common hepatic duct, that the common bile duct is not injured and that no stones are left in the common bile duct. Three

techniques can be employed to help in achieving these aims. (a) Retrograde cholecystectomy helps in defining the junction of the cystic duct with the common hepatic duct and prevents injury to the common bile duct. (b) Operative cholangiography, used with discretion, ensures that stones are not overlooked in the common bile duct and (c) mobilisation of the head of the pancreas allows palpation of the lower common bile duct, the ampullary region and the head of the pancreas.

The value of these techniques is emphasised by one of the patients in the series who had had a cholecystectomy elsewhere and within twelve months became jaundiced. She did not have either cholangiography nor mobilisation of the head of the pancreas and her common bile duct contained one large stone. Unforunately, she died as as result of a cerebro-vascular accident following choledochotomy.

Conclusions

The presumptive cause of jaundice is difficult to establish with certainty before operation and even at laparotomy no abnormality may be found in the common bile duct. We believe that the techniques which have been outlined not only help to avoid the error of leaving stones in the common bile duct, but also reduce the number of unnecessary choledochotomies. Retained common duct stones and negative choledochotomy cause a considerable morbidity and any manoeuvre which diminishes this is worth employing.

Summary

A series of 100 patients with jaundice is considered and the diagnoses discussed. The difficulties of establishing the presence of choledocholithiasis prior to exploration of the common bile duct are considered and the usefulness of operative cholangiography in this respect is stressed.

The aetiology of jaundice in cholecystitis without choledocholithiasis is discussed and ascending cholangitis is thought to be the most likely cause. Jaundice due to stones and following cholecystectomy is believed to be avoidable if careful attention is paid to surgical technique and several recommendations are made to this end. The surgery of tumours of the head of the pancreas and ampulla of Vater is conconsidered.

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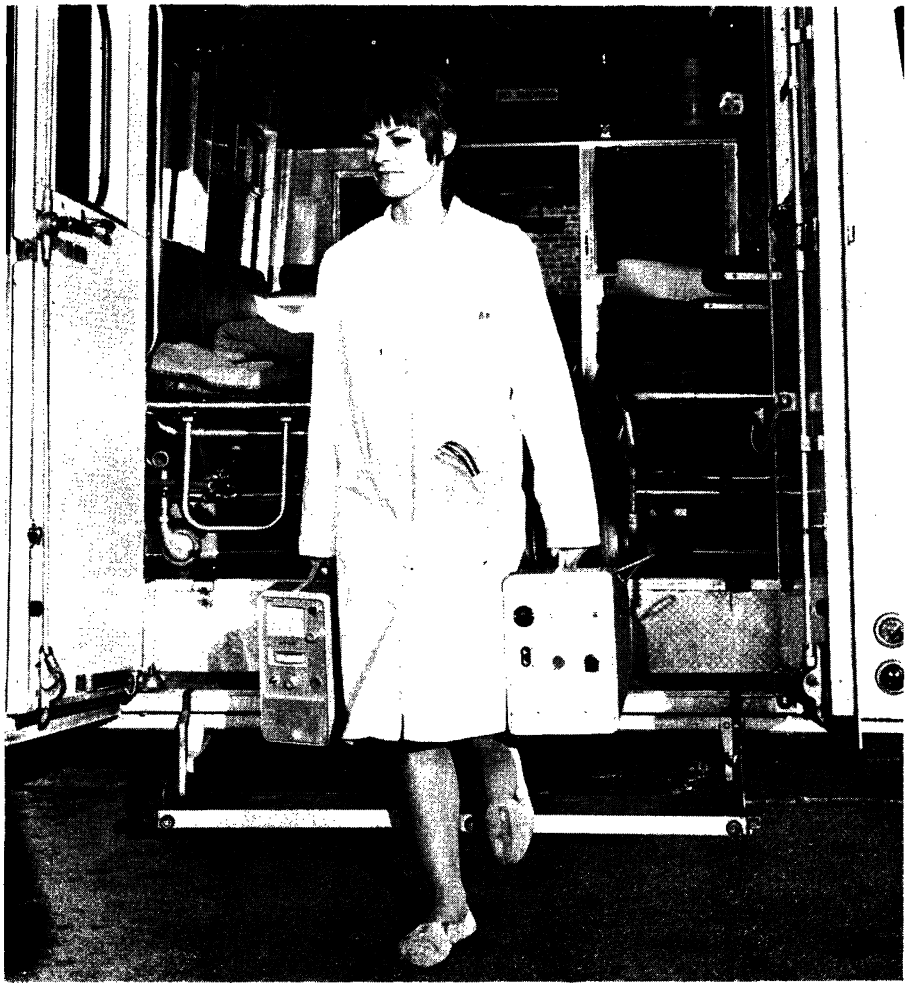

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THE HALF-LIFE OF IMMUNE GLOBULIN G IN CHRONIC BENIGN CRYPTOGENIC HYPERGAMMAGLOBULINAEMIC PURPURA WITH PIGMENTATION

And a Report of a Case

by T. K. BELL* and J. S. LOGAN†

THE purpose of reporting this case is to add evidence that the syndrome is truly an entity, to record the high level of immune globulin G, and to report that the half-life of the immune globulin G in this case is normal or diminished. The elevation of the serum immune globulin G is due to excessive production, and not to slow or diminished removal from the plasma.

Waldenström reported the syndrome in 1943, and then reported this and a different dysproteinaemic disease, macroglobulinaemia, in a single paper in 1948. Physicians are still sometimes confused because the hyperglobulinaemia and the macroglobulinaemia both have borne his name. It has also been confusing that purpura occurs in the course of several hyperglobulinaemic diseases. Chronic benign cryptogenic hypergammaglobulinaemia with purpura and skin pigmentation differs from macroglobulinaemia *inter alia* in the patient remaining generally well, the course being benign, the bone marrow being normal, the lymph glands not being enlarged, and the dysproteinaemia being an excess of immune globulin G and not an excess of a macroglobulin. It is more rare than macroglobulinaemia.

Not every case of purpura and hyperglobulinaemia is Waldenström's hyperglobulinaemic purpura, which is very uncommon. It is characterised by frequent crops of small purpuric spots, repeated over many years, predominantly on the lower legs, the spots being obscured in time by permanent heavy brown pigmentation of the affected skin. The serum protein electrophoresis shows a high peak in the gammaglobulin area. The main rise is in the immune globulin G fraction which reaches 3 grammes and over. There may be occasional swelling of a parotid gland. The lacrimal glands may be affected, with some diminution of tear production. Corneal damage may occur and probably is in some degree due to dryness of the eyes. Dryness of the mouth is not severe, nor is the dryness of the eyes. As time goes by, the pigmentation of the lower legs deepens. Eventually the pigmentation is much more striking than the original purpura, and then, though the purpura still occurs, it can hardly be seen. Small keratoses may appear in the pigmented skin. The disease lasts so long as life itself. The only serious disability is impairment of sight if the corneal damage is severe. There is no bleeding tendency. The cause is unknown. The dark skin and the protein changes are reminiscent of kala-azar, but no infection or infestation has been identified.

Case Report

The present patient is a married woman born in 1925. The skin changes and the general condition can be seen in Figures 1 and 2. One of us has observed the

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FIG. 1. *Shows good general condition and the pigmentation of the lower legs.*

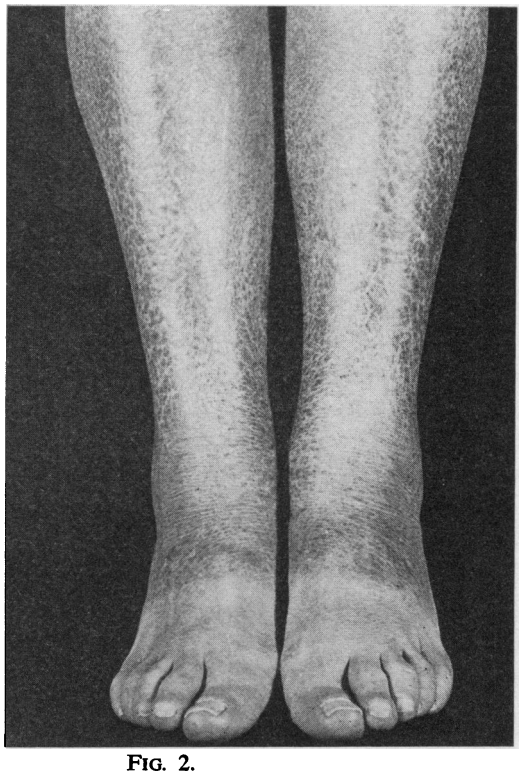


FIG. 2.
The pigmentation of the lower legs.

patient for 17 years, since the purpura first appeared in 1955. She remains well from a general point of view, and indeed never was generally ill. The main disability is some opacification of the cornea, due at least in part to dendritic ulceration. Fresh purpuric spots on non-pigmented skin may occasionally be seen on the forearms if she has been carrying a basket, or very infrequently on the lower abdomen. Multiple keratoses have arisen on the pigmented skin of the lower legs. There is no itching and there are no ecchymoses. The abnormality does not resemble lichen amyloidosus. There has been no oedema. There was one short spell of unilateral parotid gland swelling. In earlier years the spleen tip could just be palpated, but lately that is not so. There has regularly been a moderate anaemia with nondescript peripheral blood findings. There was no granulocytopaenia and no lymphocytosis. Platelet count normal. The total white cell count has ranged from 3,600 to 5,400. The white cells contained no inclusions. The serum iron has been low and on one occasion the serum folic acid was low. For a long time she was troubled with pain about the left temporal area, for which no cause could be found. Perhaps it was due to the keratopathy or lacrimal adenopathy. There have been no signs of arthritis, arteritis, renal disease or tubular acidosis. In 1963 there was rather severe herpes febrilis on the face in the course of an attack of bronchopneumonia. Earlier in the same year she had

FIG. 3 (right): *Serum protein electrophoreses.*

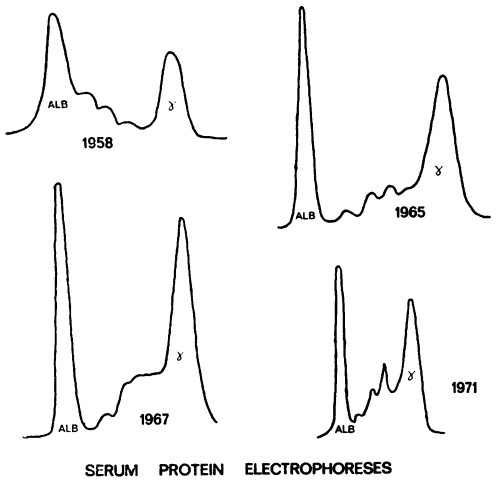
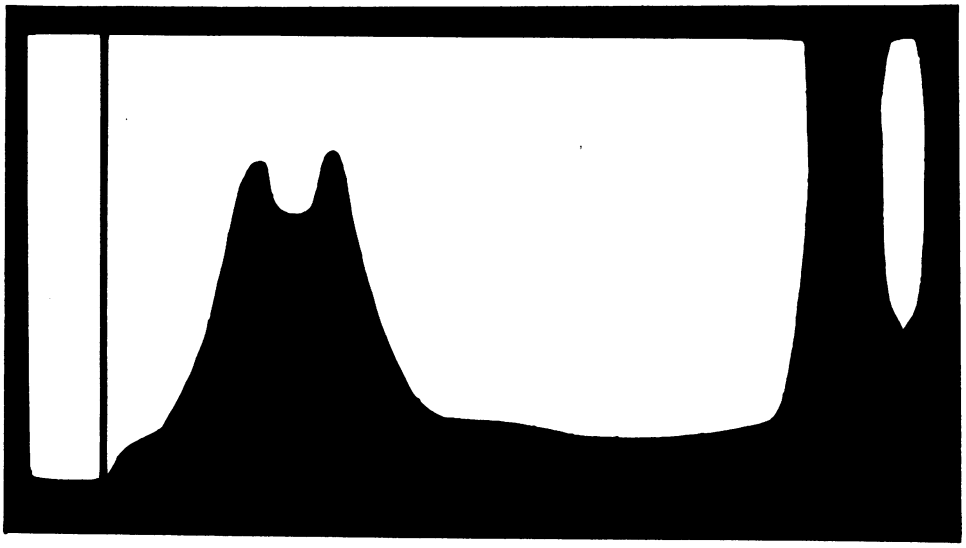


FIG. 4 (below): *Ultracentrifugation pattern showing an excess of the 7 S component, and no excess of macroglobulins.*



had herpes zoster. Except with such occasional infections there has been no fever. She has had no frequent or severe or unusual infections. There has been no enlargement of lymph glands, no eosinophilia, and no evidence of liver disease. The bromsulphthalein test was normal. There is neither hyperthyroidism nor hypothyroidism. No evidence of small intestine or colon disease or chronic bronchopulmonary disorder has appeared. Menstruation has been regular. Cold produces no ill effects. There is no peripheral circulatory or ischaemic abnormality. There is no enlargement of the thymus to be seen in the chest x-ray. The bone marrow is normal. Blood group is A, Rh positive. The colour vision is normal and chromosome analysis 46/XX.

The serum protein electrophoreses showing the high gammaglobulin peak can

TABLE I. *Serum immune globulin estimations, showing the high IgG level and the modest rise in IgM.*

Date	*IgG*	*IgA*	*IgM*	*IgD*
1967	2750	470	200	
1968	4400	252	312	Trace
1971	3400	310	220	
1971	3600	340	220	

be seen in Fig. 3. The serum untracentrifugation pattern showing an excess of 7 S component can be seen in Figure 4. The serum immune globulin estimations showing the high level of immune globulin G and a modest rise in immune globulin M can be seen in Table I. Serum albumin is normal, serum fibrinogen 380 mgm. per cent and serum cholesterol 139 mgm. per cent. The plasma specific gravity is 1.035 and E.S.R. 120. The urine contains no abnormal protein and no light chains. There has been no amino-aciduria. Histological examination of keratotic lesions on the leg showed no evidence of amyloid.

The following serological tests are positive – antinuclear factor, smooth muscle antibodies, and rheumatoid arthritis latex test. Wassermann and Reiter protein complement fixation tests anticomplementary. Antistreptolysin titre is 1/625. The following tests are negative – mitochondrial antibodies, parietal cell antibodies, intrinsic factor antibodies, complement fixation test against thyroid microsomes, tanned red cell agglutination, Rose-Waaler, venereal diseases reference laboratory, fluorescent treponemal antibody, Paul-Bunnell, brucella, Widal, and leptospiral agglutination. Direct Coomb's test is negative. There are no irregular red cell antibodies and the anti-B titre is 1/4.

Australian antigen negative in immune diffusion test. Serological tests for the following viruses all showed results, as the reciprocal of antibody titre, of less than 10 – adenoviruses, psittacosis/lymphogranuloma, Q fever, mycoplasma pneumoniae, mumps V, measles, lymphocytic choriomeningitis, herpes simplex and louping ill.

Her father and mother were not related. She is one of 10 brothers and sisters. The rest are healthy. She has one son who was considered to have coeliac disease in early childhood and was treated with a gluten-free diet. He is now tall and is athletic. The son has no abnormality of his serum proteins, nor have the three brothers and four sisters who have been examined.

MEASUREMENT OF IgG TURNOVER

The method of investigation followed the techniques described in detail by Veall and Vetter (1958) for plasma protein turnover studies. The IgG fraction was separated from the patient's serum and labelled with Iodine-125 by Dr. A. S. McFarlane, to whom we are deeply indebted. Lugol's iodine solution was given daily to the patient and a control, starting two days before administration of the radioactive dose and continuing throughout the study, to block the uptake of radioiodine by the thyroid. One hundred microcuries ^{125}I–IgG were administered intravenously to the patient and the control, and samples of plasma and 24 hour

urine specimens were collected daily for 14 days. The radioactivity in the plasma was expressed as a percentage of the 10 minute plasma sample, and the quantity of radioactivity in the 24 hour urine collections expressed as a percentage of the dose given, from which the percentages remaining in the total body of each subject on successive days were calculated. These values are displayed on semilogarithmic paper against time in Figure 5, and Table II summarises the results obtained from both the patient and the control subjects.

The equilibrium time, Te, at which the amount of labelled IgG passing from the plasma to the extravascular fluid equals the amount passing in the opposite direction, is less for the patient than the control, being 3.2 and 4.5 days

TABLE II. *Summary of results obtained in patient and control, using the patient's labelled IgG to examine turnover.*

Results	*Patient*	*Control*	*Units*
Weight	68.2	89.1	kg
Plasma IgG concentration	3.5	0.95	g/100 ml
Plasma Volume	45.7	39.5	ml/kg
Plasma IgG pool	1.60	0.38	g/kg
Plasma IgG Degradation Rate Constant (k_1)	12.8	8.3	% per day
Plasma IgG Metabolic Degradation Rate	0.205	0.032	g/d/kg
Equilibrium Time (Te)	3.2	4.5	days
Plasma IgG Half-life ($T\frac{1}{2}$)	5.4	8.3	days
Intravascular: Extravascular distribution	1: 0.86	1: 0.80	
Total IgG Pool	2.98	0.69	g/kg
Total IgG, Half-life	10.1	14.9	days

respectively. The plasma IgG pool was calculated by multiplying the plasma volume, determined from the radioactivity detected in the 10 minute plasma sample, and the plasma IgG concentration. For each 24 hour period the plasma IgG degradation rate constant was obtained by dividing the percentage of the dose of radio-iodine excreted in the urine by the average amount remaining in the plasma during the same period. The average plasma IgG degradation rate constant (k_1) was 12.8 per cent per day for the patient and 8.3 per cent for the control. These values are the slopes of the tangents to the plasma curves at the respective equilibrium times shown in Figure 5.

Utilizing the relationship that the half-life ($T\frac{1}{2}$ days) equals 0.693 divided by the plasma degradation rate constant k_1, the metabolic degradation of the plasma IgG pool in the patient and the control was found to be characterised by a half period 5.4 and 8.3 days respectively. The difference between the percentage of the radioactive dose remaining in the total body and that in the plasma provides the percentage remaining in the extravascular IgG pool, and from this the total IgG pool in the patient and the control were determined. The half-life of the total IgG pool estimated from the total body curve was 10.1 and 14.9 days for the patient and the control respectively.

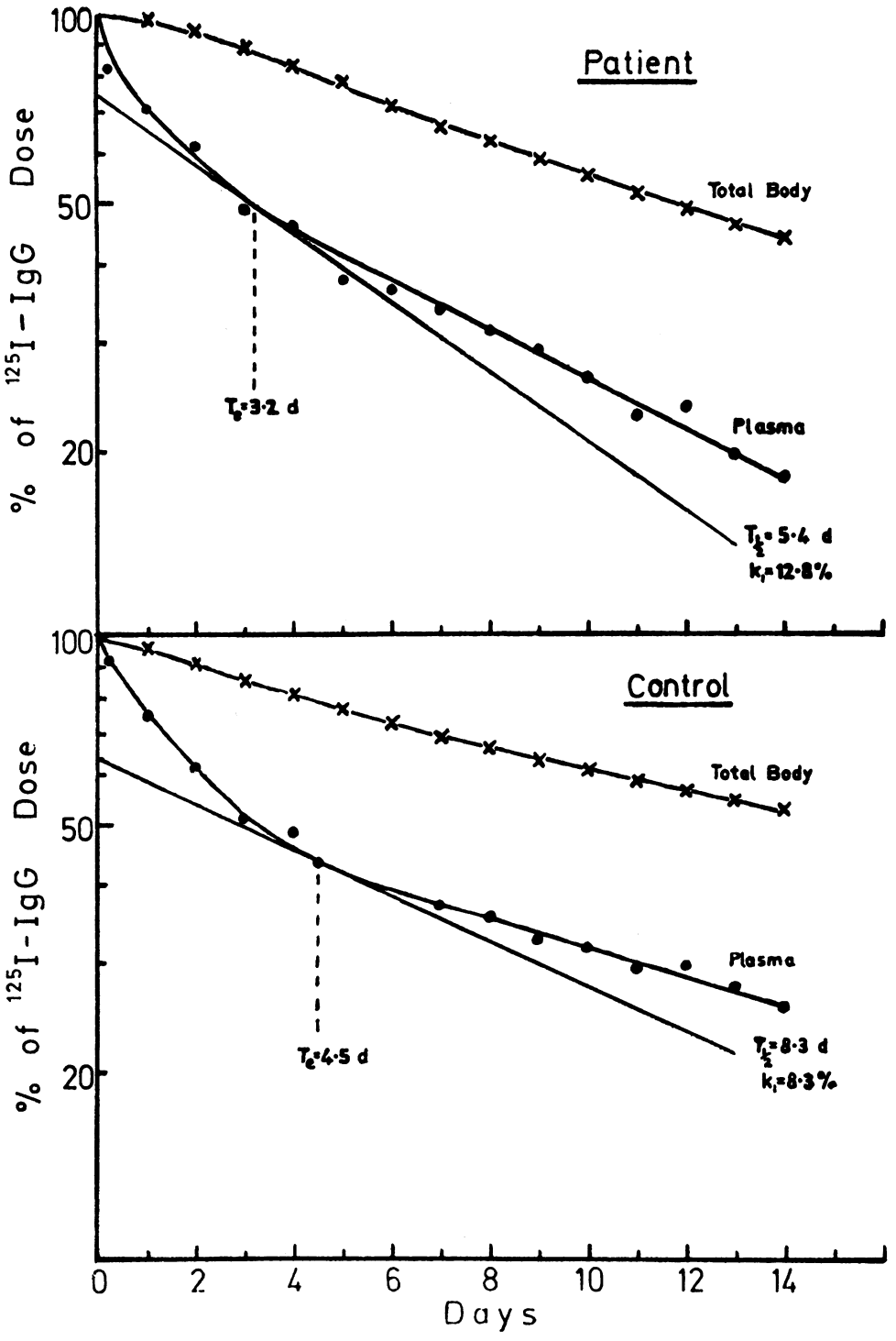


FIG. 5. *Rates of disappearance of the patient's IgG from the plasma and from the total body in the patient are more rapid than in a control.*

These results indicate that the high plasma concentration and total IgG pool in the patient are due to an increased production of immune globulin G. The breakdown of this labelled protein is more rapid in the patient, in whom its half-life is shorter, 5.4 days, compared with 8.3 days in the plasma pool of the control subject.

Discussion

These cases are very rare, but the reports of Waldenström (1948, and 1952 – cases 5 and 6), Taylor and Battle (1954), Sheon *et al* (1966), Kay and Robertson (1955), Seiden and Wurzel (1956), Hambrick (1958), Strauss (1959) and Weiss *et al* (1963) lead us to think that this is a disease *sui generis*. It has to be distinguished from other pigmented purpuric eruptions (Hambrick 1958, Randall *et al* 1951), and from other examples of dysproteinaemia with purpura such as occur in macroglobulinaemia, cryoglobulinaemia, myeloma and Hodgkin's disease (Krauss and Sokal 1966). Nor does the case of Savin (1965) belong to this syndrome. Though there was purpura for 14 years, it was intermittent. The globulin was a beta globulin. There was a marrow plasmacytosis. There was extreme lipidaemia, and the patient died of coronary artery occlusion. We think that the lack of disability, the benign course for many years, the type of chronic purpura and pigmentation described and illustrated here, a serum immune globulin G over 3 grammes, and the absence of known causes of hyperglobulinaemia (such as plasmacytoma, leishmaniasis and lymphogranuloma venereum) are sufficient to make a provisional diagnosis. Solitary plasmacytoma should be excluded by x-ray examination of the skeleton.

Though the course may be generally benign for many years, tumorous or neoplastic complications may in some cases occur in the end. The case of Taylor and Battle (1954) in the seventeenth year of observation developed a plasmacytoma of tongue (Sheon *et al* 1966). It was treated with radiation and the patient was alive and well four years later. The case of Rogers and Welch (1957) was probably one of hyperglobulinaemic purpura of this kind, and myeloma supervened in the eleventh year. Although there was no purpura or pigmentation, the case of 'benign' chronic hyperglobulinaemia of Kyle and Bayrd (1966) developed myeloma in the eighteenth year of observation. Nevertheless such an outcome would not invalidate the original diagnosis. Such a tumorous complication may be analogous to carcinoma occurring after many years in ulcerative colitis, or in a Plummer-Vinson stricture. It may be a result of a longstanding disturbance (in this case at least immunological) and not a part of it from the beginning.

In Hambrick's case (1958) the spleen was examined histologically. The pulp contained a "considerable number" of plasma cells. The lymph glands showed a "moderate number" of plasma cells. In case 5 of Waldenström (1952) the spleen was examined histologically and nothing remarkable found. Bone marrow biopsy in these cases has shown no evidence of myeloma, unless or until myeloma supervened. We have found no report of amyloidosis being observed.

The half-life of the total IgG pool in normal people using their labelled IgG has been reported to be from 17 to 32 days (Solomon *et al* 1963). The half-life of the patient's IgG in herself is much less than that.. There is no evidence of any

loss of IgG or of its breakdown products in the patient's urine and, although we cannot exclude loss from the alimentary tract mucous membrane, there seems no reason to suppose it. The shortened half-life must then be due to a rate of katabolism quicker than normal. The half-life of the patient's IgG in the control is similar to, if a little less than, the reported normal. It must be remembered that we do not know what the life of IgG from a normal person would be in the patient. Rapid katabolism cannot however explain the high serum level of IgG, which must be due to over-production. The over-production of IgG cannot be accounted for by any tumour, nor by hypertrophy of any tissue. We have not found an increase in the plasma cell population. We cannot explain the shortened half-life of the patient's IgG in the patient compared to the control, unless perhaps an antibody to her own IgG is present, or unless the IgG is in part an antibody rapidly reacting with an antigen and being removed quickly from the IgG pool. Capra *et al* (1971) have reported the presence of antigammaglobulins of IgG type in hyperglobulinaemic purpura, and they consider that in the majority of such patients the increase in IgG is mainly due to an increase in antigammaglobulin of IgG type.

Summary

A case of chronic hypergammaglobulinaemic purpura with pigmentation has been observed for 17 years. Corneal damage is the main disability. The course has been otherwise benign, and consistent with the disorder being an entity distinct from other dysproteinaemias. The pattern is that of the type case of Waldenström's original description.

Immune globulin G is much increased in amount in the patient's serum. There is a modest increase in immune globulin M. The half-life of the immune globulin G is less than normal, and not prolonged, as had been thought possible.

Criteria for diagnosis are suggested. Precision is necessary in distinguishing the various dysproteinaemic syndromes associated with purpura.

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GERIATRIC CARE IN A WELFARE HOME

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The History of Geriatric Care in Institutions

Townsend (1962) traced the development of the concepts of caring for people in institutions. It goes back to the obedience of early Christians to the commandment of mercy and compassion. Institutions were first established in the East by the Christian Church in the third and fourth centuries. Many were differentiated in their social and medical functions i.e. Gerontochia for the aged, Nosocomia for the care of the sick, Ptochia for the helpless poor. Western Europe followed much more slowly and Noscomia were established in the fifth and sixth centuries in Italy and France. By medieval times, there were infirmary almshouses and houses of pity for the aged, destitute, sick and disabled in England run largely by groups living under monastic rule. In the sixteenth century this system of religious institutions was broken up by the dissolution of the monasteries by the Reformation Parliament. This abolished hospitals in England for the best part of two centuries. Then the edge was taken off distress by a system of public relief administered by the parishes, and this was succeeded by the poor houses established under the Poor Relief Act 1601. This system prevailed till the eighteenth century when the system of voluntary hospitals began to emerge. In 1834 the Poor Law Commissioners was set up and this established the workhouse. England and Wales were divided into 643 "unions" replacing the former 15,500 small authorities and each "union" was administered by a Board of Guardians. Reforms in local government today seem like history repeating itself! Hundreds of workhouses were built between 1830 and 1840, and these gave care to the infirm, aged and chronic sick for over 100 years, but there was a gross neglect of these groups between 1910 and 1946, a period when the population over 65 years doubled.

Although the Welfare State in 1948 decreed that new accommodation of small residential homes be made available, this was not possible because of lack of finance and these groups were a low priority, and so, it was a question of making do with old, large institutions for many years to come, but in 1954 the Ministry of Health began to attach importance to the conversion of large houses and to design smaller homes with single and double bedrooms in order to produce a homely atmosphere, and in 1961, the Ministry stated—"Many now regard 60-bedded homes as too large for the creation of a homely atmosphere and too wearing on staff when the residents are of the more infirm group".

The Roddens

The Roddens is an example of such a small purpose-built welfare home built for the County Antrim Welfare Committee and opened in March 1971. It has accommodation for 42 residents, is a two storeyed building sited in its own grounds near a trunk road and near to the public library. It consists of two wings and the bedrooms are either single or double; there are four sitting-rooms, a dining-room, kitchen, staff dining-room, matron's office, doctor's consulting room with a small

waiting-room, which is also used as an interview room for relatives and clergy, an occupational therapy room, and a small laundry. The decor and furnishings are bright and cheerful and show great taste. In one of the bathrooms there is a medicbath and in another there is an ambulift for lifting patients into the bath. There are many other aids to living like hand rails in all corridors, aids in toilets, small slit lights one foot above floor level in corridors and bedrooms. Each person has a wardrobe and a dressing-table unit with one drawer which locks and they adorn these with little private possessions like photographs and pictures. No personal furniture is allowed. The staffing consists of matron, deputy matron, nurse, cook, assistant cook, four full-time and two part-time domestic staff and seven female attendants and one male making a total of 19.

Method of Selection

The selection of an old person for admission to the home is controlled by the Welfare Department Headquarters. Residents may be admitted because:

(1) They are physically so frail that they require supervision and assistance in the activities of daily living.
(2) They are so confused mentally that they are at risk living at home.
(3) They suffer from a mental disorder as a result of which it is inadvisable for them to live alone.
(4) They are difficult personalities and cannot accept help fom community resources or have worn out all available local resources.
(5) They need to maintain improvements secured by hospital treatment, i.e. many old people deteriorate on return home from hospital, and quickly lose any independence they have regained.
(6) The inability of community services to provide supporting services because of poor or isolated surroundings.
(7) Inadequate housing.

The applications come from the social workers in the field who are contacted by a variety of agencies i.e. family doctors, health visitors, district nurses, clergy, relatives, neighbours, hospitals, Abbeyfield homes and private homes. Each is screened as to his circumstances by the local social worker who makes a report to headquarters, together with a simple medical questionaire filled in by the family doctor. This form asks such questions as, previous health, present medical disabilities, present medication, physical and mental state. If there is a vacancy and if the person is suitable, headquarters then notify the matron to receive him. There were 52 people admitted to the Roddens during the first year; 27 (51.9 per cent) from their own homes, 19 (36.5 per cent) from hospital, 5 (9.6 per cent) from other welfare homes, and 1 (2 per cent) from an Abbeyfield home. Of these, there were two who did not settle and were discharged; and there were two transfers to other homes nearer their relatives and friends.

Medical Care

Every new entrant is subjected to a full physical examination to provide a baseline for future deviations. It speaks well for the screening process and simple medical form that out of 52 entrants in the first year of operation there were only

three surprises; one with a haemoglobin of 6 g/100ml; one with a haemoglobin of 8 g/100ml. and one with an undetected chronic urinary infection. Table I shows the medical conditions on entry.

TABLE I

Old Stroke	4	Hypochromic anaemia	5	Cardiac	2
Arteriosclerosis	4	Psychiatric	6	Glaucoma	2
Parkinson's disease	3	Diabetic	3	Cataract	2
Osteoarthritis of knees	3	Cardiac asthma	1	Congenital syphilis	1
Epileptic	1	Chronic pyelonephritis	2	Pernicious anaemia	1
Hypertension	2	Rheumatoid arthritis	2	Incontinent	1

In this age group the incidence of multiple pathology is highest and Table II sets this out.

TABLE II

1	Epileptic and incontinence of urine
1	Hypochromic anaemia and hypertension
1	Diabetic, cardiac and anaemia
1	Rheumatoid arthritis and cerebro-vascular accident
1	Cardiac and rheumatoid arthritis
1	Hypochromic anaemia and cataract
1	Cardiac and arteriosclerosis
1	Pernicious anaemia and arteriosclerosis
1	Arteriosclerosis, rheumatoid arthritis and cardiac failure
9	TOTAL

Table III gives the age distribution of the community.

TABLE III

64	65–69	70–74	75–79	80–84	85–89	90	TOTAL
2	4	5	13	18	7	3	52

The sex distribution was 11 males and 41 females, and this gives a ratio of 1:3.7. Green and Lodge (1965) in their large survey found the largest number of residents of welfare homes in the 80–84 age group and the sex distribution 1 male to 1.2 females.

The total number of visits which were paid to the home in the first year was 162 of which 5 were after midnight and there were 13 emergencies. The causes of the emergencies were two sudden deaths, one cardiac asthma, two dementia, one broncho-pneumonia, one coronary thrombosis, one terminal, and five cases requiring suturing.

Undoubtedly, the commonest disability to manifest itself is that of dependent oedema of the feet, ankles and legs. This has a great immobilising effect on the

old people and has to be treated enthusiastically. They were treated by diuretics, supporting stockings and keeping the legs elevated when not walking.

Drug Therapy

"A great deal of treatment that is given to the young and middle-aged is intended to prevent troubles in the distant future, and some nuisance in the present may be accepted to obtain this end. It is, of course, obvious that old people have no distant future, yet they are often continued on treatment which however correct it might have been, can no longer benefit them" Harman (1971).

Residents are admitted on regular drug therapy which they may have been on for a long period and this regime tends to be accepted and continued as long as the patient is well, active and mentally alert, but in a small community of 32 residents (which was the occupancy rate for the home at this time) this drug therapy, when aggregated, can be quite large. The following tables give the drug therapy for the residents of the home for one day—a grand total of 259 tablets or 8.20 tablets per resident.

Table IV

Psychiatric	47
Diuretics	71
Hypnotics	25
Cardiac	14
Parkinson's disease	11
Miscellaneous	91
TOTAL	259

It can be seen that the commonest conditions are psychiatric, dependent oedema of feet, ankles and legs, insomnia and cardiac. Then after this there is a wide spectrum of conditions ranging from Parkinson's disease to mild diabetes which are supervised. Examining the drug list for one day might seem to be an example of over-prescribing and in order to test this, the drug therapy of 32 unselected patients of 65 years and over were noted as they appeared in the Health Centre or were visited in their homes by the author (so that the same doctor was prescribing for the two groups of geriatrics). Their drug therapy was 166 or 5.18 tablets per patient. The average age of the residents was 80.2 years and the control group 71.9 years.

The following table gives the drug therapy for the patients outside the welfare home.

Table V

Psychiatric	6
Diuretics	15
Hypnotics	4
Cardiac	19
Hypertension	23
Rheumatism	42
Miscellaneous	57
TOTAL	166

The difference in the daily drug therapy between the two groups was 93 tablets (259–166=93) and this was accounted for by two groups of drugs, psychiatric and diuretics.

The reason for more psychiatric problems in the home than in the community is probably due to the change in environment and to learning to live as a community for the first time; and the reason for the great increase in the use of diuretics is probably explained by the older age group in the home. Apart from these two groups of drugs, the remainder seem similarly prescribed in the home and in the community.

Facilities for Medical Care

The facilities for medical care consist of a medical officer, three qualified nurses, a chiropodist, a physiotherapist, occupational therapist and a local dentist. The chiropodist and the physiotherapist visit when required, and the occupational therapist weekly to give instruction and give out work for the week ahead. The author is aided in his work by being on the staff of the Health Centre and the local Cottage Hospital and thus is able to admit patients for the treatment of acute illnesses. The residents are, therefore, still being cared for by the same doctor and this provides a sense of security. During the year there were nine deaths. When a resident dies the body is transferred immediately to the small chapel of the hospital and there is little disturbance in the home.

Further Aspects of Geriatric Care in a Welfare Home

Occupational therapy has been mentioned, but a variety of other activities take place. The local library is on the same site and can provide large print books; a short Sunday morning service is conducted by the local clergy; entertainment groups give shows, and the local Evergreen Club meets weekly, and there the residents meet other members of the local geriatric community. Special efforts are made to inculcate a feeling of security and this is done in a number of ways. For instance, when a resident is admitted, his home or flat is not given up immediately and this prevents the new resident feeling he has made an irrevocable decision. Equally, when a resident is admitted to hospital his room is kept for him for a minimum period of six weeks. All efforts are made to combat "the effects of living in a Home" as described by Townsend (1962) which are: —

(i) Loss of occupation.
(ii) Isolation from family, friends and community.
(iii) Tenuousness of new relationships.
(iv) Loneliness.
(v) Loss of privacy and identity.
(vi) Collapse of determination.

Discussion

A welfare home is a place where old people who are ambulatory in one form or another (i.e. they are not bedfast), and who can no longer care for themselves, are admitted. While a great many are physically and mentally fit, nevertheless,

they all suffer in different degrees from the degenerative diseases. One can subsequently follow the slow progress of this as time goes on, they move to the phase of being mentally duller, physically slower, becoming more dependent on the staff until they are chairbound, or some sudden terminal illness strikes. "Geriatric care means (in whatever setting) much more than treating the acute episodes and the terminal illnesses that occur in this group. It means the slowing down, where possible of the process of ageing; and the provision of various medical and welfare aids to enable them to retain their independence" (Burns, 1969). While it is imperative to provide good medical and para-medical care it is equally important not to allow the residents to become too dependent on the staff. It is this field that the staff have a very important part to play, for they also have to recognise when the resident is becoming less and less independent mentally and physically and to act sympathetically and compassionately. A welfare home should be small enough to provide the homely atmosphere and to give a sense of security to the residents. Its occupants should be encouraged to integrate with the local community as much as possible so that they do not become institutionalised. By keeping residents occupied and providing good regular medical facilities and interest in life both inside and outside the home their lives are being prolonged in an active state. These should be the ideals of geriatric care in a welfare home.

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ECHOVIRUS TYPE 4 OUTBREAK IN NORTHERN IRELAND DURING 1970-71

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AN extensive outbreak of Echovirus type 4 took place during 1970–71 in Northern Ireland. Echovirus type 4 is not only a rare virus to isolate from patients but this was also the third major enterovirus outbreak in Northern Ireland during the past four years. The other outbreaks were associated with Echovirus type 6 during 1968 (Connolly and O'Neill, 1970) and Coxsackie A9 virus during 1970 (Connolly and O'Neill, 1971).

MATERIALS AND METHODS

Faeces, CSF, throat swabs and acute and convalescent sera were obtained from patients with aseptic meningitis while faeces and/or throat swabs were obtained from other cases.

Primary rhesus monkey kidney cell cultures were used for virus isolation. At the beginning of the outbreak the first virus isolates could not be typed using the Echovirus diagnostic serum pools supplied by the Standards Laboratory, Central Public Health Laboratory London. The first virus isolates were typed using an Echovirus type 4 (strain Pesascek) neutralising antiserum from Microbiological Associates Inc. which was not included in the Echovirus diagnostic serum pools. It was found that the Echovirus type 4 (strain Du Toit) neutralising antiserum supplied by the Standards Laboratory when used at the recommended dilution of 1: 640 would not neutralise our isolates, but worked satisfactorily when used at a final dilution of 1: 40. Acute and convalescent sera were available from 62 patients from whom virus was not isolated and who had aseptic meningitis during the period of the Echovirus type 4 outbreak. The convalescent sera were tested at a final dilution 1: 20 against 100 TCD_{50} of Echovirus type 4 (strain Du Toit) in a four hour neutralisation test at 37°C. and the acute and convalescent sera of those which had antibody were then titrated. The sera from all aseptic meningitis patients were also tested for rising titres of antibody against mumps, measles, herpes simplex, louping ill and lymphocytic choriomeningitis viral antigens using the overnight complement fixation test at 4°C. (Bradstreet and Taylor, 1962).

RESULTS

In Northern Ireland during 1970–71 Echovirus type 4 was isolated from 169 patients. Echovirus type 4 was isolated from the faeces of 154 patients and from the throat of 33 patients. The virus was isolated from the CSF of 33 patients (19%) with aseptic meningitis. Antibody could not be demonstrated in acute and convalescent sera from three patients from whom Echovirus type 4 was isolated when 100 TCD_{50} of an Echovirus type 4 which had been isolated from the CSF of a patient in the current outbreak was used in the neutralisation test. However, four fold or greater rises in antibody were found in these three patients when TCD_{50} of Echovirus type 4 (Du Toit strain) was used in the neutralisation test. Sixty-two

patients with aseptic meningitis during the current outbreak from whom Echovirus type 4 was not isolated were tested and four fold or greater rises in Echovirus type 4 neutralising antibody were found in fourteen patients making a total of 183 patients diagnosed with Echovirus type 4 infection. A five year old boy with aseptic meningitis had serological evidence of recent infection with herpes simplex and mumps virus and Echovirus type 4 was also isolated from his throat and faeces.

The number of patients with Echovirus type 4 infection and the month of onset of their illness are shown in Table I.

TABLE I

Nov.	Dec.	Jan.	Feb.	Mar.	Apr.	May.	June	July	Aug.	Sept.	Oct.	Nov.
3	—	4	5	7	17	29	28	42	19	16	12	1

The outbreak began in November 1970 and ended in November 1971 while 99 cases (54 per cent) occurred in May, June and July 1971 with a peak incidence during July. One hundred and twenty-six patients (69 per cent) lived in Belfast and surrounding suburbs, an area which has a population of approximately 500,000. The clinical attack rate for that area was 25 per 100,000 population. There were 57 patients (31 per cent) outside this area in Co. Antrim (25), Co. Armagh (14), Co. Tyrone (8), Co. Down (6),and Londonderry Borough (4). The clinical attack rate for Northern Ireland as a whole was 12 per 100,000 population.

The illness associated with the Echovirus type 4 infections and the age and sex of the patients are shown in Table II.

TABLE II

Illness, Age and Sex of patients with Echovirus type 4 infections during 1970/71

Illness	*Age in Years*						*Sex*		*Total*	
	<1	1–4	5–9	10–14	15–19	>20	*Male*	*Female*	*Number*	*Per cent*
Aseptic Meningitis	2	12	48	43	28	39	97	75	172	94.0
Respiratory	2	2	1	—	—	1	3	3	6	3.3
Pyrexial	3	1	—	1	—	—	3	2	5	2.7
All Clinical Categories	7	15	49	44	28	40	103	80	183	100.0

One hundred and seventy-two patients had aseptic meningitis which was the predominant illness accounting for 94 per cent of all cases. Three patients had a rash associated with their illness which included a two-month-old girl and an eleven-month-old boy with pyrexia and a three-month-old boy with aseptic meningitis. The respiratory cases included two three-month-old girls and a four-year-old boy with pneumonia, a one-year-old boy and an eight-year-old girl with pharyngitis, while a twenty-six-year-old man had pleurodynia. Three of the five patients with a pyrexial illness were less than one-year-old. There were no deaths.

The outbreak was confined mainly to children with over half the cases occurring in the 5—14-year-old age group and more males than females were affected. The youngest patient in the outbreak was two-months-old. In the aseptic meningitis group males predominated and the 5—14-year-old group was affected most. The youngest patient with aseptic meningitis was a three-month-old boy and the oldest was a 46-year-old woman.

There were nine families where two or more members developed aseptic meningitis associated with Echovirus type 4 infection as shown in Table III.

TABLE III

Family outbreaks of Echovirus type 4 Aseptic Meningitis in Belfast 1971

Family No.	*Date of onset*	*Age in years*	*Sex*
1	Jan. 18	7	M
	20	6	M
2	April 17	6	M
	18	5	M
3	April 28	20	F
	May 4	11	M
4	May 9	7	F
	27	5	M
5	May 31	11	F
	31	13	M
6	July 1	7	M
	1	27	M
7	Sept. 9	16	M
	10	9	M
8	Sept. 13	11	F
	20	14	F
	21	5	M
9	Oct. 16	7	F
	22	12	M
	25	15	F
	31	10	M

Two children in each of five families developed aseptic meningitis. In family number 6 a father and son and in family number 3 a boy and his adult sister were affected. In family number 8 three children were involved while in family number 9, four children developed aseptic meningitis. Within each family the onset of their illnesses was closely associated in time.

Apart from the family outbreaks there were outbreaks of Echovirus type 4 infection in 14 separate streets as shown in Table IV.

TABLE IV

Street outbreaks of Echovirus type 4 Aseptic Meningitis 1971

Street No.	*Date of Onset*	*Age in years*	*Sex*	*Location*
1	April 14	29	M	Suffolk
	Aug. 3	1(1)	M	Co. Antrim
2	April 28	27	F	Dundonald
	June 25	4	F	Co. Down
3	May 10	20	F	Castlewellan
	July 22	14	M	Co. Down
4	May 23	5	M	Belfast
	May 31	3	M	
	June 4	14	M	
5	May 24	4	F	Belfast
	May 28	7	F	
6	May 25	2/12(2)	F	Belfast
	June 20	17	M	
7	June 29	14	M	Armagh
	July 7	14	M	
8	July 4	7	F	Rathcoole Co. Antrim
	July 26	6	F	
	July 27	5	M	
9	July 13	5/12(3)	M	Belfast
	Aug. 24	12	F	
10	July 17	8	F	Belfast
	July 18	6	M	
11	July 19	4	M	Belfast
	Aug. 7	5	M	
12	July 25	9	M	Belfast
	Sept. 14	14	M	
13	Aug. 13	8	F	Belfast
	Aug. 15	9	F	
14	Oct. 4	26	F	Belfast
	Oct. 8	11	F	

(1) Child had pharyngitis and convulsions only.
(2) Child had pyrexia and rash only.
(3) Child had pyrexia and vomiting only.

Two children in each of six streets had Echovirus type 4 infection and in four streets an adult and a child were affected. Three children in each of two streets had aseptic meningitis. In street number 9, four children (two of them being in family number 6) had Echovirus type 4 infections while in street number 12, six children had aseptic meningitis (four of them being in family number 9). Fifty-one patients (28 per cent) were involved in family and street outbreaks of Echovirus

type 4 infection. It was also observed from the patients' addresses that many individual cases of aseptic meningitis lived in adjoining streets.

Discussion

Usually Echovirus type 4 is one of the more uncommon types isolated in the United Kingdom, there being only fifty-four infections reported in the five years 1966–70 (Brit. med J., 1971a). During 1970–71 the two largest outbreaks began in Teeside during September 1970 and in Belfast during November 1970 (Brit. med. J., 1971b).

The Echovirus type 4 outbreak in Northern Ireland was typical of enterovirus infections in that it had a peak incidence during the summer months and over half the cases were in children aged 5–14 years. Proportionally more patients were affected in the older 10–19 year age groups in this outbreak when compared to the previous Echovirus type 6 and Coxsackie type A9 outbreaks. The clinical attack rate for Northern Ireland as a whole was 12/100,000 population which was eight fold higher than the rest of the United Kingdom, but direct comparisons are difficult because many areas in the rest of the United Kingdom were spared.

The predominant illness associated with the Echovirus type 4 outbreak in Northern Ireland was aseptic meningitis accounting for 94 per cent of all cases. The patients investigated in this outbreak were, however, highly selected in that their illnesses were severe enough to require admission to hospital. There were probably many more minor illnesses, and subclinical infections in the community associated with Echovirus type 4.

Enteroviruses spread by direct person to person oral transfer of human faeces or from the respiratory tract, and this is substantiated by the nine family oubreaks of aseptic meningitis where close contact between individuals is known to occur. The outbreaks of aseptic meningitis and other illnesses in fourteen streets could be explained on the basis of play-contacts. The individual cases of aseptic meningitis which occurred in adjoining streets could be explained either on the basis of play-contacts or possibly contact at school.

Our results show that only the Du Toit strain of Echovirus type 4 was neutralisable and not the strain isolated from patients in the outbreak. Barron and Karzon (1961) investigated an epidemic of Echovirus type 4 aseptic meningitis and found that attempts to show rises of neutralising antibody in patients' sera with prototype virus (Pesascek strain) or patients' own isolate were generally unsuccessful when used in a tube neutralisation test whereas the Du Toit strain was neutralisable. Wallis and Melnick (1967) showed that virus aggregation was the cause of the non-neutralisable persistent fraction of Echovirus type 4 which constituted 30 per cent of the infective units of the unfiltered Pesascek strain but only 0.1 per cent of the antigenically related Du Toit strain.

Summary

In Northern Ireland 183 patients were shown to be infected with Echovirus type 4 between November 1970 and November 1971. The peak incidence was in July 1971 and the outbreak was largely confined to Belfast and its environs. One hundred and three males and eighty females were affected and over half the patients

were in the 5—14-year-old age group. One hundred and seventy-two patients (94 per cent) had aseptic meningitis. There were nine family outbreaks and fourteen street outbreaks where two or more people in each family or street had aseptic meningitis. Individual cases of aseptic meningitis also occurred in adjoining streets. Neutralising antibody in patients' sera could only be demonstrated using the Du Toit strain of Echovirus type 4.

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SIGNIFICANT BACTERIURIA IN PREGNANCY

A Study in Khartoum, Sudan

by

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SIGNIFICANT BACTERIURIA in pregnancy has been well investigated by Kass (1955; 1957; 1962), Sanford (1956), Brumfitt et al (1961), Turner (1961), Mustafa and Pinkerton (1970). The majority of the studies on significant bacteriuria have been carried out in Europe and the United States of America. The incidence in pregnancy has been found to be between 5 and 10 per cent. Very few studies on significant bacteriuria have been carried out in Africa where the climate and the standard of nutrition are different from those of Europe and the United States of America. An additional difference in the Sudan is the common practice of female circumcision.

This is an investigation of the incidence of significant bacteriuria in antenatal patients admitted to Khartoum Hospital during the year 1971.

Patients and Methods

Five hundred and fifty antenatal patients were investigated. Catheter specimens of early morning urine were obtained from antenatal patients on the second day of admission to hospital and the specimens were examined within 2 hours of collection. Logarithmic dilutions of the urine (from 1: 10 to 10,000,000) were made in nutrient broth. One ml. of each dilution was transferred to a MacConkey plate and incubated at 37°C overnight. The plates were examined in the morning and a growth of coliforms was suspected when large lactose-fermenting colonies were seen on MacConkey plates and large mucoid colonies on nutrient agar plates. The identity of *Escherichia coli* was confirmed by standard biochemical tests (Cowan and Steel, 1965).

Significant bacteriuria in this study is defined as the presence of 100,000 (10^5) or more E. Coli per ml. in two or more consecutive daily specimens of urine.

Results

Out of 500 patients examined during the antenatal peroid 31 had significant bacteriuria. This is an incidence of 5.6 per cent.

Discussion

The incidence of significant bacteriuria in pregnancy in Khartoum Hospital is 5.6 per cent. In a study in the Royal Maternity Hospital, Belfast, Northern

Ireland, 4.7 per cent of the patients had significant bacteriuria (Mustafa and Pinkerton, 1970). The two studies, however, are not identical. Catheter specimens of urine were obtained in Khartoum while midstream specimens were obtained in Belfast. The vast majority of the patients in the Khartoum series were circumcised. Female circumcision entails removal of the clitoris and almost complete fusion of the labia minora except for a small orifice barely adequate for passing urine and satisfactory intercourse. This orifice in some patients can only admit the tip of the small finger. As separation of the labia minora by the circumcised patient when collecting a midstream specimen is impossible, a high degree of contamination of the urine is likely to occur giving a false high incidence of significant bacteriuria. In order to avoid this, catheter specimens were obtained in the Khartoum study.

The incidence of 5.6 per cent of significant bacteriuria in Khartoum is comparable with the incidence of 7 per cent (Turner 1961), 4.4 per cent (Kaits and Hodder 1961), 5.5 per cent (Little 1965), 4.8 per cent (Pinkerton et al 1967), 5.1 per cent (Dixon and Brant 1967).

The findings in this study show that neither the hot climate nor the practice of female circumcision increase the incidence of urinary tract infection in pregnancy.

Summary

Significant bacteriuria occurred in 5.6 per cent of antenatal patients in Khartoum Hospital. This incidence is comparable with the incidence reported from various parts of the world. It is concluded that neither the hot climate nor female circumcision increase the incidence of urinary tract infection.

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NORTHERN IRELAND COUNCIL FOR POSTGRADUATE MEDICAL EDUCATION

IN the last issue of the Journal it was stated that during 1972 the Council had three main objectives: the implementation of plans for the postgraduate training of married women doctors; the setting up of a career advisory and information service; and the approval or recognition of hospital posts as suitable for postgraduate training by the various colleges and faculties. Good progress has been made with the first two; slower progress with the third, which is primarily the responsibility of the colleges and faculties.

Postgraduate training for married women doctors is dealt with more fully below. Council has been fortunate in securing the services of Dr. C. W. Kidd, a former President of The Ulster Medical Society, to advise and help married women doctors.

The response to the Career Advisory Service has been encouraging. Sixty-four out of the one hundred pre-registration doctors completed the questionnaires. Of these, 20 per cent were uncertain about their career goal, 33 per cent intended to enter general practice, and the remainder were spread fairly evenly among other specialties. Ninety-three per cent received advice and information during interviews with the Chairmen of Specialty Committees or the Secretary of Council.

A questionnaire is now being sent to all who participated in the scheme, in the hope that improvements may be suggested.

One improvement contemplated is the establishment of a Careers Library at Council's offices (107 Botanic Avenue), where a wide range of career literature will be made available to senior students and recently qualified doctors. It is also hoped to hold a career symposium for final year students during the autumn.

The specialty committees will be helped in the planning of training programmes by the proposal that in the restructured health services, SHO appointments will be made centrally under the aegis of the new Central Services Agency, with which the Council will maintain close liaison.

Recently Council formally accepted responsibility for dental postgraduate education as did the other Postgraduate Councils. In its role as a Regional Postgraduate Committee it has been responsible for some time for the continuing education of general dental practitioners, with Professor W. A. S. Alldritt in post as Postgraduate Dental Tutor. Its remit has now been extended to include all fields of postgraduate dental education in which it will be advised by a dental committee, representative of all branches of the profession. The chairman and one dentist selected by the committee will be members of Council.

The following have been appointed as Postgraduate Clinical Tutors for the year 1972/73 :

Altnagelvin Hospital, Londonderry . .	Mr. W. L. Robinson
Belfast City Hospital . . .	Mr. W. A. Hanna
Craigavon Hospital	Dr. A. W. Dickie

Royal Victoria Hospital . . .	Mr. G. W. Johnston
Ulster Hospital, Dundonald . . .	Dr. J. K. Nelson
Waveney Hospital, Ballymena . .	Dr. R. J. Kernohan
Dental Tutor	
School of Dentistry, Royal Victoria Hospital .	Prof. W. A. S. Alldritt
Obstetric Tutors	
Daisy Hill Hospital, Newry . . .	Dr. E. L. Holland
	Dr. A. C. C. Pinion
Route Hospital, Ballymoney . . .	Mr. C. G. Irwin

J.E.McK.

POSTGRADUATE TRAINING FOR MARRIED WOMEN DOCTORS

It is not surprising that medical education in the past two decades has been greatly influenced by the dramatic advances in clinical diagnosis, therapy and technology. Until recently the undergraduate medical curriculum was designed to produce a 'safe doctor'. Today it is designed to produce a doctor with a basic scientific training, who will need further training and experience in whatever branch of medicine he or she intends to practice. In future, this means that doctors will have to undertake postgraduate in-service training after registration which may extend from three years for general practice to seven or more years for the other specialties, if they wish to attain full professional status as consultants in the specialist services or as principals in general practice. This applies to all medical graduates but has special implications for women doctors. Many marry soon after registration or have domestic or other ties which make it difficult for them to undertake postgraduate training in the health services under the usual arrangements.

The contribution married women can make to staffing the health services is vitally important because women now constitute a rising proportion of the rapidly increasing entry into medical schools. In some medical schools in Great Britain the number of women entrants is well over 40 per cent, and at Queen's University it has averaged 39 per cent over the last three years. It is clear therefore that it is of prime importance that married women graduates should be specially facilitated to obtain postgraduate training and experience leading to full professional status. Otherwise it will not be possible to provide the increasing numbers of doctors essential for the development of the health services.

Married women doctors may be divided into three main groups:

(i) *Those who will be able to continue their postgraduate training and medical careers with little or no interruption.*

The postgraduate training needs of this group can be met through the normal arrangements regarding annual and maternity leave, though some extension of the prescribed postgraduate training period to take account of time lost through the latter may be necessary.

(ii) *Those who will be able to continue their postgraduate training and medical careers on a part-time basis.*

The popularity with women doctors of posts which offer set hours of work and opportunity for part-time service may be due partly to the pressures of family responsibilities, but another factor is that many of these posts have not until now demanded extensive postgraduate training. This may not operate in future and it is felt that, given the opportunity to complete postgraduate training on a part-time basis, more women will wish to attain full professional status in common with men by obtaining appropriate higher qualifications and experience in their chosen branch of medicine.

It is realised that in the past women doctors (including unmarried doctors) have found greater difficulty than men in obtaining training and career posts because the possibility as well as the reality of family responsibility has influenced appointing committees, who feared that domestic ties might prevent a woman completing her training or conflict with the duties of a career post. It is, however, clear that such attitudes have changed and, indeed, must change if the health services are to be staffed adequately.

The postgraduate training needs of this group can be met by administrative arrangements already in existence which make provision for part-time appointments in both the hospital service and in general practice though, of course, this means that the normal postgraduate training period must be extended.

(iii) *Those who will be unable to practice even on a part-time basis for a period (say, five to ten years), but who hope to return ultimately to medicine in some capacity.*

Two difficulties facing a married woman doctor are limited time and mobility. Commitments to a young family or other domestic ties may make it impossible for her to undertake sufficient medical work to be of educational value and for such doctors the new Retainer Scheme is commended.

The Retainer Scheme is designed to help married women doctors to maintain a continuing professional link whilst bringing up their families, and it will come into operation on 1 September 1972. The Scheme will make it possible for any doctor under the age of 55 whose domestic commitments currently preclude practice but who intends subsequently to resume a full medical career in the health services, to do a small number of specially arranged paid clinical sessions and attend some postgraduate medical education sessions each year.

Members of the scheme will receive an annual retainer of £50.00 to help cover professional expenses. Leaflets and application forms are now available.

Northern Ireland Council is of the opinion that much of the organisation of postgraduate training of married women doctors will need some detailed negotiation with the doctor concerned and with the service authorities. Considerable flexibility in arrangements and the provision of information and advice regarding careers will be required. Finally, there must be willingness by all concerned to accord greater recognition to the importance of meeting the requirements of married women doctors in obtaining training and experience.

Council has therefore decided to appoint, as a member of its secretariat, a doctor conversant with the problem who can provide a point of contact for women doctors seeking postgraduate training and experience in Northern Ireland. Dr. C. W. Kidd, formerly Chief Medical Officer, Ministry of Health and Social Services, has kindly agreed to accept this responsibility which will involve maintaining a close relationship with the chairmen of Council's specialty committees and the medical administrative staff of the Area Health Boards when these come into being.

It is hoped that in future it may be possible to make similar arrangements in respect of married women dentists.

Any women doctors who are interested in obtaining career information or in discussing postgraduate training are asked to write to Dr. C. W. Kidd, Northern Ireland Council for Postgraduate Medical Education, 107 Botanic Avenue, Belfast BT7 1JP.

J.E.McK.

ANAESTHETICS COMMITTEE

The Anaesthetics Committee currently has six members—Professor J. W. Dundee (Chairman), Drs. R. King, J. Moore, R. S. J. Clarke, S. M. Lyons, and I. Carson. Dr. J. E. Galway who was the junior anaesthetics staff representative on the Committee resigned after his appointment as a consultant and Dr. I. Carson replaced him.

The Committee met regularly during the year and its work was concentrated under four headings:

1. *Future Junior Anaesthetic Staffing*

The rotational training scheme for junior anaesthetic staff will be affected in some degree by the formation of the new Area Health Boards. Though the rotation of junior staff will still be organised by Council, each of the new area boards will be independent in respect of their service needs. The senior anaesthetics staff in the different areas were visited and consulted about their junior and senior anaesthetic staffing requirements and a memorandum was produced setting out these requirements. This report was approved by Council and sent to the Northern Ireland Hospitals Authority as a firm recommendation.

2. *Faculty of Anaesthetists*

During the year the revised criteria for the recognition of hospital posts for the training of staff for the F.F.A.R.C.S. Examination were circulated to all Faculty Regional Educational Advisers. Two items in these revised criteria particularly affect the training programme in Northern Ireland.

(a) There was difficulty in many regions in organising sufficient training in anaesthesia for both electroconvulsive therapy and dental anaesthesia and the Faculty recommended each region to investigate its own position and if necessary improve it. The Committee enquired in which hospitals E.C.T. was most widely practised and arrangements were made to rotate trainees to see and

practise this type of anaesthesia. With regard to dental anaesthesia, the Committee met Mr. W. H. Morrow, Dr. J. McA. Taggart, Medical Officer of Health for Belfast, and Dr. W. M. Brown, Lecturer in Dental Anaesthesia to discuss the possibility of allowing trainees to see and practise dental anaesthesia where this was most widely practised, i.e., at school health clinics and in dentists' surgeries. These possibilities were further investigated and with the sympathetic help of the dental profession and Dr. Taggart adequate training facilities can now be arranged.

(b) The Faculty also recommended that all hospitals recognised for the training of junior anaesthetists should have regular morbidity and mortality conferences. These recommendations were passed on to the relevant hospitals in Northern Ireland and such conferences are now taking place.

3. *Postgraduate Training*

During the past year the Anaesthetics Department in conjunction with Council, undertook the organisation of regular and comprehensive classes for all anaesthetists of whatever grade. These are a feature of the training programme and allow anaesthetists of all grades to meet for mutual benefit.

The Department also ran courses in the Autumn and Spring for both the Primary and Final part of the F.F.A.R.C.S. examinations. Each course lasted one week and many senior registrars and consultants took part. Dr. A. R. Hunter from Manchester and Professor G. W. McDowall from Leeds were the guest lecturers for the courses.

The overall results in the postgraduate examinations give some idea of the benefit which is derived from these courses and thanks are due to the Department for their enthusiasm and to Council for their help and encouragement.

4. *Staffing*

With its responsibility for the rotation of trainee anaesthetists, the Anaesthetics Committee became concerned at the end of the year about the problems of filling the junior staff posts. Due to the loss of senior staff of both consultant and senior registrar grade, the intake of new recruits to anaesthesia, though slightly greater than other years, is inadequate for the present situation. While the service needs appear more important in the short term, the Committee felt very strongly that the training of junior anaesthetists should not be compromised by service needs, otherwise the problem might very well in the long term become worse.

J.W.D.

COMMUNITY MEDICINE COMMITTEE

The major changes involved in the reorganisation of the health services in Northern Ireland will result in all medical staff employed by local authority services and in the Northern Ireland Hospitals Authority coming under the control of the new Area Boards on April 1, 1973. General practitioners although employed by the Area Boards will still continue in their present role as private contractors. The impact of the change will be felt most by those medical officers of the local

authority services and the Northern Ireland Hospitals Authority who are engaged wholly or substantially on administrative medical duties. When the health services are reorganised on a unified basis these doctors will come together to form a new corps and in effect a new speciality in medicine. Their work will be altered, requiring different attitudes and fuller use of the established methods of medical administration and research.

In order to prepare these doctors for their new roles the Community Medicine Committee during 1971 organised an intensive programme of reorientation and retraining. The Chief Medical Officer of the Ministry of Health and Social Services kindly permitted Dr. Geoffrey Carey to be seconded as the whole-time training organiser: he was assisted by Dr. Roger Blaney, Department of Social and Preventive Medicine. The Committee decided that there should be four phases in the retraining programme.

(1) *Symposium for Senior Community Physicians*—18–20 *November*, 1971

This non-residential symposium which dealt with such topics as Research and Intelligence, Management in the Health Services and Planning a Total Care Service, was attended by thirty doctors including medical officers of health, senior administrative medical staff of the Hospitals Authority and the Northern Ireland General Health Services Board, senior academic staff of the Department of Social and Preventive Medicine and senior staff of the Ministry of Health and Social Services.

(2) *Management Courses for Community Physicians*

The Committee had hoped to include a course on 'Management in the Health Services' as part of their reorientation programme but owing to the limited time available it was not possible for the N.I. Staffs Council for Health & Welfare Services to undertake this. Thanks to the ready co-operation of the N.I. Hospitals Authority it was found possible to include 24 local health authority medical officers in two residential 5 day management courses which the Authority were organising during February and March, 1972 for their consultants and hospital medical staff. Medical Officers unable to take advantage of these management courses will have the opportunity to attend courses administered by the N.I. Staffs Council.

(3) *Reorientation Courses in Community Medicine*

Some 48 medical officers attended two residential courses, each of two week's duration, held during March and April, 1972. Much time was spent on syndicate work and among the subjects dealt with were, (a) background to the present health services; (b) the restructured health services; (c) the ascertainment of need; (d) the availability and development of resources, including man-power, finance, etc.; (e) problems of administration.

Dr. Geoffrey Carey appplied himself with great diligence and ability to the detailed organisation and administration of the above courses. Their success was due in no small part to his hard work and enthusiasm. His untimely death in May was much regretted by his many friends and colleagues and the Community

Medicine Committee would wish to pay tribute to his tireless endeavours on their behalf.

(4) *Attachment Scheme for Community Physicians*

Thanks to the co-operation of the Senior Administrative Medical Officer of the Hospitals Authority, and his staff, local authority medical officers are given the opportunity, over a three week period, to gain knowledge of administration of the hospital services, including the working of the authority headquarters departments, e.g., legal, works, supplies and staffing. Attachment to the Health Services Board is also included and candidates are encouraged to gain knowledge of the work of the 'primary care team', health centre administration, etc.

Courses in Paediatrics—October and November 1972

The Committee are organising the above refresher courses of one week's duration mainly for whole or part-time staff of local health authorities who are engaged on clinical work and who will continue in this field in the reorganised health services.

The Community Medicine Committee wish to record their appreciation of the continual help given by the Secretary, Administrative Officer and staff of Council, in organising the past year's training programme.

J.McA.T.

GENERAL PRACTICE COMMITTEE

Vocational Training

Ten trainees began their training under the Northern Ireland Vocational Training Scheme for General Practice on 1 August, 1972. Seven trainees completed their training course on 31st July, 1972.

The first review of teaching practices has been completed and some new practices have been appointed. This review entitled a visit to each teaching practice by a sub-committee of the general practice committee. Many applications which were otherwise suitable had to be turned down either because the accommodation available was unsatisfactory or because sufficient teaching time was not available.

The profession has recently accepted the principle of vocational registration by 1977 and this will mean that thereafter all newly-appointed principals in general practice must be vocationally trained. In Northern Ireland this implies that between thirty and forty trained general practitioners will be required each year and that therefore the Northern Ireland Vocational Training Scheme must be expanded substantially over the next few years. This expansion will involve the provision of an adequate number of suitable hospital training posts and a further increase in the number of teaching practices.

The Review Body has recently awarded increased payments to teachers in charge of teaching practices and as an inducement to undertake training the vocationally trained doctor will in future receive an increased vocational training allowance. This increased allowance will compensate the young doctor to some extent for

the extra remuneration which he would have received if he had gone straight into general practice and not spent three years in training.

A recent study of teaching practices in Great Britain and Northern Ireland by Dr. Donald Irvine, published by the Royal College of General Practitioners, draws attention to the number of teaching practices in Northern Ireland which have not direct access to diagnostic radiology. Northern Ireland compares poorly with the rest of the United Kingdom in this respect. Steps are now being taken to initiate a diagnostic radiology service for teaching practices in the Belfast area. Otherwise the report shows that our practices compare not unfavourably with those in the rest of the United Kingdom.

Courses for general practitioners held in the Spring of 1972 showed a reduction in attendance compared with the previous year. This drop can be explained by the almost complete cessation of attendances at our courses of practitioners from Great Britain due to the present civil disturbances which have also had an effect on the attendance of Northern Ireland practitioners.

We have continued to reduce the number of five-day courses and have planned only one such course for this autumn. The number of one and two-day courses has been increased and the geographical spread has been widened to make it easier for general practitioners to attend a course in their own area.

The three extended courses will be held this autumn—

1. *Introduction to General Practice.* This new course is for trainee general practitioners who are in their hospital training period. It is now apparent that trainees need exposure to general practice early in their training programme and the course is an initial step in this direction.

2. *General Practice Course.* This course which is for trainees in their general practice training year and for other young practitioners will continue as before, but will now be held on Thursdays instead of Tuesdays. Previously this course was designed as an eighteen month course, but in future it will be a one year course.

3. *M.R.C.G.P. Course.* This short extended course is being held this Autumn because of the large number of local candidates for the Membership examination of the Royal College of General Practitioners. Upwards of twenty candidates are expected to sit the examination in November 1972. This course will be repeated each Spring and Autumn, if necessary.

The following general practitioners have obtained postgraduate qualifications:

M.R.C.G.P.

Mr. D. R. Delargy, Belfast; Dr. P. T. McGeough, Belfast; Dr. P. H. McKenna, Dungannon; Dr. D. S. P. McKeown, Belfast; Dr. G. Moles, Killinchy; Dr. R. C. Simpson, Ahoghill.

D.R.C.O.G.

Dr. R. S. Finch, Portadown; Dr. J. R. B. Kane, Holywood.

N.D.W.

LABORATORY MEDICINE COMMITTEE

This Committee has now been active for a year although its first formal meeting was not held until 1 April. At that meeting, Professor M. G. Nelson, the Chairman, explained that the Committee was set up under the Council to represent the speciality of laboratory medicine and that its members in fact represent the four main sub-divisions of that specialty. The membership was as follows: —

Professor M. G. Nelson—Chairman
Dr. J. M. Bridges—representing haematology
Dr. J. E. Morison—representing morbid anatomy
Mr. D. W. Neill—representing biochemistry
Dr. W. T. Shepherd—representing bacteriology

It was agreed that Mr. Neill should act as Convener of the Committee. At the first meeting there was a discussion of the functions of the Committee and it was agreed that these should be the examination of the facilities available for postgraduate medical education in laboratory medicine and arrangements for the provision of appropriate course and guidance to trainees.

The Royal College of Pathologists acts as the examining body for specialists in laboratory medicine and has organised a careers advisory service. The Chairman of the Committee has been appointed as the regional careers adviser for the Royal College of Pathologists and he suggested that each member of the Committee should fulfil the Royal College of Pathology function through him.

During the year, a study has been made of the facilities available and the present position of teaching in this specialty in Northern Ireland. Only two hospitals are recognised for training, the Royal Victoria Hospital complex and the Belfast City Hospital complex. While this clearly simplifies problems of staffing, it is essential that all trainees in their first two years should circulate through each of the laboratory divisions even though the requirements of the Royal College of Pathologists are now for a final single subject examination. Much discussion has taken place in achieving this.

There has been considerable disquiet throughout the year resulting from the Committee's realisation that there is a considerable shortage of trainees coming forward in this specialty and this taken in conjunction with the relative shortage of consultants augurs very poorly for the future.

The specialty Committee has thus, during its first year, defined its ideas on training, clarified the position with regard to trainees already in post and defined facilities currently available for providing suitable training in this specialty.

D.W.N.

MEDICINE COMMITTEE

The Committee carries responsiblity for postgraduate education in General Medicine, its major related specialties, and the subjects of Geriatric Medicine and Paediatrics.

The members of the Committee are:

Dr. A. H. G. Love (Chairman); Professor G. F. Adams;
Dr. J. H. Bruce; Dr. P. G. Nelson (Junior Medical Staff);
Professor R. G. Shanks (Joint Committee on Higher Education liaison);
Professor J. Vallance-Owen; Dr. R. A. Womersley; Professor I. Carre.

The Committee provides a Careers Advisory Service and advises Council on the provision and organisation of training programmes in medicine, geriatrics and paediatrics and the posts required for them.

Because of the wide responsiblity of this Committee a Sub-Committee has been formed to allow full local participation in advising on careers and postings. This Sub-Committee consists of:

Dr. A. H. G. Love (Chairman); Dr. D. Burrows (Dermatology); Professor I. Carre (Paediatrics); Dr. J. Donaghy (Mater Infirmorum); Dr. E. James (Chest Diseases); Dr. R. J. Kernohan (Ballymena); Dr. R. Lowry (Belfast City Hospital); Dr. F. A. McAleenan (Ulster Hospital); Professor J. F. Pantridge (Cardiology); Dr. A. Pollock (Geriatrics); Dr. T. J. Robinson (Craigavon); Dr. M. Swallow (Royal Victoria Hospital: Neurology); Dr. R. G. Vine (Londonderry).

In this past year the Committee has provided career guidance to a number of postgraduates and it is hoped that junior staff will make even greater use of this service in the future.

There is presently a more organised approach being taken to training by the Royal College of Physicians which will entail the recognition of certain posts as being suitable for postgraduate training. This will cover the period of general professional training where reciprocation with demands of other Royal Colleges will take place, and also the development of specific specialty training. The Committee are actively engaged in surveying the needs of this scheme and liaising with the N.I.H.A. to ensure a proper balance is being kept between training and service needs.

Rotational training programmes at senior house officer level have been commenced at the Belfast and Royal Victoria hospitals to include in a two-year period one year of general medicine and two six-month periods in related specialties. It is hoped that this type of training will be developed in other areas. The Committee has striven for flexibility to suit the needs of trainees rather than rigid programmes of posting.

The training provision in General Medicine is being used by some trainees in general practice and the Committee will also be considering the possible needs of other specialties for inclusion in their programmes, e.g. Psychiatry and Radiology.

The Advanced Medicine Course has now been organised on a day-release basis with ward rounds, case discussions, X-ray sessions, and a formal lecture session. These activities have been confined to Tuesdays in the past session but it is hoped this year to have more ongoing teaching so that more days in the week will provide regular postgraduate training.

PSYCHIATRY COMMITTEE

Dr. P. J. Curran has been invited to join the Committee as a representative of the trainees in the place of the late Dr. P. J. Quinn.

Career guidance about Psychiatry has been given to a number of doctors expressing interest following Council's questionnaire circulated to pre-registration doctors. The Chairman and members of the Committee are willing to offer guidance to interested doctors, at any time, and this can be arranged through the Council office.

Planning discussions are proceeding with a view to arranging rotating training in many branches of Psychiatry and allied subjects for all trainees in the future. It is hoped that these will be facilitated by changed arrangements for employment of trainee doctors after the establishment of Area Boards in 1973.

W.O.McC.

RADIOLOGY COMMITTEE

In the period since its previous report, the Committee has been concerned with the practical implementation of the theory that it had developed regarding the new syllabus of the Faculty of Radiologists. The results achieved were considered satisfactory, in that four out of five candidates achieved the Fellowship of the Faculty of Radiologists and the Committee would wish to congratulate Drs. D. B. Crawford, S. J. Eakins, A. L. P. Martin and C. J. Sinclair. Three of five candidates achieved the Primary Fellowship. The latter results were somewhat disappointing but were not unexpected, as the information on which the Committee had been required to act had, at all times, been felt insufficient and it was obvious that the course for the Primary had struck rather the wrong balance between Physics and Radiological Technique. The Committee had, in fact, pointed out to the Faculty as early as December of last year their fear that this might prove the case.

Due to the change in regulations, whereby all candidates for the Fellowship must undertake one post-registration year in clinical medicine, no course for Primary Fellowship will be undertaken in the coming year.

The Committee has also considered at length the problem of continuing post-graduate education for the young consultant, this being particularly necessary in Radiology, where consultant status is achieved in the early thirties. We would hope that Council and the other specialist committees will act in this respect.

As yet, there has been no action on an integrated policy regarding the implementation of teaching aids but this is also a very necessary thought for the future.

The members of the Committee are: Dr. E. M. McIlrath (Chairman, Royal Victoria Hospital), Dr. A. D. Gough (Royal Victoria Hospital and the Ulster Hospital), Dr. R. S. Crone (Royal Victoria Hospital and Musgrave Park Hospital) and Lieut. Col. D. G. C. Whyte (Altnagelvin Hospital).

E.M.McI.

SURGERY COMMITTEE

During 1962/63 the Junior Hospital Staff Group in Northern Ireland wrote memoranda on the need for more organised postgraduate training in a variety of specialties. These reports were presented to the Medical Education and Research Committee of the Northern Ireland Hospitals Authority in September, 1963. As a result, at a meeting of the Board of Surgical Studies in early 1964, it was proposed that a Surgical Training Committee be set up. Initially, this consisted of representatives from the University, the Royal Victoria Hospital, the Belfast City Hospital, the peripheral hospitals, the Hospitals Authority and a secretary.

It was agreed in principle that junior hospital staff should be represented whenever matters of general policy concerning them were to be discussed and whenever they felt disposed to send a representative. As much of the junior rotation revolved round the Royal Victoria Hospital and Belfast City Hospital, the secretaries of the respective Surgical Sub-Committees were later invited to serve on the Surgical Training Committee in order to establish better communication with consultants.

Following a period of fairly rapid rotation, trainees usually spent their second and third years in posts of longer duration and greater seniority. Although it was policy not to send registrars to peripheral hospitals until they had obtained their Fellowship, the service requirement in relation to available staff often meant a break in this principle.

As time passed, the system began to work more smoothly and, with regard to the junior hospital staff, it was based on establishing trust in its overall fairness. One of the most significant improvements in administration came when it was agreed to employ senior house officers for the Royal Group and South Belfast Group on an interchangeable basis. One of the drawbacks of the present system is that rotation for registrars is more difficult to organise that is rotation for senior house officers, and as most trainees are seldom employed as senior house officers for more than one year, their rotation may suffer as a result. A recent proposal, which has not yet been effected, is that the grade of senior house officer should be eliminated in the training programme so that all junior trainees graded as registrars would have interchangeable posts. A new rotation has already been evolved on paper on the assumption that this fundamental change will be effected shortly.

During the year 1971/72 Mr. G. W. Johnston and Mr. J. D. A. Robb visited Glasgow, Edinburgh, Newcastle-upon-Tyne, Manchester and Liverpool to study the respective training schemes in surgery at these centres. As a result, a new rotation covering the first two years of training has been planned in the form of eight circuits. Trainees would be appointed to a circuit, and at the end of two years they would be expected to spend one year in the periphery and thereafter decide on their higher surgical training with regard to specialisation. For those unable to find suitable posts in this category, certain posts nominated as holding posts would be available. In the event of certain aspects of a particular circuit being unacceptable to the trainee he could arrange with another trainee to swop circuits, provided the consultants concerned were agreeable and the Training Committee sanctioned the change.

J.D.A.R.

BOOK REVIEWS

ESSENTIALS OF RESPIRATORY DISEASE. R. B. Cole, M.A., M.D.(Contab.), M.R.C.P.(Lond.), (Pp. x+278; Illustrated. £2.75). London: Pitman Medical, 1971.

WHEN I was a student I never bought a textbook of medicine. I cannot remember that I formulated any policy or that I thought the matter out in any way but I had a definite feeling that the big books were not for me. Had I not seen a statement by a reviewer 'The new edition of X's Textbook of Medicine has grown in girth but not in stature'? Well actually I had not. That brilliantly succinct and damning comment did not appear until years later

But I did find it worthwhile and so did many of my colleagues to buy smaller and more specialised books. I remember very dearly Thomas Lewis' book on hearts, Walshe's on nervous diseases and Coope's on chests. That was the order of merit too, for Coope's did not have the perspective and wisdom of the other two.

The student of today is now better served that I was on chests, for Dr. Cole's book is excellent. It is short, well written and sensible. Part 1 on clinical methods includes a splendid chapter on how to examine chest radiographs. Part 2 is a concise but remarkably full account of modern concepts of pulmonary physiology and includes a run down of the uses and limitations of spirometry, arterial blood gas analysis and other respiratory function tests. Part 3 describes the common varieties of lung disease. Acute infection, asthma, chronic bronchitis and malignant disease quite correctly dominate this section, but it includes useful sections on industrial lung disease, pulmonary thromboembolism, collagen diseases of the lung and diffuse pulmonary fibrosis.

This is a book which all students and most doctors must buy. Do not borrow it. Buy it because Dr. Cole's approach to disease is so right. It is the approach of an experienced scientifically based physician who has thought deeply about his subject.

This book, written by a Senior Lecturer in the Department of Medicine at Queen's, will be widely acclaimed. It will bring credit not only to Dr. Cole and to the Department, but to the Medical School and the teaching hospitals of Belfast. O.L.W.

PERSONALITY AND SCIENCE. An Interdisciplinary Discussion. Edited by I. T. Ramsay and Ruth Porter (Pp. ix+158. £1.00 paper; £2.25 boards). Edinburgh and London: Churchill Livingstone, 1971.

THIS is a report of a series of meetings supported by the Ciba Foundation in which the broader area where recent developments in medical science raise moral issues directly related to the status and development of human personality were discussed by a group of medical scientists, philosophers, legal experts and theologians. As with most problems in which one endeavours to reach the ultimate truth it soon becomes apparent that even definitive definitions of many of the subjects discussed are extremely difficult to arrive at, so that final judgements are premature if not impossible. Still the problems raised are forcing themselves upon the medical profession and sooner or later, though the philosophic content of such problems may still be open to debate, the profession must find a consensus of opinion that will support the current practice of the times. It is a debate that is only beginning, and for the solution of these problems the medical profession may well have to seek the help of scholars in many other fields, and indeed to consider the reaction of the public as a whole. It is interesting to read one important conclusion. "All the members of the group, medical and non-medical, were in strong agreement that if the patient's personal doctor ceased to support him—the whole ethic of the profession, intact since Hippocrates, would be radically and

BOOK REVIEWS

ESSENTIALS OF RESPIRATORY DISEASE. R. B. Cole, M.A., M.D.(Contab.), M.R.C.P.(Lond.), (Pp. x+278; Illustrated. £2.75). London: Pitman Medical, 1971.

WHEN I was a student I never bought a textbook of medicine. I cannot remember that I formulated any policy or that I thought the matter out in any way but I had a definite feeling that the big books were not for me. Had I not seen a statement by a reviewer 'The new edition of X's Textbook of Medicine has grown in girth but not in stature'? Well actually I had not. That brilliantly succinct and damning comment did not appear until years later

But I did find it worthwhile and so did many of my colleagues to buy smaller and more specialised books. I remember very dearly Thomas Lewis' book on hearts, Walshe's on nervous diseases and Coope's on chests. That was the order of merit too, for Coope's did not have the perspective and wisdom of the other two.

The student of today is now better served that I was on chests, for Dr. Cole's book is excellent. It is short, well written and sensible. Part 1 on clinical methods includes a splendid chapter on how to examine chest radiographs. Part 2 is a concise but remarkably full account of modern concepts of pulmonary physiology and includes a run down of the uses and limitations of spirometry, arterial blood gas analysis and other respiratory function tests. Part 3 describes the common varieties of lung disease. Acute infection, asthma, chronic bronchitis and malignant disease quite correctly dominate this section, but it includes useful sections on industrial lung disease, pulmonary thromboembolism, collagen diseases of the lung and diffuse pulmonary fibrosis.

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adversely changed". Yet it is sometimes difficult to apply in all its ancient simplicity the Hippocratic ethic to the modern problems of organ transplantation, of tissue donors, of drug trials, of operations involving personality changes etc.

The book covers a wide range of these potential problems—Disturbances of behaviour in endocrine disorders: Effects of temporal lobectomy on personality: Effects of leucotomy on personality: Can drugs affect personality: Legal observations on the effects of science on personality: Human Personality: and many allied problems.

Though coming to no dogmatic conclusions this book is well worth study and should be read by all of the profession who are interested in finding an ethical norm for the problems of modern scientific medicine. J.H.B.

THE NORMAL CHILD—Some Problems of the Early Years and their Treatment. R. S. Illingworth, M.D., F.R.C.P., D.P.H. Fifth Edition. (Pp. x+402; figs. 52. £3.00). Edinburgh and London: Churchill Livingstone, 1972.

IN the fifth edition of this well-known and deservedly popular book, the text and references have been brought up-to-date and many sections have been extensively revised, e.g. those dealing with obesity, artificial feeding, immunization, crying, discipline, etc. A new chapter has been added entitled "The young school child", in which the author deals with such problems as the mentally superior child, the backward intelligent child, dislike of school, bullying, delinquency, etc.

The author's principal aim when planning the first edition of this book was to describe the variations in normal behaviour and development which may occur during early childhood. Though not of serious import in themselves, these nonetheless cause considerable parental anxiety and childhood suffering if not correctly interpreted and managed. When first published in 1953, the book filled an important gap in the paediatric literature of the time. The passage of time and the publication of four further editions has done nothing but enhance the book's intrinsic value. The author's extensive and meticulous study of this subject of child care, combined with the lucid and common-sense manner in which the subject matter is presented, renders this book essential reading for all involved in the care of children. In these days of escalating costs, it is excellent value at £3. I.J.C.

CIRCULATION by Björn Folkow and Eric Neil. (Pp. 595; Illustrated. £6.00) London, New York, Toronto: Oxford University Press, 1971.

BJORN FOLKOW and Eric Neil occupy the Chairs of Physiology at the University of Göteborg in Sweden and at the Middlesex Hospital Medical School in London respectively. They are men with very individual personalities, strong ideas and independent minds and have made distinctive contributions to the present day understanding of the circulation. In this sense, the book represents a remarkable feat of co-operation. The dedication reads "This book is dedicated to Anglo-Swedish friendship, which barely survived it".

The result makes good reading. It presents a general survey of modern cardiovascular physiology. The first few chapters deal with the biophysics of blood flow. Then there are some chapters on heart function. The following chapters deal with the characteristics of the various regional circulations. Throughout the book great stress is given to the regulatory mechanisms controlling the heart and blood vessels and the ways in which the functions of the circulation are integrated. The alterations in normal function produced by disease are described where appropriate and methods of cardiovascular assessment are discussed.

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THIS is a very satisfying book to read, and to read it, for the opthalmologist or the neurologist, is to wish to own it. The concise presentation of the subject is greatly helped by the line drawings of the nervous tissues of the visual pathways and their related structures and of the visual field defects caused by pathological processes as they impinge on these structures at the differing levels from retina to cortex. Stress is laid on the value of observing whether disproportion exists between the fields recorded by stimuli of varying strength, e.g. 2 in 2,000 white and 20 in 2,000 red. From these conclusions regarding prognosis are deduced more readily than from a single field recording.

That the authors have been at pains to introduce into the text much new material since the original edition of 1960 is evident from the references to original articles at the end of each section, many of which are dated in the '60's and several in 1970.

In particular, a new chapter is added regarding the new approach to visual field recording by static perimetry. A concise account of this technique is included and an indication of its value can be gathered by the inclusion of illustrations of appropriate profiles shown as they are related to scotomata and relative scotomata. The figures are obtained by plotting along a chosen meridian of the visual field the minimum stimulus perceived. A rather elaborate perimeter devised by Professors Aulhorn and Harms of Tubingen is used and the recording of the fields is a time consuming process. It is, nevertheless, likely to be increasingly used in the future in opthalmological and neurological departments.

The authors express the hope that in addition to being of use to the medical specialities of opthalmology and neurology, their book will be of use to the technical staff who will be needed to assist in the glaucoma and perimetry clinics of the future. One can foresee that this will be a bench book in all such clinics and it will also be a considerable aid to anyone wishing to grasp the anatomy and function of the visual pathways, forming as they do a recognisable structure on which the remaining parts of the brain can be built. J.A.C.

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THIS book is a product of the Glasgow School and is essentially for those who wish to learn the practice of clinical gynaecology. As Professor Ian Donald states in the foreword, gynaecology is changing so fast that the author of a textbook requires as much sympathy as encouragement. Emphasis keeps shifting like the mudbanks of a river estuary and in recent years it is shifting away from the minutiae of surgical technique whose peak had already been reached by the great surgeons of the past. Preventive gynaecology, diagnostic gynaecology, and endocrine gynaecology have all made rapid forward strides, and it is in these fields that the reader is gently led throughout the pages of this book.

Medical students and recently qualitfied doctors who are bent on entering general practice need not, unless they so desire, prepare themselves to practice the science and art of obstetrics, but a thorough clinical knowledge of gynaecology, as outlined in this book, has become essential.

The author was stimulated to write this book when his daughter reached the final year of her medical studies and asked for a short and practical textbook of gynaecology. He acknowledges help from Dr. John McVicar who wrote the chapter on the problem of early pregnancy, from Dr. James Willocks who wrote on uterine displacements, from Dr. M. A. C. Cowell who wrote on radiotherapy, from Professor M. C. McNaughton who collaborated in the chapter on the sex hormones and Professor John Milne who helped with the chapter on epithelial dystrophies of the vulva.

One must congratulate him on the success of his achievement. It is not a sound proposition at this time to re-edit an old textbook and bring it up-to-date. As Professor Donald says, there are times when a fresh start must be made and Wallace Barr has made it.

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PERIPHERAL VASCULAR DISEASES. Allen-Barker Hines. Fourth Edition. Edited by J. F. Fairburn, J. L. Juergens and J. A. Spittell. (Pp. xiii+797; Illustrated. 10.65). Philadelphia, London, Toronto: Saunders, 1972.

THIS well known and excellent textbook on Peripheral Vascular Diseases has now reached its 4th Edition. The text has been largely rewritten and brought up to date with a number of new chapters. In a specialised field of medical science which has developed rapidly in recent years the contents crystallise the views of the many experts from the Mayo Clinic—physiologists, pathologists, physicians and surgeons.

Each chapter is introduced by a short, informative historical review of one of those whose writings and research have made a major contribution to the subject and contents of the section.

While the book is long and difficult to read, its chapters contain a mass of information which can best be used and digested in relation to the individual vascular problem. It is essentially a book of reference to be used piece-meal by the physician or surgeon rather than a book to be read as a continuous narrative.

The excellent chapter on the physiology of blood flow in the limbs comes from the pen of a distinguished Queen's graduate—Professor John Shepherd; much of his material has its origins in the detailed studies in blood flow which were carried out in the Vascular Department in Belfast over the past 25 years.

The editors of this book have produced an edition which is a worthy successor to that produced by the pioneers of this subject and the extensive information covering a wide field is recommended to all those who have to deal with cases of periphereal vascular diseases.

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CROHN'S DISEASE. James Kyle, M.Ch.(Belf.), F.R.C.S. (Pp. xiii+202; illustrated. £3.00). London: William Heinemann Medical Books Limited, 1972.

OSLER in his day considered that pneumonia and typhoid provided the best exercise for young doctors in the principles and practice of medicine. Nowadays their place has been taken by ulcerative colitis and Crohn's disease. This important book is based on a continuing survey of 166 cases of Crohn's disease in the Aberdeen area, 162 of them observed and followed by the author. The study was prospective from 1960 onwards. It was a period when knowledge of Crohn's disease was growing, and the disease in the colon was being recognised. It was being realised that the search for the cause of Crohn's disease might lead not only to improved treatment, but perhaps also to the discovery of new principles in pathology. Mr. Kyle has matched the importance of this subject with careful clinical and operative observations, prolonged purposive thinking, and wide reading.

The monograph considers fully aetiology, pathology, clinical features, medical and surgical treatment, and prognosis. Many will be interested in the description of the disease in the rectum, the note on rapid spread of the disease in the colon (unusual in the small intestine), and in the minor peak in incidence in elderly females. Operative procedures are described in detail. Sulphaguanidine is rightly given a place in the medical management. The reviewer thinks it can frequently replace sulphasalazine. Corticosteroids were found useful as is the general opinion, but there is little encouragement to use azathioprine. There is a good discussion on nutrition, though it is not necessary to be so cautious about the use of folic acid and vitamin B_{12}. If injections of iron can minimise the use of blood transfusion, especially in young women, it must be right to make freer use of them.

Touching on these points in a review cannot give a sufficient idea of the sustained value and interest of the book. It is full of information and deserves general reading, especially by the young, who could find in it a model for working and thinking. The x-ray illustrations are good. There are no photographs of findings at laparotomy or of fresh resected specimens. They would be helpful to physicians who do not see the living pathology. There is a minimum of misprints. On pages 80 and 95 the plural of "diverticulum" is wrongly printed.

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THE HEALTH SERVICES — ADMINISTRATION, RESEARCH AND MANAGEMENT. Edited by H. P. Ferrer. (Pp. xii+379, £7.80). London: Butterworth, 1972.

THIS is an interesting and easily read book on the health services which will be of particular interest to doctors who may be more involved in management under the new Area Board structure than they would have been in the past. It should, however, be noted that the pattern of English hospital and local health authority services described is not the same as the pattern in Northern Ireland, due to change in April, 1973, and it will soon be mainly historical in Great Britain too.

While this book is undoubtedly interesting, one is continually aware that it has been written as a series of essays by a number of contributors. This leaves one with a feeling that there is a lack of co-ordination between the chapters and a variation in the depth with which some subjects have been treated.

Chapter 2 on the Administrative Structure of the Health Services and Future Developments sets the scene. However, it refers to the future pattern of the health services and while future developments in the service are unknown, one feels that the book is incomplete or will have to be rewritten at a later date. A valid point is made that there are very few persons who are conversant with the problems of all the services which are to be integrated and perhaps fewer still who have been trained to look at the health problems of a community as a whole.

The following chapter on The Medical Practitioner and Management is one of those which lacks co-ordination with what has already been written. The section on management techniques is interesting but it is over simplified in relation to later chapters which give detailed examples of techniques such as operational research. Chapters 4 and 5 are not written in any great depth nor does Chapter 5 blend particularly well with the chapter which follows.

Much of what has been included in Chapter 6 under the title Use of Management and Administrative Techniques on Nursing does not apply to nursing alone and should in my opinion have been included in a chapter applicable to all staff. There is a section in this chapter on "The Communications Function : The Management Decision and Control Function —A structured approach to problem solving and Management Information and Control". These are management techniques for application not only in nursing but in all aspects of the health services. For example, Hospital Activity Analysis is given as a thumb-nail sketch in this chapter although it provides information for all sections of management.

It is a pity chapters 7, 8, 9 and 10 had not all been written by the same person as this would have avoided the unbalance which occurs in the treatment of certain quantitative techniques, for example, model solutions and the applications of operational research.

Financial Management in the Health Service, while being a necessary subject for study, is dealt with in greater detail than is necessary in a book which is primarily an introduction to management.

Chapters 12 and 13 are two chapters which are interesting to read by themselves but together they are rather confusing in content and would have been better written by one person.

The bibliography and references throughout the book are excellent and invaluable to anyone wishing to study the subjects further.

Generally speaking, the impression of this book is of a series of essays, hastily gathered together and not particularly well edited. The book would serve as an introduction to the health services and give an idea of lines of study to pursue in future but it would not form a complete text-book. Ideally, it should be followed up by other books on the subject. For an introductory book, however, it is much too expensive at £7.80.

J.A.

AN INTRODUCTION TO CLINICAL RESEARCH. By W. P. Small and Urban Krause. (Pp. ix+125; figs. 46. £1.50). Edinburgh and London: Churchill-Livingstone, 1972.

THE authors' aim is to set out, simply and clearly, the methods and components of clinical research (other than drug trials) which they do in the book's four chapters: "Clinical Research—its Problems and Faults"; "The Collection and Recording of Clinical Data"; "Evaluation"; and "The Presentation of Results". Clinical research they describe as dealing "directly with the patient, his diseases, his responses to treatment and his reactions to normal or pathological stimuli", and they recognise as its three main purposes "(1) to determine the results of treatment, (2) to learn the natural history of the disease, and (3) to search for the factors that cause disease". Within this framework they have in general succeeded and the potential clinical researcher, especially junior staff, will benefit from the authors' clear and coherent exposition in simple terms of the precepts and problems, and the organisational, logistical, and technical aspects of the subject.

But in some ways the book is too simple—not always a good fault. Chapter 2 ("The Collection and Recording of Clinical Data") consists mainly, for the well-trained clinician, of statements of the obvious: much of this aspect of the subject is, or should be, taught to undergraduates—though certain practical suggestions are useful to the researcher. Chapter 3 ("Evaluation") is a useful statement but is in fact an oversimplification of quite a complex situation; while Chapter 4 ("The Presentation of Results"), though in ways a charmingly simple (and accurate) body of advice, is essentially a lecture to junior staff on how to deliver and construct a clinical medical "presentation" and write up and submit a medical paper—hardly worth a full chapter in a book of this type. If the canons of a subject cannot be repeated too often or in too simple a fashion then this book is justified. Clinical investigators, especially beginners, will find this book a useful summary of essentials which will help them to plan, or rather plan to plan, relevant projects. For many it will be more useful and certainly more comprehensible than more detailed reference works on methodology, but it should, however, be considered as no more than an introductory treatment to be augmented by more specialised reading. It can be recommended to university libraries, personal bookshelves and—most importantly—to ward and out-patient reference collections, to post-graduate centre libraries, and other hospital stocks available to junior graduate staff.

P.F.

GASTROENTEROLOGY. An integrated course. Edited by Iain Gillespie and T. J. Thomson. (Pp. ix+265; illustrated; £1.50. Edinburgh and London: Churchill Livingstone, 1972.

IT is high time that gastroenterology should be better taught. The practice of the subspecialty, so far as medicine is concerned, is not so good as it could and should be, and it will not improve until a better foundation is laid in the student's undergraduate course. This book is a creditable effort to provide a suitable text, and it has achieved some success. Nevertheless fuller clinical descriptions and more complete expositions of the natural course of diseases would be helpful to the undergraduate. Nutrition and haematology do not interpenetrate the thought and discussion as they might. Environmental factors are not neglected but could be treated more fully. It is extremely regrettable that gastric and duodenal ulcers are described under the one heading of "peptic ulcer". The policy of integration may be responsible, and if so, it is not serving gastroenterology well. There are excellent photograph and x-ray illustrations. I could not find the name of the radiologists who provided the latter.

The diagram figure 26. should be replaced by an x-ray illustration. The lateral view is not the usual appearance of Plummer-Vinson stricture.

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THIS excellent little book is unusual in several aspects. At the outset it strikes a welcome change in the title which emphasizes the fact that the statutory venereal diseases are not the only conditions dealt with by the physician who works in this branch of medicine. After dealing with anatomical details, history taking and examination of the patient (the latter in particular giving much valuable and sane advice) the author spends some time in discussing the public health aspects, medico-legal management, sociological and psychological background associated with sexually transmitted diseases. These chapters contain much valuable material often forgotten or neglected by those casually handling patients affected with these conditions. Only after dealing with these important questions does the author turn to the clinical aspects of the sexually transmitted infections.

A valuable and interesting chapter, including pathology, immunity, aetiology and the history of syphillis, is followed by an excellent account of the serological tests for syphillis and their interpretation. The chapter on the pathology, epidemiology and diagnosis of gonorrhoea is likewise valuable. The clinical descriptions of the various conditions are concise and good and include not only a description of the commonly found sexually transmitted infections but also treponematosis and endemic syphilis and a chapter on "tropical diseases affecting the genitalia". A welcome warning is given against indiscriminate treatment of congenital syphilis on page 123 and "blunderbuss" therapy of gonorrhoea on page 146, whilst the value of repeated courses of treatment in cardiovascular syphilis confirms one's own clinical experience: guarded prognosis following surgical treatment of aneurysm of the aorta and aortic valvular incompetence is stated on page 109.

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His emphasis on the rarity of gonococcal arthritis on pages 124 and 140 would be questioned in this school and the impression is given on page 141 that gonococcal infection of the conjunctiva occurs only in adults and whilst admittedly extremely rare, it is important to remember that accidental infection of the conjunctiva can occur in children also. Not all venereologists will agree that a three month follow-up after the use of broad spectrum antibiotics is sufficient.

Several spelling mistakes are almost certainly the result of incorrect typesetting e.g. "papulet" page 70, "eneurysms" page 92, "necropy" page 98, "inequal" page 103 and "seed" advice page 212 will need corrections in subsequent additions but these are only minor blemishes in an excellent and interesting book which has been produced at a reasonable price and which should be in the hands of every medical student, and which the average general practitioner will read with benefit.

J.S.McC.

CUNNINGHAM'S TEXTBOOK OF ANATOMY. Eleventh Edition. Edited by G. J. Romanes, C.B.E. (Pp. xv+996; figs. 1180. £9.00). London: Oxford University Press, 1972.

HOW can one be objective about a greatly loved textbook? "Big Cunningham" was the close companion of my undergraduate days 40 years ago and I must have read it from cover to cover at least three times in the course of two years. Nowadays few students would want to read the whole of a vast textbook crammed with information, and none need do so in order to pass their professional examinations in Anatomy. However, I should like every medical student to buy this book. He should read carefully the general sections at the beginning of each chapter, and he should make frequent reference to the rest of the book. As an atlas of gross anatomy it is superb. He would require no other atlas of normal radiological anatomy, nor a special textbook of embryology or neuro-anatomy.

The text is always clear, and beautifully expressed in a literary style which is a model for anyone who wishes to study good scientific English—and this despite the fact that the work is from the pens of nine distinguished authors, each of whom must inevitably have his own

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An attractive and useful feature of the book is the way structure and function, and structure and clinical or pathological significance, are integrated in the text. Because of this the reader cannot fail to realize that modern Human Anatomy is not simply a catalogue of visual data about the body, but the very canvas on which his medical knowledge is tapestried.

Buying the new Big Cunningham for the student would be £9.00 well spent. Anatomy, like all scientific disciplines, evolves new facts and concepts as the years go by: nevertheless the medical man who owns this book will have an accurate, useful and friendly guide to one of the major scientific bases of his craft for many years to come. J.J.P.

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The problems of the diagnosis of venous thromboembolism are well presented, the Doppler technique, radiological and isotope methods are discussed. The I^{125} Fibrinogen test for the diagnosis of deep vein thrombosis is given pride of place, and it is left to the participants in the general discussion to reveal its limitations.

The study of Rheology has made an important contribution to the understanding of the aetiology of thromboembolism. This aspect is highlighted in a chapter, which presents the results of a collaborativve study carried out by a surgeon and a bio-medical engineer into the changes in venous blood flow, before, during and after surgery. The follow up to this is a discussion of the methods for prevention of post-operative deep vein thrombosis. This section is of considerable practical value.

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A number of excellent introductory books including "Clinical Examination", McLeod, and "A Primer of Clinical Medicine", Papworth, are already available and the present text cannot be recommended as a substitute for them.

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This book by seven American and one Finnish author is an interesting and up-to-date presentation. It includes much of the ultra-structure of the cell and some account of inflammation, of host-parasite interaction and of immunity. Opinions may be divided on some aspects of the presentation of neoplasia and the chapter on hereditary differentation and development is disjointed and, like much of the book presents information which is interesting in itself, but not always well integrated and is sometimes of doubtful relevance in the context. Admittedly at present no one can be certain what is, or may be, relevant, but much data can obscure ideas.

The student well trained in biology will find this book interesting. Others may find parts of it no more inspiring than generations of students found cloudy swelling and fatty infiltration, and in the years to come parts of it will be no more relevant. The interest and excitement of studying the response of the whole organism to disease is missing and an introduction more related to the response of the patient may better stimulate and interest the average medical student.

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introduction to patients. The appreciation and interpretation of these findings can only come with experience but the medical student beginning his clinical course must learn as much about their acquisition as the final year student, since these are the building blocks of much of his education. It follows then that an introductory text to clinical skills must at least be complete and not merely serve as a stepping stone to another more detailed text. In this respect "An Introduction to Clinical Medicine" is inadequate. The early chapters on history taking, general observations and examination of the integument are good, that on history taking being particularly useful. However, the chapters relating to examination of the major systems are not comprehensive enough and contain some misleading statements, e.g. that "a pulsating liver may be found in congestive cardiac failure" without making it clear that such a finding indicates tricuspid incompetence and is not found in uncomplicated heart failure. There is not enough information presented to allow the student to understand findings such as murmurs, the abnormalities of the jugular venous pressure, and hemiplegia to mention but a few.

A number of excellent introductory books including "Clinical Examination", McLeod, and "A Primer of Clinical Medicine", Papworth, are already available and the present text cannot be recommended as a substitute for them.

J.J.C.

PRINCIPLES OF PATHOBIOLOGY. Edited by Mariano F. La Via and Rolla B. Hill Jr. (Pp. xviii+281, Illustrated £3.25) London: Oxford University Press. 1972.

THE term "pathobiology" has replaced "general pathology" for the study of the fundamental disturbances constituting disease in all living things. The foreword claims to present a concept of disease as an abnormal biological process which differs quantitatively, rather than qualitatively, from normal biological mechanisms. This permits a part of pathology to be taught to medical students as part of their training in biology, and it is useful to expose students of biology or zoology to the principles governing the variants of biological activity known as disease. In some American schools such a "core" curriculum with very little special human pathology has been adopted to allow time for electives and integrated or interdisciplinary clinical studies.

This book by seven American and one Finnish author is an interesting and up-to-date presentation. It includes much of the ultra-structure of the cell and some account of inflammation, of host-parasite interaction and of immunity. Opinions may be divided on some aspects of the presentation of neoplasia and the chapter on hereditary differentation and development is disjointed and, like much of the book presents information which is interesting in itself, but not always well integrated and is sometimes of doubtful relevance in the context. Admittedly at present no one can be certain what is, or may be, relevant, but much data can obscure ideas.

The student well trained in biology will find this book interesting. Others may find parts of it no more inspiring than generations of students found cloudy swelling and fatty infiltration, and in the years to come parts of it will be no more relevant. The interest and excitement of studying the response of the whole organism to disease is missing and an introduction more related to the response of the patient may better stimulate and interest the average medical student.

J.E.M.

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ate, with colour and black and white photographs and line drawings, this book is a pleasure to handle and enables the newcomer rapidly to grasp the essentials of many of the problems of opthalmology. Its perusal is therefore a suitable beginning for the student at the start of his study of opthalmology and, when supplemented by a reasonable amount of clinical experience, enables him to marshall his knowledge in a useful way.

The book is addressed to those in general practice and the author in this new edition has made alterations in order to keep up-to-date with the developments of recent years. Examples of this are the new illustrations, particularly those in colour, and discussions, brief but helpful, on the use of steroids and on contact lenses. J.A.C.

MEDICAL RESEARCH COUNCIL: ANNUAL REPORT. April 1971—March 1972. (Pp vi+141, Plates iv. £0.90). London: Her Majesty's Stationery Office, 1972.

AT a time when the organisation of research and its support is under critical review it is especially interesting to read this account of the work of the largest British organisation supporting medical research. The report succeeds not only in giving an overall view of the work supported by the Council, but it succeeds admirably in relating it to progress elsewhere in many fields of medicine and applied biology. To a specialised worker in one field it affords interesting and stimulating glimpses of work in other fields. The four plates included well illustrate the wide interests covered. One records the chromosome banding revealed by the new Giemsa technique, the next the automated chromosome analysis equipment in the Council's Cytogenetic Unit. A scanning electron microphotograph reveals new features in bone structure and the fourth plate shows spirometric studies in progress in the field in New Guinea. There is much else ranging, for example, from psychological reactions to abortion and juvenile delinquency to gene control and metal ions in biological systems.

All who wish to know what is happening in medicine outside their own speciality should read this report. All who desire change in the organisation of research might be better informed of the complexity of the problem by a careful study of this report. J.E.M.

GADDUM'S PHARMACOLOGY. Seventh Edition. Revised by A. S. V. Burgen and J. F. Mitchell. (Pp.vi+251; Illustrated. £2.00) London: Oxford University Press, 1972.

THIS is the latest edition of one of the classic elementary textbooks of pharmacology. Its format, a small paperback book with two columns of print and line drawing text illustrations, is in line with current practice for undergraduate textbooks. It contains a large amount of authentic pharmacological information which is well arranged and described with a list of references for further reading at the end of each chapter. But on reading through various chapters it becomes increasingly difficult to discern what kind of student is meant to use this book. I suppose there are those who wish to take up the career of academic pharmacology for whom this book might be appropriate. But its emphasis on unimportant pharmacological detail is matched by an extraordinary choice of drugs to exemplify pharmacological principles, pages are devoted to the pharmacology of for instance strychnine while heroin is dismissed in a few lines with no mention of the problem of addiction. The metabolism of drugs is mentioned in general terms but the problem of enzyme induction and the related problem of drug interactions is scarcely mentioned. This lack of orientation of the text towards the current clinical situation makes this book inappropriate for students of medicine, pharmacy or veterinary science. P.C.E.

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