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THE ULSTER MEDICAL JOURNAL

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THE ULSTER MEDICAL JOURNAL

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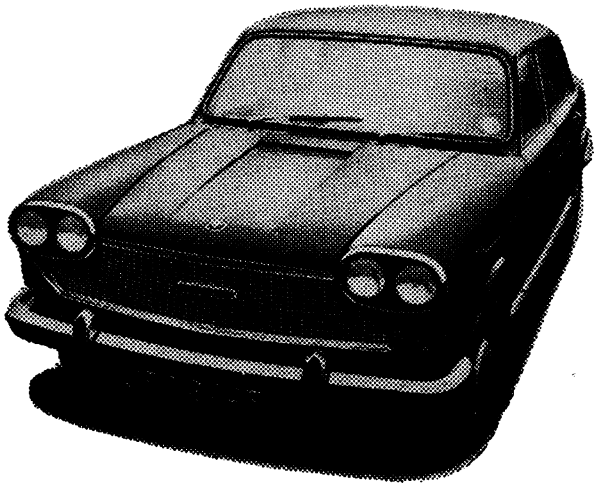

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THE
ULSTER MEDICAL JOURNAL

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SPOROTRICHOSIS IN IRELAND[1]

A REVIEW

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INTRODUCTION

SPOROTRICHOSIS is a chronic fungal infection that is usually confined to the dermis and subcutaneous tissue, presenting typically with one or more ulcerating, gumma-like granulomas. Its cause is *Sporothrix schenckii*, a mould that has its natural habitat in decaying vegetation, straw, soil and the like, and occasionally on living plants, such as barbery (*Berberis*) and gorse (*Ulex*). The sporothrix enters the tissues through superficial wounds, such as abrasions, or when the skin is penetrated by contaminated spines or thorns of plants. In some cases the initial lesion is followed by ascending ulcerative lymphangiitis (Fig. 1); lymphadenitis seldom results, even in these cases. Disseminated haematogenous ('septicaemic') sporotrichosis and visceral sporotrichosis are fortunately very rare – the mortality of these forms of the infection is very high. Cutaneous sporotrichosis, with or without lymphangiitis, may run a long course but seldom, if ever, puts the patient's life in any danger. Confirmation of the diagnosis is most regularly and reliably obtained by culturing the causative fungus from the lesions, a procedure that is usually straightforward, provided there is no bacterial contamination. Unlike virtually all other deep-seated fungal infections, sporotrichosis can seldom be diagnosed by histological examination : this is because the sporothrix is rarely demonstrable in infected human tissue (Symmers, 1964).

The disease is of worldwide occurrence. It is seen frequently in some lands and very rarely in others. The number of cases in an area may vary remarkably from

(1) The names sporotrichosis for the disease and *Sporothrix schenckii* for the fungus that causes it are used in this paper in accordance with the recommendations in Medical Research Council Memorandum No. 23, *Nomenclature of Fungi Pathogenic to Man and Animals*, 3rd edition (London, 1967: Her Majesty's Stationery Office).

year to year or decade to decade. Factors influencing the prevalence of sporotrichosis include standards of living, occupation, working conditions and climate (particularly changes in climate that favour or discourage saprophytic growth of the sporothrix in the environment [Mackinnon, 1947–49]). The disease has never been other than a rarity or curiosity in the British Isles : including the four cases that are formally reported for the first time in the addendum to this paper[2], I know of only 16 published cases of sporotrichosis diagnosed in the British Isles (Table). In at least five of these the infection was acquired oversea – of the remaining eleven no fewer than six originated in Ireland (three in Dublin, one in Belfast, one in rural Armagh and one in Fermanagh – see Case Reports in the addendum). The predominance of Irish cases has prompted this paper, and the opportunity is taken to present some hitherto unpublished observations on sporotrichosis in Ireland by doctors and laymen whose names will still be known to some readers of the *Journal* at home and oversea.

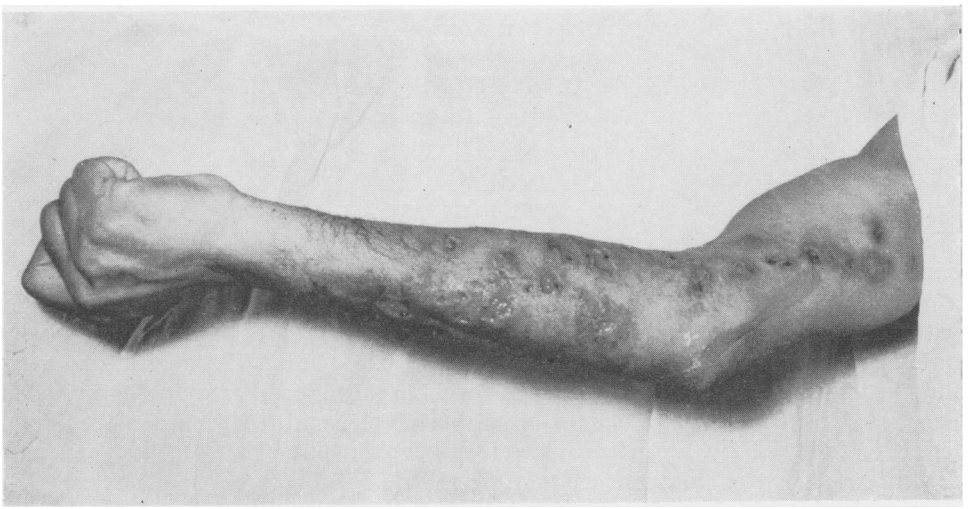

FIG. 1. *Ascending lymphangiitic form of cutaneous sporotrichosis. The lesion at the site of inoculation over the medial aspect of the hand at about the level of the neck of the fifth metacarpal bone had healed when the photograph was taken, leaving a small pigmented scar. The lymphangiitic lesions of the forearm and upper arm are at various stages of active ulceration or healing. (From a colour transparency kindly prepared by Dr. A. González Ochoa.)*

HISTORICAL NOTE

Sporotrichosis was first recognized in December, 1896, by Benjamin Robinson Schenck, a medical student, while working with Simon Flexner in the pathological laboratory of the Johns Hopkins University and Hospital in Baltimore, Maryland.

(2) Two of these four cases were described briefly in an account of sporotrichosis presented at the meeting of the Pathological Society of Great Britain and Ireland in Glasgow in July, 1963.

Schenck's observations were published in 1898, the year in which he graduated in medicine[3]. He isolated the sporothrix from the lesions of a characteristic case of the ascending lymphangiitic form of the disease.

The disease was first recognized in Europe in 1903 by Lucien de Beurmann and his house physician, Louis Ramond, at the Hôpital Saint-Louis in Paris. Their patient presented with multiple subcutaneous nodules, simulating cysticercosis. They consulted Sabouraud, the great French dermatologist, about treatment : he advised them to try potassium iodide, on the grounds that he had often found this drug helpful in cases of another fungal infection, actinomycosis. De Beurmann and Ramond cured their patient with the iodide. They share the credit for introducing iodide therapy of sporotrichosis with Lutz and Splendore (1907) of Sao Paulo, Brazil, whose first patient with this disease had been cured with iodide in 1902. To this day iodide remains the most effective and the safest agent in the treatment of cutaneous sporotrichosis (iodide is usually ineffective in cases of generalized haematogenous and visceral sporotrichosis, which are likely to end fatally unless treated with the antifungal antibiotic amphotericin B).

A most important occasion in the history of this disease was the publication in 1912 of the two volumes of the remarkable monograph, *Les Sporotrichoses*, by de Beurmann and his colleague Henri Gougerot, dermatologist to the Hôpital Saint-Louis, Paris. Between 1903, when the first French case was recognized, and the end of 1911, when their manuscript was completed, over 200 cases of sporotrichosis had been diagnosed in France : these formed the material for the book, which is still the most comprehensive account of the disease that has been written [4]. Since the 1914–18 war sporotrichosis has become a rare disease in Europe, including France – the explanation of this change is unknown, for demonstrably pathogenic strains of the fungus are still present in French soil : perhaps it is the improvements in living standards, and in nutrition particularly, that are responsible (Mariat, 1963).

In contrast to the earlier predominance of European cases in the literature, most contemporary accounts of sporotrichosis come from the United States of America, Mexico and other American lands. In Mexico, for instance, sporotrichosis is the most frequent of all the deep-seated fungal infections (González Ochoa, 1954): on one day alone of a visit to a large general hospital in Mexico in 1966 I saw more than forty patients under treatment for confirmed sporotrichosis of the skin.

One of the most remarkable circumstances in the history of this fascinating disease is the recognition of its potential importance as an occupational disease. This has been a feature of the disease right from the first recognized case – Schenck's patient had scratched his finger on a nail while at his work in the iron trade – and ever since there has been a steady flow of reports of sporotrichosis following minor injuries at work, particularly among nursery employees, professional and amateur gardeners and agricultural workers liable to suffer penetrating wounds by spiny and thorny plants or to have other skin wounds contaminated by soil or other materials that may harbour the fungus in its saprophytic state. Brickmakers and

(3) Schenck became a gynaecologist and practised in Detroit. He died in 1920, aged 47.

(4) There is much in *Les Sporotrichoses* that is regarded today as controversial. This does not detract from the historical merits of the work.

pottery workers, and others who work with straw and the like, are similarly prone to the infection. But the most outstanding instance of occupational sporotrichosis is the outbreak in South Africa among the miners in the Witwatersrand gold mines: with the occurrence of several thousand cases within a period of only a few years it was no exaggeration to state that "the economic well-being of the gold mining industry, and indeed of the whole country, was threatened" (*Sporotrichosis Infection on Mines of the Witwatersrand: A Symposium*, 1947). Luckily, the disease was brought under control following chemical treatment of the mine timbers to render them resistant to saprophytic colonization by the sporothrix: its incidence among the miners is now a twentieth or less of what was the case when the outbreaks were at their height (Pringle, 1963).

Sporotrichosis in the British Isles

No cases of sporotrichosis that had been diagnosed in the British Isles were published until 1911[5]. In that year three cases were identified and reported – one by Norman Walker at the Royal Infirmary in Edinburgh (Walker and Ritchie, 1911)[6], one by Ernst von Ofenheim at St. John's Hospital in Lewisham (von Ofenheim, 1911) and one by H. G. Adamson at St. Bartholomew's Hospital, London (Adamson, 1910–11). These cases are included in the Table. Although these are the earliest published cases, others had in fact been diagnosed in the British Isles – in Ireland – before 1911 and confirmed by isolation of the sporothrix (see below).

Sporotrichosis in Ireland

The first published case of sporotrichosis in which the infection had been acquired in Ireland was reported in 1918 in the *Dublin Journal of Medical Science* by Wallace Beatty, honorary professor of dermatology in the University of Dublin and physician to the Adelaide Hospital in Dublin. Four years later the second Irish case was published by Adamson of St. Bartholomew's Hospital in London (Adamson, 1921–22). As far as I know, no further cases of Irish origin have been published until now: four Irish cases are recorded in the addendum to this paper. That other cases have been recognized in Ireland is indicated, I believe, by the following reminiscence of a medical student's Sunday in Belfast in 1935.

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(5) It is sometimes said that a case of sporotrichosis was studied in London in 1900 by Alexander Foulerton, then director of the Cancer Research Laboratories and lecturer in bacteriology and public health in Middlesex Hospital Medical School. This is incorrect: Foulerton's study, which was published in 1901, concerned a culture of the sporothrix that had been sent to him from the United States of America by Ludvig Hektoen, professor of pathology in Rush Medical College, Chicago. Hektoen had isolated the fungus in 1899 in cultures of pus from a child with ascending lymphangiitis who was under the care of C. F. Perkins, a practitioner in Shenandoah, Iowa. It was Hektoen and Perkins (1900-01) who gave the fungus the name, *Sporothrix schenckii*, by which it is now properly known. Their patient, it is interesting to note, was still in excellent health when seen in 1964, 65 years after being cured of his infection at the age of seven years (McFarland, 1966).

(6) Walker's secretary, Miss Rae, made a fine cast of this patient's infected arm, beautifully illustrating the typical clinical picture of the ascending lymphangiitic form of the disease. The cast has been familiar to generations of students of dermatology through the coloured reproduction included in Professor Percival's *Introduction to Dermatology* (Percival, 1956).

A Sunday Round in the North of Ireland in 1935[6a]

It was the custom of Surgeon T. S. Kirk[7], then senior surgeon to the Royal Victoria Hospital, Belfast, to take his son[8] and other students[9] on his Sunday morning visit to '9 and 10' at the Royal or to the Belfast Hospital for Sick Children. Often we were then taken to his home at 10, University Square, for lunch. On some of those Sunday afternoons Kirk would take one or more of us on his visits to country doctors and their patients. Sometimes the visits provided occasions for assisting at his operations in country hospitals or in patients' homes.

It was on such a round, in the summer of 1935, that I first saw a case of sporotrichosis. On the way to visit the patient, a farmer in County Armagh, Mr. Kirk explained what the disease was. He had been familiar with it since his student days in Belfast in the early 1890s, and had seen in all about six cases in the course of almost 45 years' experience in the North of Ireland. All but one of these cases seem to have been instances of the classic ascending lymphangiitic form of the infection; the exception had presented with disseminated subcutaneous granulomas (a form of sporotrichosis frequent among the cases studied by de Beurmann and Gougerot in France between 1903 and 1911 but otherwise rarely recorded). Most, if not all, of Kirk's patients were countrymen, and about half of them gave a history of running a thorn deeply into the skin at the site of the initial lesion. The first patient whom he saw was a road-mender from near Ligoniel whose ulcers he had attended to over a period of months while a dresser in the Extern Department of the old Royal Hospital in Frederick Street, Belfast: this was before he graduated in Medicine in the Royal University of Ireland in 1893 (Schenck, whose original publication appeared in 1898, saw the disease first in 1896). Mr. Kirk did not discover the nature of the disease until the sporothrix was cultured from the lesions of his third patient by my father "not long after he came to Belfast"[10]: this patient was quickly healed with iodide of potassium by mouth.

The case of the patient whom we visited on that Sunday in 1935 is included in the addendum to this paper (Case 1). When seen then he had been on treatment with iodide for two weeks and the lesions were healing well: their distribution along a line of subcutaneous lymphatics in the forearm and upper arm was so striking that it seemed unlikely that the diagnosis would be overlooked when next a patient with this condition was seen. It was 19 years before I again saw such a patient (addendum, Case 2).

After our drive Surgeon Kirk came to my parents' home in Wellington Park for tea. As on most Sunday afternoons after my father's retirement, Professor R. M. Henry[11], then still Professor of Latin in the Queen's University, had dropped in for a chat with my father. On this occasion he was accompanied by his brother,

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(6a) This account is taken from notes made at the time.

(7) Thomas Sinclair Kirk (1869-1940).

(8) Christopher Kirk, now in practice in Dunedin, Otago, New Zealand.

(9) T. T. Baird, now working in Belfast, C. R. Murdock (1914-1968), and I were the most frequent of Surgeon Kirk's guests on these occasions, which gave added reality and purpose to our preclinical years at Queen's University, 1934-36.

(10) William St. Clair Symmers (1863-1937). He came to the Musgrave Chair of Pathology in Queen's College, Belfast, in 1904 and retired in 1930.

(11) Robert Mitchell Henry (1873-1951).

Paul[12], the Irish landscape artist. Conversation turned to the day's surgical round and Surgeon Kirk referred again to the case of sporotrichosis that he and my father had investigated together some thirty years earlier. My father recalled five or six further cases that had been proved by culture or animal inoculation during the 26 years he had spent in the pathology laboratories in Belfast. All but one of the patients had worked on farms or in gardens, and at least three had blamed the infection on deep pricks by gorse or barbery spines: one of these was a gardener who worked for a Queen's University professor living in Gilnahirk and one was a retired military man who lived in Windsor Avenue and was well known as an amateur gardener. The patient who had no particular association with the land was a schoolboy with sporotrichosis of the eye (Case 4 in the addendum).

Although the Henry brothers were not medical men, they had a remarkable knowledge of Irish lore relating to illness and folk remedies. R. M. Henry spoke that afternoon of cases he had seen of a skin disease that exactly fitted the description of the ascending lymphangiitic form of sporotrichosis: this condition had been familiar to him during his boyhood, in the 1880s, as a rare affection among country people, including fishermen on the coast, in parts of the West, North-West and North of Ireland. Paul Henry mentioned that the traditional way to treat this ulcerative disease was to apply compresses of kelp or of boiled seaweeds and to take a decoction of dulse (*Rhodymenia palmata,* the common Irish edible seaweed) internally over many weeks, until healing resulted. The efficacy of such treatment could have been due to the iodine content of the seaweeds, if, as seems to be quite possible, the disease was indeed sporotrichosis.

As far as I have been able to find out, thirty years after that Sunday tea, and three-quarters of a century after the Henry brothers knew of the condition, no disease with such manifestations is now known in any parts of Ireland, either to doctors or among the country and fishing people themselves. It would be interesting to hear if readers of the *Journal* have seen any cases of sporotrichosis in Ireland. The remarkable fall in the frequency of cases of this disease in some lands, *e.g.,* France, has been referred to already: it is possible that something comparable has occurred in Ireland.

Summary

Altogether only 16 cases of sporotrichosis diagnosed in the British Isles have been published. In at least 5 of these the infection was acquired in some other part of the world. Of the rest, 6 originated in Ireland, including 4 cases that are reported for the first time in the addendum to this paper. Reference is also made to unpublished Irish cases of which no formal records are now known to exist.

Acknowledgements

In addition to the acknowledgements that are indicated by the text of the paper and its addendum to be due to my teachers and old friends named here, I want to mention my appreciation of the kindness of the late Dr. Ivan H. McCaw of Belfast and of the late Dr. J. E. M. Wigley of London, who took over clinical care of two of the patients (Cases 2 ond 3 respectively) and who permitted publication of their clinical observations. I am also indebted to Professor Raymond Vanbreuseghem of Antwerp and to Dr. Jacqueline Walker of London for advice about the cultures in Cases 2 and 3.

Mr. R. S. Barnett helped with the preparation of the photomicrographs.

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[12] Paul Henry (1880-1958).

FOOTNOTES TO TABLE OVERLEAF

(a) This table includes only those cases of sporotrichosis diagnosed in the British Isles that have been formally published. The diagnosis has been made correctly in a number of cases that have not been reported, *e.g.*, Surgeon Kirk's and my father's cases of sporotrichosis acquired in Ireland (see text, pages 89 and 90). A more recent case of sporotrichosis acquired in England was recognized by Dr. A. J. Rook at Addenbrooke's Hospital, Cambridge, in 1964. My own unpublished cases include (*a*) subungual sporotrichosis acquired in Warwickshire by a woman who walked into a hedgehog in the dark while wearing sandals, one of the animal's spines running under the nail, (*b*) localized cutaneous sporotrichosis acquired in Hertfordshire by an amateur gardener who ran a barbery spine into one hand, and (*c*) two more cases of cutaneous sporotrichosis originating in Africa (one in the Congo and one in Malawi – the cases included in a published table of African mycoses seen in Britain [Symmers, 1966c]).

I know of only one case of sporotrichotic infection in an animal in the British Isles – a railway rat-catcher's ferret (Symmers, 1964a). Sporotrichosis appears to be rare in animals; most of the published instances have concerned horses (Ainsworth and Austwick, 1959).

(b) Several of the earlier cases in this table were reported in more or less detail in two or more publications. Only the most important reference is given here in each case.

(c) The case reported by Greig is the first on record of sporotrichosis acquired anywhere on the African mainland (a case had been reported from Madagascar by Carougeau in 1909). No further South African cases were reported until 1927, when Pijper and Pullinger described the first recognized outbreak in the gold mines (see text, page 88).

(d) Bass is a traditional name for various hard vegetable fibres used in the manufacture of coarse brushes, matting, and similar articles.

(e) It is tantalizing that Gray and Bamber did not enlarge upon the history of their patient's infection. They give no indication about her occupation or where she was when she was bitten by the boa-constrictor. Presumably the animal was in a zoo; they noted that it subsequently died from 'canker' of the mouth. I know of no records of sporotrichosis in cold-blooded animals.

CASE REPORTS

Case 1[13]

A middle-aged farmer ran a gorse spine into the ball of a thumb while clearing scrub from a field on his home farm in County Armagh in 1935. Part of the spine broke off under the skin and his efforts to squeeze it out failed. A painful, firm swelling formed round the foreign body, with reddening of the skin over it and a constant, thin and slightly bloody discharge from the puncture wound. A fortnight later the farmer went to his family doctor, who opened the sinus with a scalpel and removed the gorse spine. The doctor gave no other treatment, apart from ordering the wound to be dressed with a paste of magnesium sulphate in glycerol. The wound healed after a few days, but a tender nodule persisted deep to it. During the following three weeks or so the patient noticed the development of further nodules in the skin over the radial aspect of the wrist and up the forearm towards the fold of the elbow. These nodules, including the one at the site of the initial lesion, enlarged and became ulcerated, and within three months of the accident there was a series of shallow ulcers extending from the thenar eminence up the lateral aspect of the forearm, across the antecubital fossa and half way up the medial aspect of the upper arm. The ulcers ranged between one and three centimetres across and were a millimetre or so deep, with a moist, red base and a flush

(13) This is the case of Surgeon Kirk's patient referred to in the text of this paper (page 89).

TABLE

Published Cases of Sporotrichosis Diagnosed in the British Isles[a]

Chronological Order	Reference[b]	Country where Infected	Sex, Age (yrs.) and Occupation	Means of Infection	Form of Disease	Method of Diagnosis	Duration of Symptoms at Time of Diagnosis	Treatment	Outcome
1	Walker and Ritchie (1911)	England (Cumberland)	M 46 Iron ore handler	Bruised finger with limestone	Ascending lymphangiitic	Culture Inoculation of mice	5½ months	Potassium iodide by mouth	Recovery
2	Von Ofenheim (1911)	Not known	F 19	Not known	Subcutaneous abscess (retro-auricular); osteitis (tibial)	Culture	5 months	Surgical drainage	Not known
3	Adamson (1910-11)	Brazil	M 50 Labourer	Injury to thumb	Ascending lymphangiitic	Culture	2 months	Potassium iodide	Recovery
4	Adamson (1912-13)	England (London)	F 60	Not known	Disseminated subcutaneous 'gummas', with ulceration [Synovitis also, possibly a side-effect of iodotherapy]	Culture	2 years	Potassium iodide	Recovery
5	Adamson (1913)	U.S.A.	M 60 Publican	Not known	Disseminated ulcerative and verrucose cutaneous (simulating North American blastomycosis)	Culture	6 months	Potassium iodide	Recovery
6	Greig (1917)	South Africa (Vaal River, near Kimberley)[c]	M 39 Diamond miner	Cut finger	Subcutaneous abscess (chest and axilla)	Culture	2¼ years	Potassium iodide	Recovery
7	Beatty (1918)	Ireland (Dublin)	M 15½ Handling African bass[d] in brush factory	Accidentally pricking a pimple with piece of bass[d]	Ascending lymphangiitic	Culture	2 months	Not known	Not known

8	Adamson (1921-22)	Ireland (Dublin)	F 37	Not known	Cribriform ulcers of both legs	Culture	6 months	Iodine ('Iodeol') by mouth	Healing
9	Gray and Bamber (1931-32)	Not known	F 43	Bitten on wrist by boa-constrictor[e]	Lymphangiitic	Culture	7 weeks	Not known	Not known
10	Banks (1946)	England	F 11 mths	Not known	Membranous rhinitis and pharyngitis (simulating diphtheria); conjunctivitis; ulcerative keratitis	Culture	6 weeks	Potassium iodide; sulphon-amides	Toxaemia and death
11	Symmers (1966b): Case 11	France	M 48 Farmer and veterinary surgeon	Contact with infected horse. No remembered injury	Lymphangiitic	Culture. Sporothrix asteroids in histological sections	4 weeks	Potassium iodide	Recovery
12	Symmers (1966b): Case 12	Kenya	M 2	Not known	Facial granulomas with early ulceration	Sporothrix demon-strated in histological sections by specific immunofluorescent staining	1 year	Potassium iodide	Recovery
13	Symmers: this paper, Case 1	Ireland (County Armagh)	M Middle-age Farmer	Spine of gorse *(Ulex)* ran into thumb	Ascending lymphangiitic	Culture	3 months	Potassium iodide	Recovery
14	Symmers: this paper, Case 2	Ireland (County Dublin)	M 24 Student of law	Wound by rose thorn	Ascending lymphangiitic	Culture	3 years	Potassium iodide	Recovery
15	Symmers: this paper, Case 3	Ireland (Co. Fer-managh)	M Young adult Poacher and labourer	Wound by hook used in catching song-birds	Solitary ulcer of skin	Culture. Sporothrix asteroid in histological section	4 months	Potassium iodide	Recovery
16	Symmers: this paper, Case 4	Ireland (Belfast)	M 12	Injury to eye by sago or similar pellet	Panophthalmia	Culture	6 weeks	Removal of eye	No recurrence

(See page 91 for footnotes)

or slightly raised edge. There was induration of the tissues immediately deep to and around the ulcers, and the adjacent skin had a cyanotic appearance. It was at this stage that Mr. Kirk had been asked to see the patient and made the diagnosis of sporotrichosis. This was confirmed by the isolation of the sporothrix from the ulcers by Dr. J. C. Rankin[14], whose many practical interests in addition to being head of the Electric and V.D. Departments at the Royal Victoria Hospital, Belfast, included medical mycology (he kept a fascinating collection of fungal cultures in a small laboratory in his home on University Road, opposite the University).

Mr. Kirk's initial treatment was to dress the ulcers with urea crystals and to give the patient compressed tablets of normal horse serum by mouth. When this proved to have little effect he prescribed large doses of potassium iodide by mouth, and within a month the lesions were well healed, leaving conspicuously pigmented scars.

Comment. This was a classic case of the ascending lymphangiitic form of sporotrichosis (see also Case 2), starting with a puncture wound by a spine of a plant, initial healing of the primary lesion being followed by recurrence at its site and the formation of nodules along the course of the subcutaneous lymphatic vessels and the eventual ulceration of these secondary foci. It is noteworthy that the lesions of sporotrichosis of a limb seldom extend right up to the axilla or groin. Clinically apparent involvement of the lymph nodes is exceptional in sporotrichosis of a limb although not infrequent when the initial lesion is on the trunk or head.

The source of infection in cases such as this is clearly the penetrating foreign body, presumably contaminated by the sporothrix which is present in the environment in its saprophytic state. Infection seems as likely to result from the injury whether or not the foreign body remains implanted in the tissues.

Once the diagnosis is suspected it is quite easily confirmed, culture of the fungus seldom presenting much difficulty provided bacterial contamination can be avoided. Swabs of the ulcers are usually contaminated and therefore material aspirated from unulcerated nodules is preferable. Serological tests and skin tests have little place in the diagnosis of sporotrichosis. Even histological examination – so often the means to the diagnosis of other fungal infections of the dermis and subcutaneous tissue – has little to offer because of the rarity with which the sporothrix can be demonstrated in sections of infected tissues.

Untreated, the disease may persist indefinitely, its tendency to heal balanced by reactivation of the lesions. In most cases the full extent of the infection is reached within a comparatively short time of its onset: however long the condition remains active thereafter it has little or no tendency to spread farther. Treatment with iodide in large doses by mouth is immediately effective in most cases and results in rapid and permanent healing, provided the treatment is continued for several weeks after clinical cure has been achieved. When iodide fails or when the individual patient is unable to tolerate the treatment other methods may be tried. Some authorities still advocate parenteral administration of organic arsenicals – neoarsphenamine or oxophenarsine. Neither sulphonamides nor the antibacterial antibiotics are effective against the sporothrix, and those cases that do not respond to other drugs must be treated with the antifungal antibiotic, amphotericin B, a drug that has to be administered with particular discretion on account of its potentially dangerous side effects.

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[14] John Campbell Rankin (1876-1954).

Case 2

A law student, aged 24, cornered a pathologist at a party in London and quickly overcame the latter's reluctance to listen to a socially inopportune story of ill-health by giving such a typical account of sporotrichotic lymphangiitis that even from the history alone the nature of the condition could scarcely be doubted. He described how, three years before, in 1951, he had torn the skin of the medial edge of his right hand on a thorn while pruning rose bushes in a relative's garden in County Dublin. The wound was about three centimetres long and no more than skin deep, except at the end where the thorn had dug well into the tissues. He painted the site at once with 'tincture of iodine'. After a few days it began to fester and induration developed in a zone about a centimetre and a half wide on each side. By the end of a week the wound had become a linear ulcer with a bright red floor and a soft, slightly undermined, purplish margin that bled easily when touched. The ulcer enlarged slowly and three or four small nodules appeared in the skin between it and the wrist. One of these nodules developed into an ulcer like that at the site of the wound; the others disappeared.

During the nine months following the injury a succession of nodules formed in the subcutaneous tissue along the line of the lymphatic vessels of the extensor and medial aspects of the forearm and in the antecubital fossa and for a short distance above the elbow along the medial aspect of the arm. The nodules broke down, discharging a small amount of blood-stained matter and becoming transformed into chronic ulcers. There was considerable induration of the tissues between the ulcers. Pain was not troublesome and the patient suffered little physical discomfort. He lost seven kilograms in weight during the first year or so of the illness but after that his weight was steady. His general health was scarcely disturbed. By the end of the first year the disease had reached its greatest extent: there was little change in the lesions during the following two years, apart from a tendency to heal over, with some scarring, and then break down again. From time to time he noticed transient enlargement of lymph nodes in the right axilla.

The patient saw a succession of doctors during these three years. Various diagnoses were suggested, including syphilis, tuberculosis, angiosarcoma, malignant melanoma and mycosis fungoides. One surgeon considered the lesions to be self-induced, the result of stubbing lighted cigarettes on the skin; he recommended psychiatric treatment, but the psychiatrist referred the patient back with the dry comment that a physical cause should be sought for a physical malady. Biopsy specimens were taken on three occasions: each time the histological picture was merely that of a simple, unspecific, ulcerative inflammatory reaction; no micro-organisms were seen either in the sections or in stained films of the exudate from the ulcers. Swabs from the lesions were cultured on several occasions: these yielded growths of various bacteria, among them *Staphylococcus aureus, Proteus vulgaris* and *Pseudomonas pyocyanea,* but treatment with appropriate antibiotics never had more than a slight and transitory beneficial effect on the condition. Two of the biopsy specimens were also cultured: both were reported as sterile, although the laboratory records were later found to include a note that one of the specimens gave a growth of a "peculiar yeast-like fungus, presumably a contaminant" that was not investigated further.

By the time when the patient was introduced to the pathologist at the party he

had begun to regard his disease as beyond both diagnosis and cure. A week later the diagnosis of sporotrichosis had been confirmed by isolation of *Sporothrix schenckii* from an unulcerated nodule freshly excised from the forearm. Three weeks after this, following administration of 300 grams of sodium iodide by mouth (5 grams thrice daily), all the ulcers had become completely covered by epithelium and the inflammatory induration was subsiding. Treatment with iodide was continued for a further month at the same dosage, and then withdrawn by progressively reducing the dose during one more week.

There has been no recurrence of the disease during the period of almost 14 years since the diagnosis was made. The site of the lesions is marked by extensive and very unsightly scarring and pigmentation of the skin.

Comment. The initiation of this patient's disease by a wound while working in a garden, with the subsequent development of ulcerating nodules along the lymphatics, ought to have indicated the diagnosis at once. The only condition clinically simulating sporotrichosis that might arise from a similar 'garden' wound is the rare lymphangiitic form of infection by *Nocardia brasiliensis,* an actinomycete of tropical and subtropical lands that ordinarily causes mycetomas resembling 'Madura foot' and that has not been recognized as occurring naturally in the British Isles. The long failure to recognize the presence of sporotrichosis in this patient's case can be explained only by his doctors' unfamiliarity with the disease.

The various bacteria grown from the ulcers are to be regarded as secondary invaders. The 'peculiar yeast-like fungus' that was grown from one of the biopsy specimens may well have been no more than what it was at the time considered to be, a contaminant – but it may have been the sporothrix itself. It is always advisable to regard any fungus isolated from any specimen as possibly pathogenic until the opposite has been adequately established after consideration of all the clinical circumstances.

In view of the efficacy of oral administration of sodium iodide in the treatment of the infection it is of interest that the use of an iodide-containing iodine solution as a first-aid application to the initial wound seems to have had no inhibitory effect on the development of the infection. However, it is relevant that nothing is known about how iodotherapy works in overcoming sporotrichosis – it is possible that the effect of iodide is primarily on the infected tissues of the host rather than on the infecting organism itself.

Case 3

An Irish labourer was referred to hospital in London for treatment of a chronic ulcer on the right side of his chest. The ulcer had been present for almost four months. It began while he was living in County Fermanagh: he was catching blackbirds on lines of baited hooks laid among bushes when he was spied by a party of bird-watching Boy Scouts – while running away from them through shrubbery he got entangled in one of his lines and a hook lodged in his side. That evening he removed the hook, a barbed one, in the traditional way, cutting its haft and pushing the point onward and out. The resulting wound did not heal: after about two months it had become an ulcer, some three centimetres in diameter and two or three millimetres deep. The ulcer was at the centre of an indurated area about seven centimetres across. Having reached these dimensions the lesion did not change appreciably in size or appearance.

The disease was well established when the patient left Ireland for the first time and went to work in England, a month before he was seen at the hospital. He took a job on a building site in London: as it was outdoor work in warm autumn weather he stripped to the waist. Other men on the site, seeing the ulcer, took him to have some sort of venereal disease, refused to work alongside him, and downed tools. He left the job. A few days later he went to a doctor who sent him to hospital with the clinical diagnosis of carcinoma of the skin.

Clinical and serological investigations at the hospital showed no evidence of syphilis or other venereal diseases. A wedge of tissue was excised from the edge of the ulcer: histological examination showed chronic suppuration, tuberculoid foci, suppurating pseudotubercles (Symmers, 1960) and fibrosis – the possibility of sporotrichosis was indicated by the finding of a characteristic sporothrix asteroid in the pus at the centre of a suppurating pseudotubercle (Fig. 2); there was no

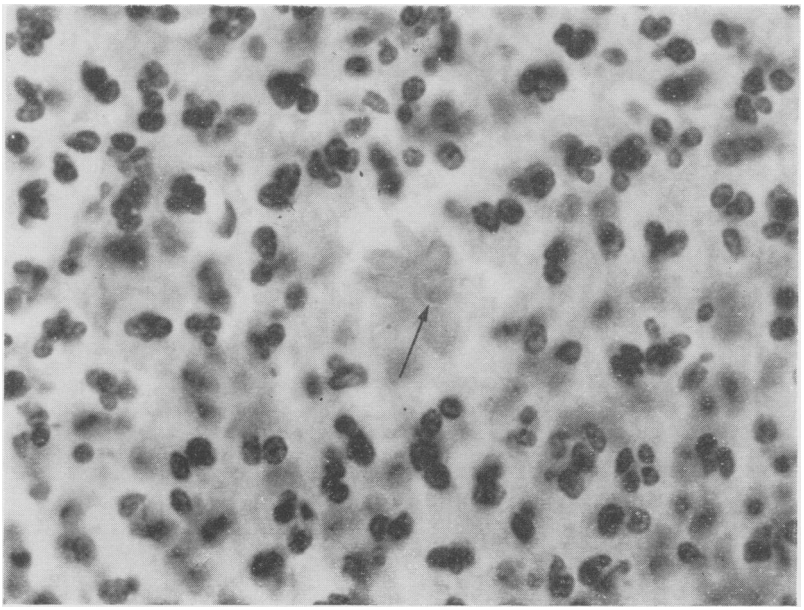

FIG. 2. *Sporothrix asteroid. The fungal cell is arrowed, lying almost buried in a cup in the hyaline, palely stained deposit of radially disposed coagulum occupying the clear centre of this collection of neutrophile leukocytes. Haematoxylin-eosin.* x *1,000.*

evidence of any neoplastic condition. Only diphtheroid bacilli and nonpathogenic staphylococci were grown from swabs of the surface of the ulcer. Further material for culture was then obtained by needle aspiration through intact skin just outside the margin of the ulcer: *Sporothrix schenckii* was isolated from this specimen.

Treatment with large doses of potassium iodide by mouth resulted in healing of the lesion within four weeks. As a precaution against relapse the treatment was continued for six weeks after the ulcer had become completely covered by epithelium. When last seen, four years later, the patient had had no further symptoms and his only complaint was of the unsightliness of the rather puckered and heavily pigmented scar.

Comment. Clinically this was a typical example of a solitary sporotrichotic lesion. In such cases the correct diagnosis is likely to be made only if the clinician thinks of the possibility of sporotrichosis, or if – as in this patient's case – a lucky chance leads to detection of the fungus in the course of laboratory investigations.

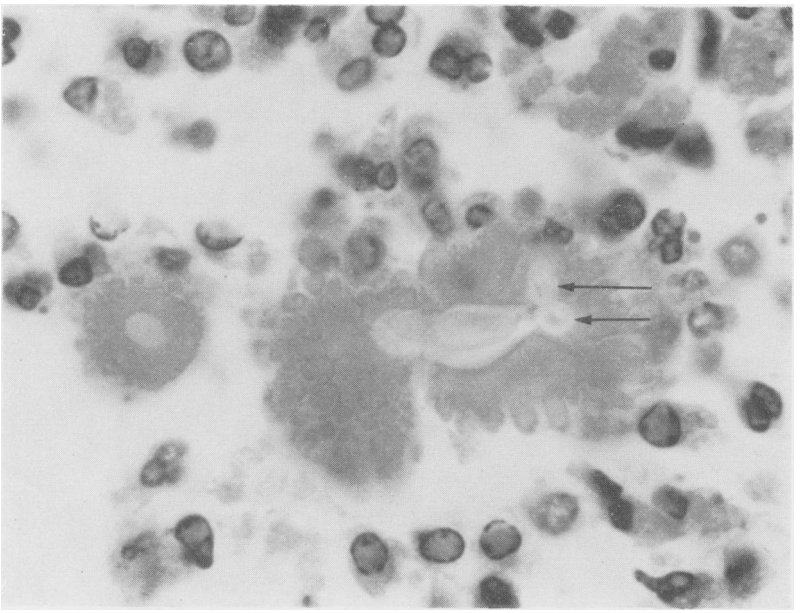

FIG. 3. *Candida asteroids for comparison with the sporothrix asteroid in Fig. 2. The smaller asteroid is indistinguishable from a sporothrix asteroid. The larger one shows the development of the elongated and segmented pseudohypha from the arrowed candida spores. The radially patterned mass of hyaline coagulum formed from the inflammatory exudate is readily seen. (From an unpublished case of chronic* Candida albicans *septicaemia.) Haematoxylin-eosin.* x *1,000.*

In general, biopsy is to be avoided in cases of sporotrichosis. Biopsy wounds are liable to heal slowly, particularly if treatment is delayed, and this may increase the unsightliness of the inevitable scarring that accompanies recovery from the infection. Also, unlike other deep-seated fungal infections, sporotrichosis is characterized by the difficulty of demonstrating the causative fungus in tissue sections (or, for that matter, in stained films of exudate), even with the help of the special staining methods that are in general use for showing the presence of fungi[15]. In exceptional cases the sporothrix is found in the form of the so-called asteroid: this consists of a hyaline, eosinophile complex of fibrin and globulin derived from the

(15) It is now possible to demonstrate and specifically identify certain fungi, including *Sporothrix schenckii,* in tissues by treating histological sections with the appropriate specific antiserum in which the antibodies to the fungus have been labelled with the fluorescent dye, uranin (fluorescein). The labelled antibody becomes attached to the fungal elements in the infected tissue and these can be recognized by their fluorescence when the section is examined microscopically in ultraviolet light (Kaplan and Ivens, 1960). The method is not available outside specialist laboratories.

inflammatory exudate in the host's tissues and deposited with a more or less well marked radial orientation on the surface of the fungal cell (Fig. 2). These asteroids are easily seen in haematoxylin-eosin preparations. A comparable reaction takes place in some other conditions, *e.g.*, in the formation of the 'clubs' at the surface of the colonial grains of *Actinomyces israelii* and *Streptomyces madurae*, round the hyphae of the fungi responsible for subcutaneous phycomycetosis, and round some metazoan ova in the tissues. However, none of these structures is likely to be confused with the sporothrix asteroid: in contrast, the asteroid of certain cases of coccidioidomycosis and of exceptional cases of septicaemic candidosis may be sufficiently like the sporothrix asteroid to be mistaken for it – of these candidosis is obviously the one that might cause confusion in practice in the British Isles (coccidioidomycosis does not occur here naturally [Symmers, 1967a]). In candida asteroids the fungi are present both in yeast-like form and as pseudohyphae (Berge and Kaplan, 1966–67): the latter (Fig. 3) do not occur in sporotrichosis, a point that should be valuable in distinguishing between sporothrix and candida asteroids. These fungal asteroids are, of course, quite distinct from the finely radiating structures in the multinucleate giant cells of some cases of sarcoidosis and other tuberculoid granulomas that have also been referred to as asteroids (Symmers, 1966a): the fungal asteroid always has a demonstrable fungal cell at its centre, and nothing likely to be confused with this is present in the asteroid of tuberculoid giant cells.

In view of the circumstances in which this patient acquired his infection it is worth noting that there is no evidence that birds play any part in the ecology of the sporothrix or in the aetiology of sporotrichosis, as they unquestionably may do in relation to histoplasmosis (Ajello, 1967) and cryptococcosis (Symmers, 1967b). In the case under discussion it is probable that the hooks used to catch birds were contaminated by the fungus through contact with the shrubs in which the lines were laid.

Case 4[16]

A 12-year-old boy, while at school in Belfast in 1929, was hit in the right eye by a pellet of sago or the like projected from a 'pluffer'[17]. The point of impact was on the sclera, a few millimetres lateral to the limbus. The injury caused a small haemorrhage into the conjunctiva. Generalized conjunctivitis developed during the next week, with very marked hyperaemia and considerable oedema. This reaction was greatest over the injured area, and a small superficial ulcer appeared at the site of impact. The ulcer had a yellow base and was surrounded by a ring of particularly intense hyperaemia. There was some mucopurulent exudate in the conjunctival sac. The family doctor advised frequent bathing with a boric acid lotion and

(16) This report has been compiled from contemporary notes of observations by Mr. James Craig, Sir Thomas Houston and my father.

(17) The 'pluffer' was standard pocket armament among otherwise reasonably responsible children in some schools in Belfast, and doubtless elsewhere, possibly under other names, at the end of the 1920s. For all I know, it still may be so. It was a straight piece of laboratory glass tubing, five to ten centimetres long and of a bore little larger than the the average grain of sago, barley or rice, which was the usual ammunition. The propellant was air, forcibly expelled from the mouth into the loaded end of the tube, which was held in the lips and aimed in the general direction of blackboard, windows, lamps or schoolfellows.

instillation of silver nitrate solution. Two weeks after the injury much of the generalized conjunctival reaction had subsided. In contrast, the ulcer had enlarged to about five millimetres in diameter and there was well-marked circumcorneal vasodilatation. The child complained increasingly of pain in the eye and blurring of vision.

Four weeks after the injury the patient was admitted to hospital and was seen for the first time by an oculist (Mr. James Craig [18]), who found that the inflammation had extended into the bulb of the eye: there was severe, generalized iridocyclitis, a hypopyon and clouding of the cornea. The disease progressed: two weeks after admission to hospital the eye was excised because its disorganization had advanced so far that clearly there was no possibility of its sight being recovered, and because of the risk of sympathetic ophthalmia.

The eye was examined in the fresh state in the laboratory by Sir Thomas Houston[19] and my father. Cultures gave a pure growth of *Sporothrix schenckii;* the identification of the fungus was confirmed by Henri Gougerot, then *professeur de clinique des maladies cutanées et syphilitiques* in the Faculty of Medicine of Paris, to whom subcultures were sent[20]. No micro-organisms were found in histological sections of the eye; the sections showed much of the normal structure to have been replaced by chronic suppurative and tuberculoid granulomatous tissue.

The post-operative course was uneventful. There was no evidence of residual infection of the orbit, and the disease did not recur.

Comment. The source of the infection in this child's case is uncertain. The missile that struck the eye may have carried the fungus, or the latter may have been a subsequent invader of the injured tissue. Sir Thomas investigated the fungal flora of several samples of sago, rice and barley that had been carried by schoolboys as ammunition for their pluffers: he found several varieties of moulds, including two strains of *Sporotrichum.* Neither of these sporotricha had the characteristics of *Sporothrix schenckii* or was pathogenic to guinea-pigs or rabbits, and both were therefore classed as examples of commonplace saprophytic species.

The patient was a town boy, living in a gardenless part of the city and with none of the pursuits that might have carried a particular risk of exposure to infection by fungi in soil or on plants or other vegetable matter. He seldom went into the country, and he did not often take part in outdoor games.

Ocular sporotrichosis occurs frequently enough to need particular notice among the fungal infections that involve the eyes. Nevertheless, it is rare, and appreciably rarer than, for instance, mycotic keratitis due to various species of *Aspergillus* (Gingrich, 1962). The most recent review of ocular sporotrichosis dates from 1947, when Gordon analysed 48 published cases that had been so diagnosed: in about a third of these cases the ocular infection was secondary to sporotrichosis elsewhere in the body. Only six of the 48 patients in the series reviewed by Gordon suffered involvement of the interior of the eye.

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(18) James Andrew Craig (1872-1958), ophthalmic surgeon, Royal Victoria Hospital, Belfast.

(19) Sir Thomas Houston (1868-1949), clinical pathologist, Royal Victoria Hospital, Belfast.

(20) Gougerot, whose collaboration with de Beurmann in the early days of the history of this disease has already been mentioned (page 87), remained interested in sporotrichosis throughout his life. In 1947, at the first conference on medical mycology to be held in the United States of America, he summarized over forty years' personal experience of the disease (Gougerot, 1950). He died in 1955, aged 73.

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DIATHERMY CONING IN THE TREATMENT OF NON-MALIGNANT CONDITIONS OF THE CERVIX

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JOBERT DE LAMBALLE (1843) advocated and practised treatment of the eroded cervix by cauterisation using a glowing iron; he noted that the procedure was painless. Later, Brandes (1846) in Germany popularized the method, using a wooden or ivory speculum to avoid burning the vaginal epithelium and followed the cauterisation by a douche of cold water.

In more recent years various methods of chemical cauterisation have been recommended, but they have never been as popular as the actual cautery. Hunner (1906) suggested treating cervical lesions with deep radial cauterisation, and Dickinson (1911) used a fine nasal tip cautery to produce the same effect. Hyams (1933) reported on the use of an electrosurgical cutting and coagulation technique which has been termed 'diathermy coning of the cervix'.

The present study deals with 100 patients with chronic cervicitis treated by this technique in the Royal Victoria Hospital, Belfast, from January 1964 to June 1965.

Selection of Patients

McLaren (1955) emphasized the difficulty of differentiating between the simple non-infected erosion of the cervix and chronic cervicitis. He suggested, however, that the combination of symptoms, signs and cervical biopsy will usually indicate the type of lesion present and Pinkerton (1963) considered that chronic cervicitis is a common symptom complex consisting of vaginal discharge, deep dyspareunia, lumbo-sacral backache and occasionally recurrent attacks of cystitis.

The majority of patients were seen at the gynaecological out-patient department and many had more than one complaint (Table I). In two patients the cervical lesion was an incidental finding – one patient had a Bartholin's abscess and the other was referred for tubal ligation; 9 patients were referred for treatment from the Royal Maternity Hospital with postpartum cervical erosions; 4 patients complaining of vaginal discharge were taking oral contraceptives.

Table I

Symptom	*Before operation*	*After operation*	*Percentage cured*
Vaginal discharge	80	4	95
Low backache	31	10	60
Intermenstrual bleeding (or bleeding following coitus)	15	1	93
Deep dyspareunia	12	6	50
Urinary symptoms	5	3	40
Menorrhagia	10	6	40

In every patient a Cusco's speculum was passed and the cervix inspected. The characteristics associated with chronic cervicitis are cervical erosion with contact bleeding, hypertrophy of the cervix, Nabothian follicles, laceration and ectropion, polyps and muco-purulent discharge.

A cervical smear was routinely taken for cytological examination but in no case were malignant cells found. Bimanual examination was then performed and in each case the cervix was lifted upwards and forwards, and the utero-sacral ligaments examined for thickening and tenderness (Pinkerton 1963).

Twenty-five patients were between the ages of 21 and 30 years, 44 between 31 and 40, and the remaining 31 were over 40 years of age. The distribution of the cases in respect of parity was – 3 nulliparous, 18 primiparous, 56 between 2–5 parity and 23 were more than para 5.

Technique of Operation

All patients were admitted to hospital the day before operation. The anaesthetised patient was placed in the lithotomy position. A weighted Sims' speculum was introduced into the vagina and the anterior lip of cervix grasped with volsellum forceps. The cervix and vagina were painted with Lugol's iodine solution.

Three sizes of Hyam's diathermy electrode were available and after examination of the anatomical characteristics of the cervix the most suitable 'loop' was chosen, to ensure that the cone removed would include areas of the ecto-cervix which were eroded or showed a positive Schiller test. The current was switched on and the electrode inserted into the cervical canal up to the proximal shoulder of the loop which was then rotated through 360° in a continuous movement, thus removing a cone of cervical tissue. Bleeding points in the coned area were coagulated as necessary with a ball electrode. An endometrial biopsy was usually taken, but only in those cases where an indication existed was full curettage performed. The internal cervical os, however, was always dilated up to 10 or 12 mm. using Hegar's dilators; this is regarded as important in preventing subsequent cervical stenosis. Triple sulpha cream was now inserted into the cervical crater by means of a sterile vaginal applicator. The coned out portion of the cervix was placed in fixative and sent for histological examination.

All patients remained in hospital for 3 days postoperatively. They were warned to expect some vaginal bleeding and discharge for up to 3 weeks after leaving hospital, and were told to seek medical advice if bleeding was excessive.

Results

The patients were reviewed 6 weeks after operation. Ninety-four attended, and in all the cervix was fully epithelialised. Seventy-four had no symptoms, and the complaints of the remaining 20 patients are shown in Table I.

Postoperative Complications

Secondary haemorrhage occurred in 5 patients, two requiring admission to hospital. Cervical stenosis did not occur in any case.

Pregnancy ensued in 10 patients within 18 months of operation and 9 of them had normal deliveries at term. The average duration of labour in this group was not prolonged. The remaining case is reported below.

Case Report: Mrs. R.S., a 30-year-old gravida 3, para 2, had diathermy coning performed for complaints of vaginal discharge and dyspareunia. Two previous pregnancies had terminated with normal deliveries after short labours. She became pregnant again 9 months after operation. The pregnancy was uneventful until the onset of labour one week before the expected date of confinement. At examination after 6 hours of established labour the cervix had failed to dilate and was noted to be thick and scarred. A lower segment caesarean section was performed and a living 8 lb. infant delivered.

Discussion

These results demonstrate clearly that diathermy coning of the cervix is an effective method of treating the chronically infected and eroded cervix. Symptomatically the cure rate varies with each complain. Vaginal discharge and intermenstrual bleeding were, as might have been expected, most often cured.

In contrast to most cervical amputations, particularly the Sturmdorf operation, this procedure is almost bloodless and primary haemorrhage is not a problem. The procedure is not, however, without drawbacks, and on review of this small series some important side effects have been observed.

There were 5 patients with secondary haemorrhage, all occurring 8–14 days postoperatively. In 3 of these no active bleeding was noted at the time the cervix was inspected, and treatment was unnecessary. In the remaining 2 cases a general ooze was seen to be coming from the healing cervix. Both patients were admitted to hospital and vaginal packs were inserted for 24 hours. The bleeding ceased without further intervention.

Many cases of cervical stenosis have been reported following diathermy coning. Millar and Todd (1938) reported an incidence of 6.42 per cent, while Schulman and Ferguson (1962) reported 3.5 per cent, and Hester and Reid (1960) 7 per cent, the latter using the cold knife method. Cashman (1945) used deep cauterisation of the cervix and emphasised the importance of cervical dilatation after operation to prevent stricture of the cervix. Harer (1959) stressed the importance of sounding of the cervix for stricture at the 6 weeks follow-up examination. Beard (1964) considered the cervical canal 'stenosed' if a No. 3 Hegar dilator could not be introduced 6 weeks after the operation. Using this criteria he found 7 patients out of 50 who had undergone coning of the cervix, to have cervical stenosis, but in only one of these was there a minor disturbance of menstrual function. In this series of 100 patients dilators were not passed, but there was no evidence of cervical stenosis on macroscopic examination of the cervix, nor was there any complaint suggestive of menstrual obstruction; if menstrual flow is not disturbed it is unlikely that cervical stenosis per se would influence subsequent fertility.

Reid (1955) noted that Raoul Palmer and other workers had suggested that radial cervical fulguration in younger patients may so alter the cervical secretion that sterility would result. On the other hand, Pinkerton (1963) and Stein and Kaye (1950) state that in couples of low fertility, when no other cause is found, treatment of chronic cervicitis may be followed by conception. In this series, indeed, 10 patients conceived within 18 months of the operation.

The danger of damaging the internal os with risk of subsequent abortion and cervical incompetence has been mentioned (Brews 1955). Beard (1964) examined hysterectomy specimens which had been coned previously and concluded that provided care was taken to avoid inserting the shoulder of the Hyam's electrode

into the cervical canal, damage to the internal os is unlikely to occur; with variations in the length of the cervical canal it remains a possibility. Millar and Todd (1938) found an increased incidence of abortion and premature labour in a follow-up of 747 diathermy conisations performed before the menopause. They suggested that this tendency to early interruption of pregnancy might mean the limitation of the procedure to women past the child-bearing period.

Another disadvantage arising from operation on the cervix particularly involving trauma to the internal cervical os is cervical dystocia in labour (Kirtz 1956; Harer 1959). Schulman and Ferguson (1962) reported on a follow-up of 486 cold knife conisations of the cervix concluded that the operation had no extraordinary effect on the ability to become pregnant or to be delivered. In this series no cases of abortion or premature labour occurred but one case of cervical dystocia, attributable to diathermy coning, is reported.

It has been suggested that the proper treatment of the diseased cervix will prevent the development of cancer of the cervix in all but rare instances (Cashman 1945; Mohler 1956).

The epithelium of the ectocervix is often columnar and continuous with that of the endocervix. Frequent changes occur from time to time, the squamous epithelium advancing and retreating relative to the external os. This epithelial unrest may be a factor in the development of carcinoma of the cervix (Pinkerton 1963), and is a strong argument in favour of treatment of all cervices that are not covered by healthy squamous epithelium right up to the external os. Roblee (1956), however, was of the opinion that the elimination of infection and structural removal of a benign lesion does not in any way lessen the incidence of carcinoma of the cervix.

An interesting observation in this series is that 4 patients were taking oral contraceptives. These patients had attended the family planning clinic prior to starting contraceptive treatment and in all cases the cervix was noted to be normal. The patients had been on treatment for almost a year when they complained of vaginal discharge and on examination had well marked signs of chronic cervicitis, and biopsy material was also reported as chronic cervicitis. This suggests that oral contraceptives might in some way be responsible for the production of a condition indistinguishable from chronic cervicitis.

Several authors have noted the influence of hormones on the cervix. Roblee (1956) accumulated evidence to support his theory that the aetiology of cervicitis is related to hormonal changes affecting the pH of the vagina and portio of the cervix by contact. He gave oestrogen to castrate women and many developed chronic cystic cervicitis confirmed by biopsy. Pinkerton *et al.* (1962) in the study of postpartum erosions noted that earlier squamous epithelialization of the cervix occurred in patients who were breast feeding, and suggested that this quicker healing of the portio vaginalis was due to associated differences in hormone production. Jackson (1955) treated chronic cervicitis by applying hydrocortisone ointment locally and noted 'improvement', the hormone perhaps acting by inhibition of inflammatory reaction and later reduction of fibroblastic proliferation. All these factors point to some relationship between the lesion of 'chronic cervicitis' and the effect of hormones.

In this hospital punch biopsy of the cervix used to be carried out prior to diathermy coning, but as noted, this technique has been abandoned and now the

tissue removed by the Hyam's diathermy loop is fixed and examined histologically. Our experience is that only a small portion of the cervical tissue is rendered unsuitable for histological examination by heat distortion. This method provides more extensive material for histological examination than even multiple punch biopsies and the entire squamo-columnar junction is available. Our experience is thus in marked contrast to Offen and Ferguson (1960) who claim that the specimen removed by 'hot conisation' is a charred piece of tissue often beyond histological recognition and valueless for diagnostic purposes. Nevertheless, if there has been a positive or doubtful cervical smear cold knife cone biopsy is still preferred.

Summary

Diathermy coning of the cervix provides a useful method of treating chronic cervicitis and in all cases reviewed at 6 weeks after operation the cervix was fully epithelialised and appeared otherwise normal. Symptomatically the results of the operation are not so consistent, apparently because of the difficulty in defining the clinical syndrome of chronic non-specific cervicitis.

The complications of the procedure, and in particular its occasional ill-effect on a subsequent pregnancy must be considered when the operation is used in women of the childbearing age. In older woman diathermy coning is an ideal method of treatment for chronic cervicitis.

Acknowledgements

I wish to thank Professor J. H. M. Pinkerton for his continued encouragement and advice during the preparation of this paper. Grateful acknowledgment is also made to Mr. H. I. McClure and Mr. G. Boyd for access to case records of patients under their care.

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THE INTESTINAL EPITHELIAL CELL

By D. H. SMYTH, M.D., F.R.S.

The Campbell Oration delivered on 2nd May, 1968

I SHOULD first like to thank you for inviting me to be the Robert Campbell Orator on this occasion. For anyone in the field of medical science it is a great honour to give this lecture, for a Queen's graduate it is a very special honour, but for a Queen's graduate who is also an exile, it is not only an honour but a very welcome opportunity to come back again to this medical school. Although my visit is a short one, I have used my time well and have taken the opportunity to see some of the great changes which have taken place since I worked here. I have been particularly impressed by what I might call the magnificent hospital campus you have got, with a wide variety of buildings and activities all within easy reach of each other. You have obviously put a great deal of careful long-term planning into the various developments of your medical school, which is going to yield rich rewards in the days to come. By some standards Queen's is a relatively young medical school, but your well-planned broad acres for development must be the envy of some of the older medical schools whose traditions are far more extensive than their building space.

The Robert Campbell Oration commemorates a great individual in Ulster medicine, but in the present context the commemoration might be extended to include not only Robert Campbell himself but others who bore his family name. I am very proud to be able to claim a fairly close contact with that name, for the late Mr. W. S. Campbell and I were exact contemporaries. We came up from school together to study medicine at Queen's. After the 2nd M.B. examination we both took time off for an honours B.Sc. in Physiology. We completed our medical course together and went to house posts at the Royal Victoria Hospital. We came back to Queen's again and spent three years as demonstrators, he in Anatomy, and I in Physiology. Knowing Bill Campbell at that time probably better than anyone else here, I should like to take a moment to pay a tribute to the brilliance of an undergraduate career, which I am sure has never been surpassed and probably never equalled. From the second year onwards he won every honour the medical school had to offer, every prize, medal and scholarship which was available. He did this with such a characteristic modesty, and with such an absence of any kind of consciousness of his own great abilities that we all entirely accepted him as first without any feeling of envy, and we were happy to compete amongst each other to be second to him. His undergraduate career was indeed worthy of the name which we are honouring this evening.

I should like to talk to you about the intestinal epithelial cell, and in doing so I shall stress a particular approach to the problem of cellular function which I and my colleagues in Sheffield have been using and which we have called 'functional topography'[1]. Let me explain first what we mean by this term. When we think about how any part of the body works we are conditioned to think in terms of structure and function in that order. It starts from our earliest training, for most of us had our first introduction to medical studies in the dissecting room, and we

learned to think about the structure of the body before we considered its functions. In the macroscopic field this has perhaps some validity for we must know something about the structure of things whose functions we are going to investigate. In the microscopic field, however, I am less certain that this principle holds. The immense developments in microscopy over the last few decades have increased greatly our capacity to see the structures in the cell, even to the level of locating the enzymes, but this in itself leaves a good deal unknown about cellular function. In the approach I wish to describe, we begin not by thinking about the structure of the cell but rather by trying to find out some of its functions and to plot these relative to each other. Topography means making a map of a region to delineate the features of it. In our topography of the cell the features are the functions not the structures, and hence we call this functional topography. The object is not to ignore the enormous amount of knowledge on cell structure, but to supplement this with parallel studies on the topography of function. Instead of asking what functions can be assigned to particular structures the microscopist has discovered, we would reverse the question and ask what structures could serve as sites for functions which can be identified in the cell, and at least in a very rough way related spatially to each other. I am not attempting to give an extensive review of the intestinal cell, but to present a type of approach, and the references therefore chiefly relate to work carried out in Sheffield. I should like to acknowledge here the great help I have received from numerous colleagues in Sheffield and in particular Drs. R. J. C. Barry, H. Newey and P. A. Sanford.

The intestinal epithelial cells absorb all the food which we need, and a good many of the drugs which we think we need. It is now well recognised that there are diseases of the cell, which form the malabsorption syndrome, in which the patient suffers because the epithelial cell is not functioning normally. As distinct from this medical interest in the epithelial cell, there is the interest of the biologist. The biologist is concerned in knowing how cells work and he seizes on any cell, if if it throws light on the general problem of cellular function. It so happens that the intestinal epithelial cell has great attractions from this point of view. It acts in a very special way as a transducer, if we may borrow the term from the engineer. A transducer is an instrument which changes energy from one form into another, and the special feature of the columar cell is that it changes chemical energy into osmotic work. Furthermore, it does this in a position which makes it very accessible to experimental investigation, and few cells in the body offer such an attraction. While there are these two approaches to the cell, the medical one and the biological one, it might be thought that to a medical audience I would have chosen the one of medical interest. Paradoxically perhaps, I have chosen not to do so, and this is because I regard my audience not only as individuals who are employed in providing a health service to the community, important though that may be, but also as biological scientists with a unique opportunity for observing the most interesting and complex of all biological creatures, the human being himself. I therefore make no apology for omitting the medical interests of the intestine and concentrating on how the intestinal epithelial cell works, with a view to throwing light on the whole problem of cell activity and how the energy of metabolism is used by the cell for its various purposes. When we can answer these problems the medical aspects of cell function will perhaps become clearer.

Let us begin by looking at a simplified diagram of the intestine in order to see the general orientation of our problem (Fig. 1). The essential part of the intestine which interests us is the layer of epithelial cells, which is in contact with the luminal contents, and which consists of two kinds of cells – columnar cells and goblet cells. The diagram omits the goblet cells, which secrete mucus and are not related to absorptive activities. The columnar cells transfer substances from the lumen of the intestine into the subepithelial fluid. From there they pass into the blood or

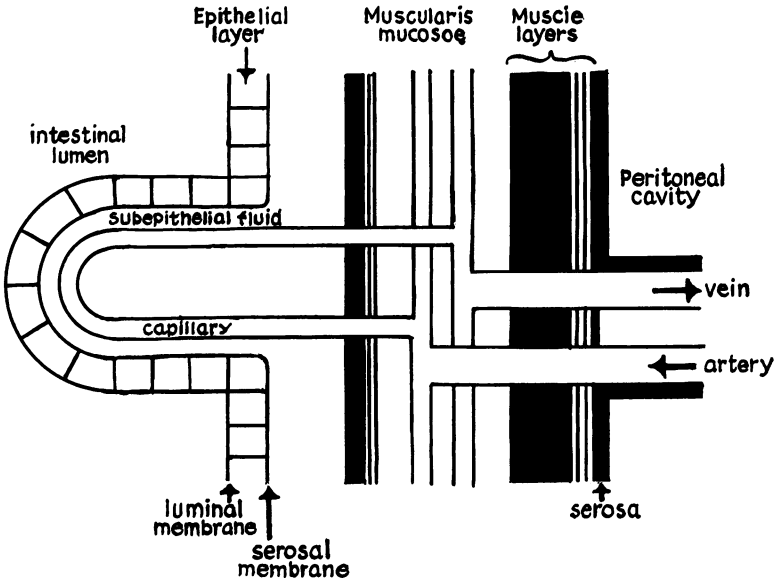


FIG. 1. Diagrammatic representation of the gut wall to show the essential structures involved in absorption (from Principles of Human Physiology. Ed. H. Davson & G. Eggleton. London: Churchill. In Press.)

lymph vessels and are removed. The process of transfer from subepithelial fluid to the blood or lymph vessels are relatively simple ones depending on the pores in the capillary walls. There is no reason to think that any more complex processes are involved, and the basic activity of absorption, i.e., the selectivity, the carrying out of osmotic work, the utilisation of metabolic energy, reside in the columnar cell, and it is on these we will concentrate.

Our experiments consist fundamentally of observing changes in the fluid on the two sides of the cell. On one side – the luminal side – there is no difficulty. The luminal fluid is readily accessible to experimental investigation. The other side – the subepithelial fluid is less accessible, and presents much more difficult problems. As substances pass into the subepithelial space, they do not remain there, but diffuse into the capillaries and are carried away. Furthermore, collection and examination of the mesenteric blood do not supply an adequate answer to the problem. For one thing they introduce enormous complexity due to the presence of the other blood constituents – particularly the proteins. But more important the rate of mesenteric blood flow means that absorption of even large amounts of

substances only cause small changes in blood composition. We must therefore look for some other method of studying the epithelial cells, even if it involves conditions different from the physiological ones.

For long it has been known that many organs can function for a short time separated from the body and with saline as a nutrient medium – e.g. heart, muscle, nerve, etc. The intestine too has been used in this way, but until recently only to study the properties of the smooth muscle in the intestinal wall. Attempts from time to time to use the isolated intestine to study absorption were all unsuccessful, until Fisher and Parsons[2] found that the intestine could function provided certain precautions were taken, and essentially these were to provide an oxygen supply to the epithelial cells. The solution of the problem was to circulate oxygenated fluid through the lumen of the intestine as illustrated in Fig. 2, and in these conditions it was found that the intestine could transfer certain substances from the fluid in

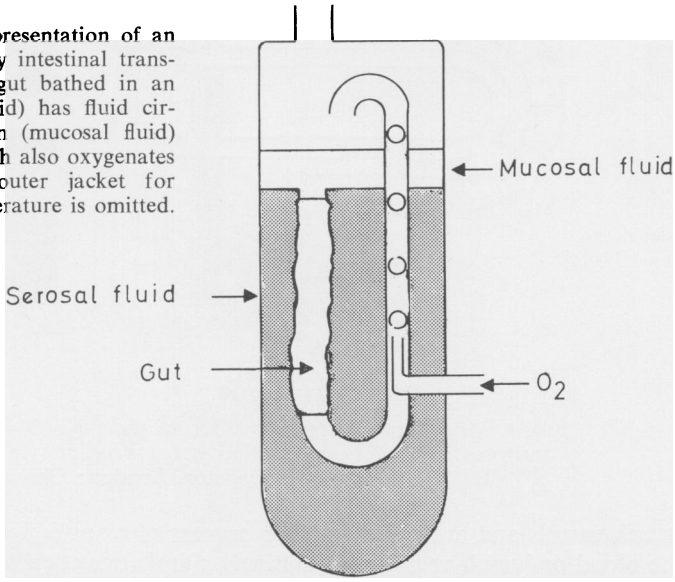


FIG. 2. Diagrammatic representation of an *in vitro* technique to study intestinal transfer. A small segment of gut bathed in an outer solution (serosal fluid) has fluid circulated through the lumen (mucosal fluid) by means of an 0_2 lift which also oxygenates the mucosal fluid. An outer jacket for maintaining constant temperature is omitted.

contact with the mucosa (the mucosal fluid) to that in contact with the serosa (the serosal fluid). A very important development of this technique was introduced in Sheffield by Wilson and Wiseman[3] who turned the intestine inside out and made the everted sac, and these *in vitro* techniques have since been modified and exploited extensively by many subsequent workers[4, 5, 6, 7]. (The term *in vitro* is applied to all intestinal preparations deprived of their blood supply, while *in vivo* means that the intestine is in situ in the living animal, or at least is receiving a blood supply through the mesenteric vessels). The success of the *in vitro* procedures is largely in their amazing simplicity, and the everted sac can readily be used as a class experiment. The essentials of the technique are seen in Fig. 3. A small animal must be used because the wall of the intestine must be fairly thin, and rat, hamster and guinea-pig are most frequently employed. A piece of intestine is everted, and then made into a sac, by tying one end, filling it with saline and then tying the other. The sac is put into a flask containing saline, the saline is oxygenated and the

flask shaken at 37° C. During this process substances are transferred from the outer fluid in which the sac is shaken (the mucosal fluid) into the fluid inside the sac (the serosal fluid). While this capacity for transfer can be readily demonstrated it is pertinent to ask its relation to physiological absorption[8]. In

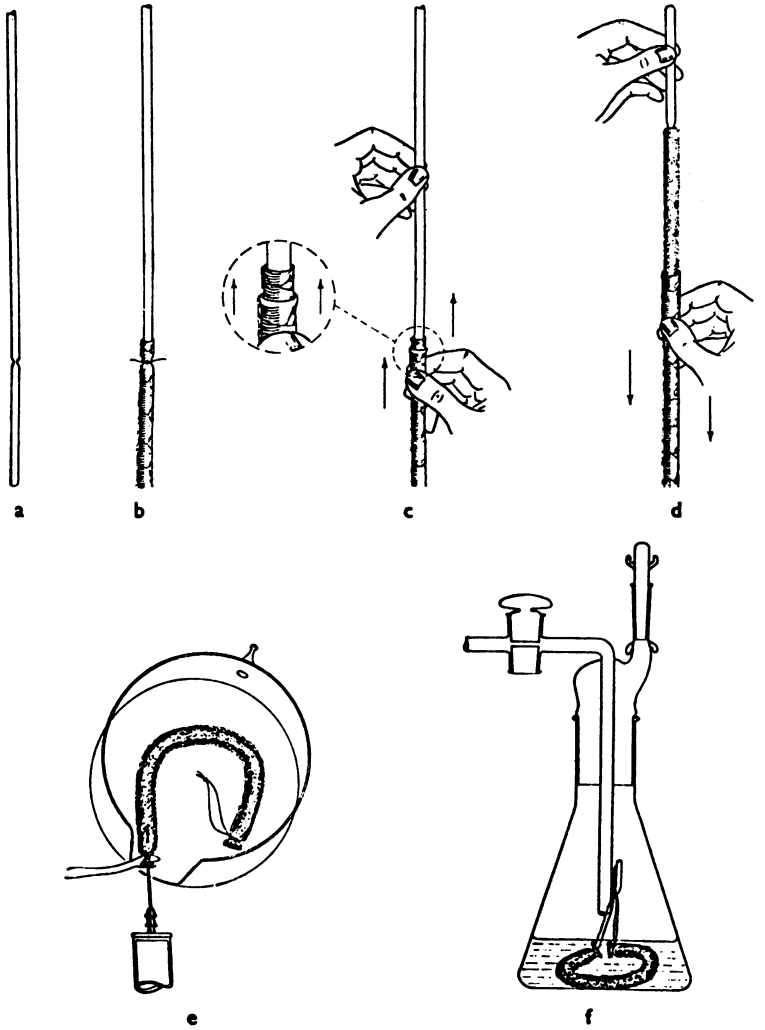


FIG. 3. Some stages in making sacs of everted small intestine for absorption studies. *Above:* Eversion of the intestine. A glass rod is used with a groove provided for a ligature (a). This is inserted into the intestine which is then tied close to the end (b). The eversion is commenced by pushing the gut upwards over the place where it is tied (c). The eversion is completed by inverting the rod and pulling the intestine downwards (d). *Below:* (e) Filling the sac, which is lying in a specially modified Petri dish used for weighing the gut. *Below:* (f) The sac in the incubation flask, which is provided with arrangements for gassing the flasks with O_2 or an O_2 and CO_2 mixture. The glass hook enables the sac to be lowered into the flask and to be removed again at the end of the experiment. (Drawing by K. Curtis), from Recent Advances in Physiology, Ed. R. Creese, Churchill: London, 1963.

physiological absorption the substances pass into the blood stream. In the *in vitro* intestine they pass through the whole layer of the wall of the intestine. The activities *in vivo* and *in vitro* are not however as different as might be thought at first sight. Physiologically substances are transferred by the epithelial cells into the sub-

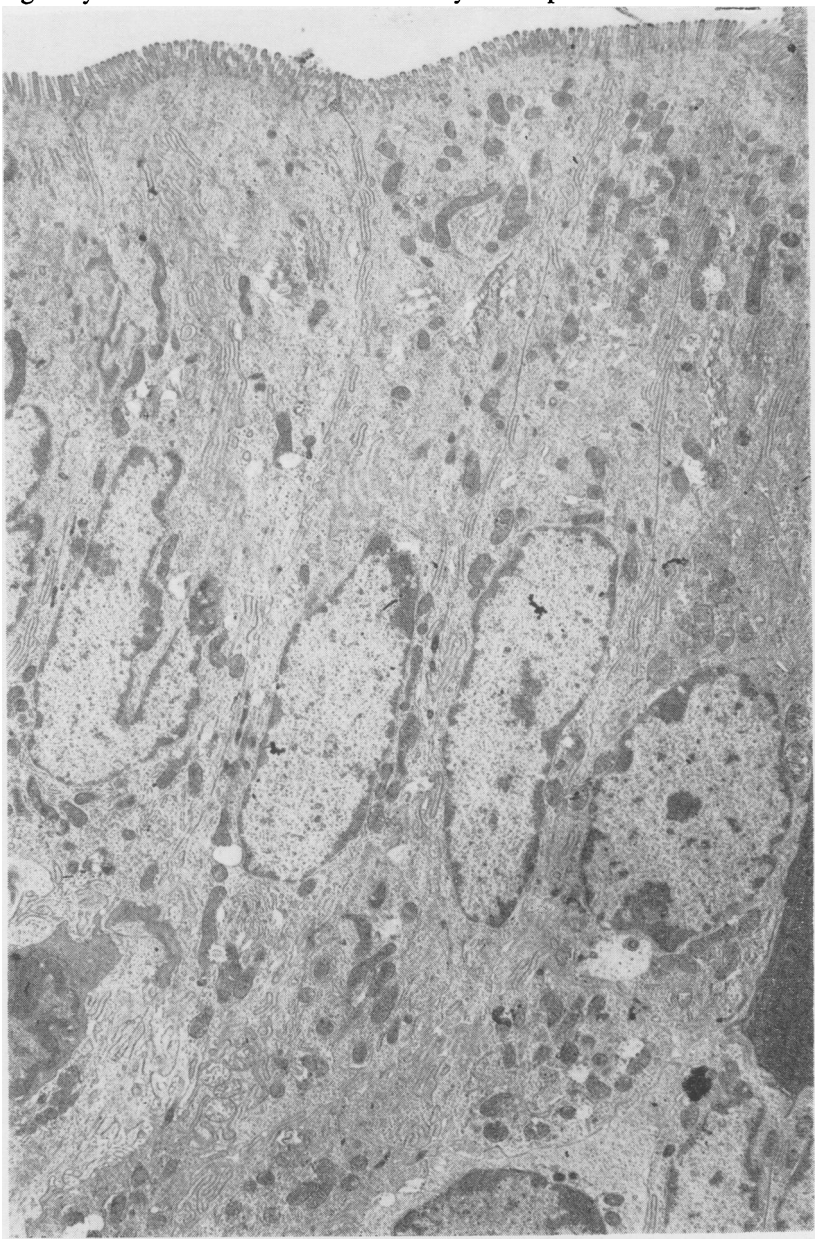


FIG. 4. Electronmicrograph of epithelial cells from rat small intestine (x 5,000). By courtesy of Mr. J. H. Kugler.

epithelial space, and then removed by the blood flowing through the capillaries. In the *in vitro* preparation the same process of transfer by the epithelial cells occurs, and the only difference is the method of removal from the subepithelial space. There is now no blood flow, and the substances escape either by diffusing through the muscle layers or by passing out through the cut ends of the blood vessels. There is good evidence that this latter process occurs, for the first fluid to be transferred is blood stained. Furthermore, a very large number of experiments have been done to compare the activities of *in vitro* preparations with the intestine in normal physiological conditions and there is an impressive body of evidence that these are very similar. There are certain differences, but these are chiefly related to the supply of metabolisable substrate to the epithelial cell, and these differences can be exploited[9] to study the relation between energy and transfer processes, a subject referred to later.

Our object was to deduce what was happening in the cell from the changes in the fluid on both sides. As we have seen this is not strictly possible, but by studying the changes in the fluid on the two sides of the gut wall, instead of on the two sides of the epithelial cell, we can approximate to the desired condition. In the experiments described here we speak of the mucosal and serosal fluids and the diagrams are simplified by ignoring the other layers of the gut wall. This oversimplification for purposes of discussing a fairly complex subject in a limited time does not mean that the difficulties have been ignored or that the limitations of the technique are not appreciated.

Let us now look at the orthodox histological structure of the epithelial cell as presented in Fig. 4, which shows the various features of the cell, the brush border in contact with the intestinal lumen, the other structures to which a variety of

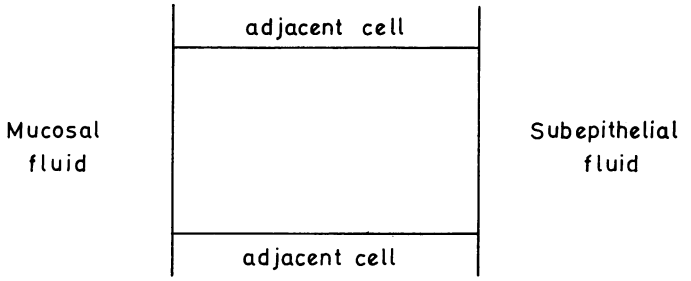


FIG. 5. Diagrammatic outline of the epithelial cell in which are defined only (a) surface in contact with the mucosal or luminal fluid, (b) surface in contact with the subepithelial fluid, and (c) surfaces in contact with adjacent cells. In all subsequent diagrams of cells it is assumed that the cell has the same orientation as shown here with regard to mucosal and subepithelial fluid.

names have been given – the terminal bar, the terminal web, the mitochondria etc. Now instead of trying to discuss what the functions of all these structures are, our functional topography begins in an entirely different way by representing the cell as a blank rectangle and attempting to map the location of the different activities (Fig. 5). The only features we label at the moment are the mucosal and serosal

surfaces, and the part in contact with adjacent cells. In practice the cell is not rectangular, but for our purposes this suffices, provided we define the mucosal side as that part in contact with the luminal contents, while the serosal side is the part in contact with the subepithelial fluid.

We begin with an experiment in which we begin with glucose on each side of the cell in the same concentration of 28mM (Fig. 6). At the end of an hour the glucose

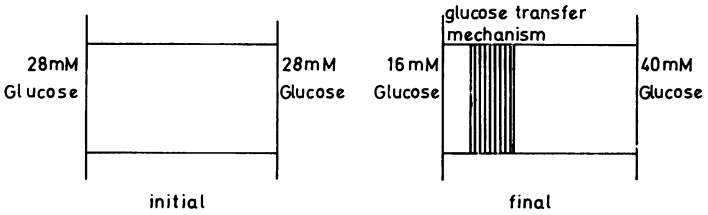
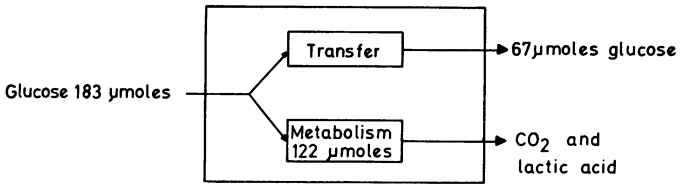


FIG. 6. Experiment showing moving of glucose against a concentration gradient, and hence need to locate in the cell a glucose transfer mechanism.

concentration in the two fluids is measured and is found to have fallen on the mucosal side and risen on the serosal side. We therefore say that the cell has got a mechanism for transferring glucose from one side to the other and we put into the cell our first function, a glucose transfer mechanism, or in the jargon frequently used now in discussing cell transport, a glucose pump. This picture can quickly be recognised as an oversimplification by including not only the concentration of glucose but the amounts involved (Fig. 7). We start off with 416μmoles glucose.

	μmoles	
Total initial glucose		416
Mucosal transfer	183	
Serosal transfer	67	
Glucose in gut wall	44	
Glucose recovered		294
Glucose metabolised		122

FIG. 7. Balance sheet of the amounts of glucose initially present, the final distribution and the calculated amount metabolished. As a result a metabolic compartment is postulated, in addition to a transfer mechanism.



We find that 183μmoles disappears from the mucosal side (we refer to this as the mucosal transfer). Of this 67μmoles appear on the serosal side (which we call the serosal transfer). We recover 44μmoles from the gut wall. If we add these together we have recovered 294μmoles of glucose so that there is 122μmoles unaccounted for, and we must assume that this has been metabolised. We therefore revise our picture of the cell and as shown in Fig. 7 the missing glucose appears as lactic acid and CO_2. The lactic acid is not simply an artifact due to the poor condition of the cells, but it is known that even *in vivo* conditions[10] much of the metabolised glucose appears as lactic acid. We therefore place in the cell two processes for dealing with glucose, one transfer and one metabolism.

Let us think of this metabolism a little more closely. In Fig. 7, glucose came from the luminal side of the cell, but physiologically glucose would also come from the other side of the cell, because like all tissues the cell would receive nutrition from the blood stream. We therefore have to assume that the epithelial cell can get glucose from both sides, from the lumen of the intestine and from the blood stream. This condition can be simulated *in vitro* by putting glucose into the serosal fluid also.. Furthermore, we can find out which side of the cell uses glucose by using ^{14}C labelled glucose on one side and ordinary glucose on the other[11]. Analysis of the specific activity of the carbon dioxide shows that glucose from both sides is metabolised, but that rather more glucose is metabolised from the mucosal side than from the serosal side.

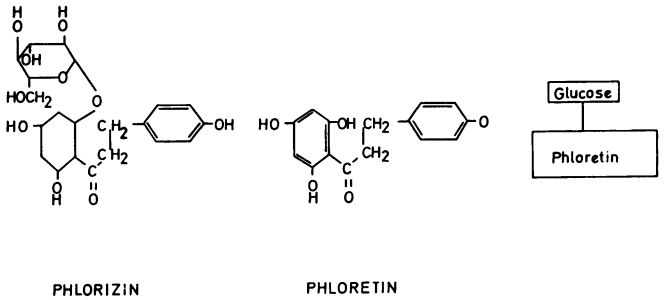


FIG. 8. Structural formula of phlorrhizin and phoretin. As indicated at the right hand side, phlorrhizin may be represented as a large phloretin molecule with a glucose molecule attached.

We now make use of a substance which for a long time has been used in the study of carbohydrate metabolism in the body, namely phlorrhizin. Many years ago it was found that if phlorrhizin was injected into the animal glucose appeared in the urine, the reason being that phlorrhizin prevented the reabsorption of glucose in the renal tubules. A long time afterwards it was found that phlorrhizin also prevented absorption of glucose from the intestine[12], and this activity can be used to throw light on the mechanism for dealing with glucose. The structural formula of phlorrhizin is shown in Fig. 8, and can be regarded as consisting of two parts, a large molecule of phloretin and attached to this a molecule of glucose. The importance of glucose will be apparent later. An experiment can readily be carried out similar to that shown in Fig. 6, but in the presence of 5 x 10^{-4}M phlorrhizin in both

the mucosal and serosal fluid and Fig. 9 shows the results of one such experiment, and illustrates the dramatic effect of phlorrhizin in inhibiting glucose transfer. No glucose disappears from the mucosal side and the concentration on the serosal side does not rise but actually falls. (This fall is due to glucose diffusing from the serosal fluid into the gut wall, and need not concern us further here). It can be assumed then that some part of the transfer process is phlorrhizin-sensitive. This can be investigated further by examining the metabolism of glucose in the presence

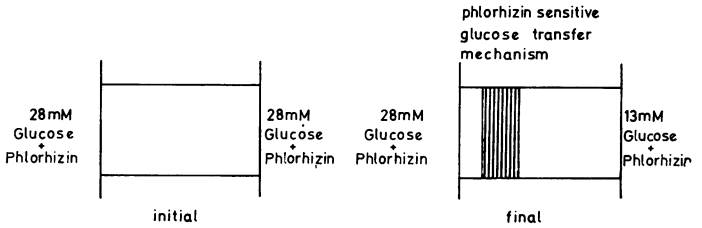


FIG. 9. Experiment showing the effect of phlorhizin (5×10^{-4}M) in inhibiting glucose transfer, and hence postulation of a phlorrhizin-sensitive transfer mechanism.

of phlorrhizin and this is shown in Fig. 10. In these experiments ^{14}C glucose is used in the mucosal fluid and unlabelled glucose in the serosal fluid[11], and the experiments are done in the presence and absence of phlorrhizin. In the absence of phlorrhizin glucose is metabolised from both sides, so that the CO_2 from metabolism is partly labelled. In the presence of phlorrhizin no labelled CO_2 appears. From this it can be concluded that phlorrhizin prevents the entry of

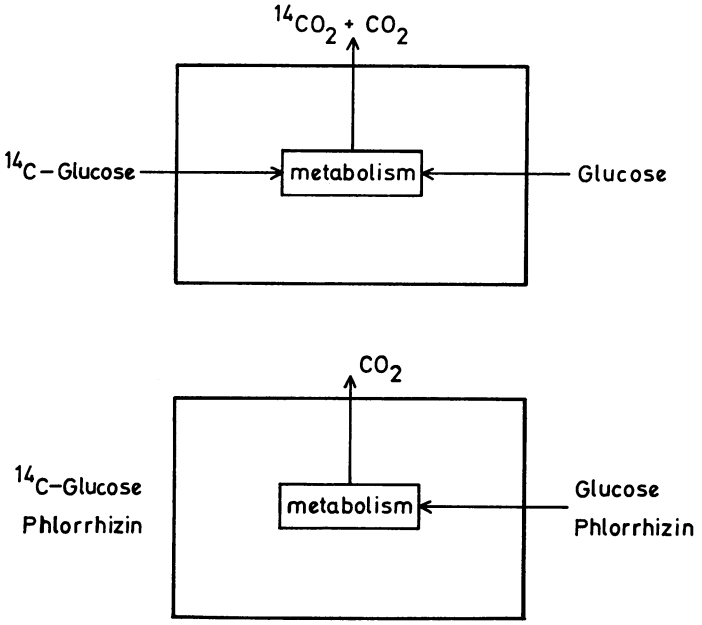


FIG. 10. Experiment to show the effect of phlorhizin on the metabolism of glucose initially present in the mucosal or serosal fluid.

glucose from the luminal side of the cell but does not prevent entry from the serosal side. In other words we have shown clearly that the cell is not symmetrical with regard to phlorrhizin. One side is different from the other and entry of glucose from the mucosal side depends on some mechanism which is sensitive to phlorrhizin. We therefore put into the cell a mechanism which is phlorrhizin-sensitive and which must lie between the lumen of the intestine and the site of glucose metabolism (Fig. 11). We are thus beginning the process of localisation of functions in relation to each other.

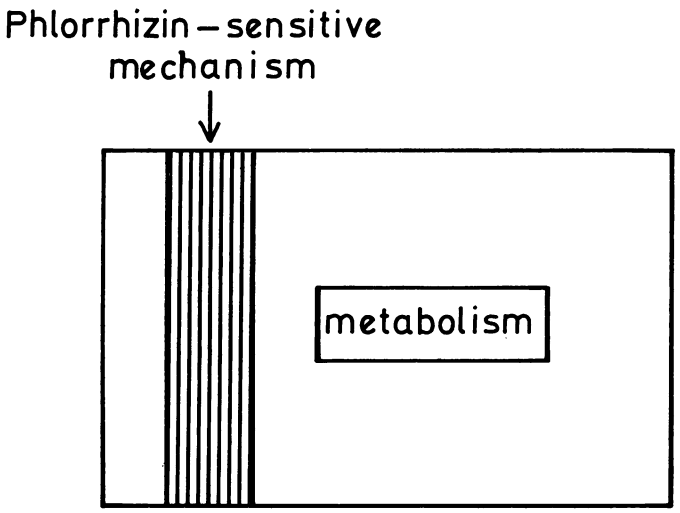


FIG. 11. Location of a phlorrhizin - sensitive mechanism between the luminal border of the cell and the site of metabolism.

So far only glucose has been considered in this discussion. Glucose forms only a small part of the carbohydrate intake, which is mainly in the form of starch. This is broken down by amylase, present in saliva and pancreatic juice, to maltose and the disaccharide is then broken down to glucose by the enzyme maltase. It was long believed that maltase was present in the succus entericus, which represented a digestive secretion analogous to gastric or pancreatic juice. This view of the succus entericus has been questioned from time to time since Starling[13] showed that if the juice is centrifuged, it consists of a clear supernatant and a deposit and the clear supernatant was much less active enzymatically. It therefore follows that the maltase activity is present mainly in the deposit. We know that this deposit consists of shed epithelial cells and the maltase must be present in these dead cells which have been shed off into the lumen of the intestine. It is easy to argue one step further[14]. If the maltose can penetrate into these dead cells and get hydrolysed, might it not also penetrate into the living cells lining the gut. In other words might some of the maltose activity not occur intracellularly? This can easily be tested experimentally, and such an experiment is illustrated in Fig. 12.

We make two identical sacs of everted intestine and incubate each of them in saline for 60 minutes in a small conical flash[15]. In one case 675μmoles of maltose is present in the saline and in the other case no maltose is present. At the end of 60 minutes we remove the two sacs and in the maltose experiment we estimate the

amount of glucose present and find 672μmoles. This must have been due to maltase activity which could have been present either in the epithelial cells or could have been secreted into the surrounding fluid. In order to show which, we now add

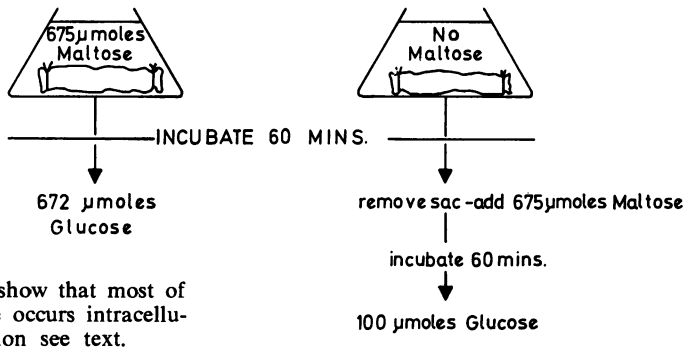


FIG. 12. Experiment to show that most of the hydrolysis of maltose occurs intracellularly. For explanation see text.

675μmoles of maltose to the fluid in which the sac was incubated without maltose, and we incubate a further 60 minutes. We find that only 100μmoles of glucose is present. This experiment shows quite decisively that the hydrolysis of maltose must have taken place mainly in the epithelial cells of the intestine and was not due to maltase which has passed into the surrounding fluid. We therefore must place in

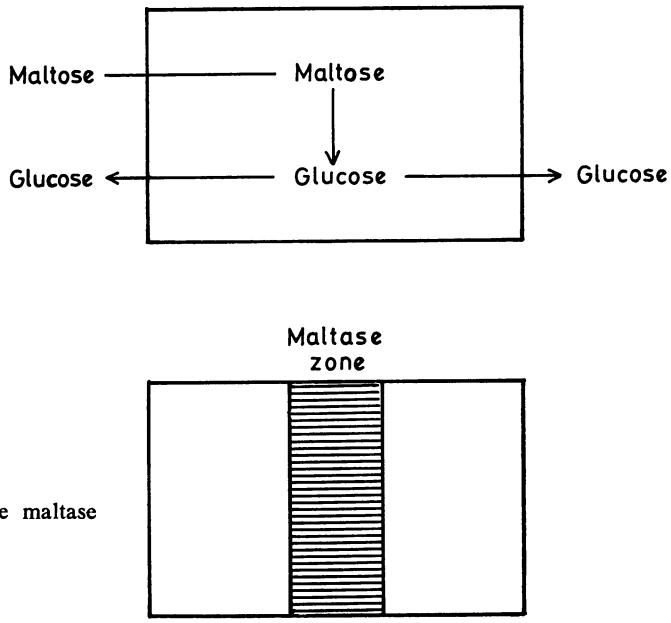


FIG. 13. Postulation of the maltase zone in the cell.

the cell a maltase zone (Fig. 13) and for the moment we insert this without relation to the other cellular functions. (This concept of intracellular hydrolysis was in fact first used in relation to peptide digestion [16] and later applied to disaccharides[15 & 17].

Having decided there is maltase activity in the cell, can we localise this in relation to the topography of Fig. 11. This in fact can be done by use of phlorrhizin[15]. An experiment was carried out with the everted sac of intestine in which maltose was initially present in the serosal fluid (Fig. 14). At the end of an hour we find that 15μmoles of glucose is present in the mucosal fluid and 16μmoles is present in the serosal fluid. Some glucose must also be present in the gut wall and some must also have been metabolised. It is thus clear that maltose initially present

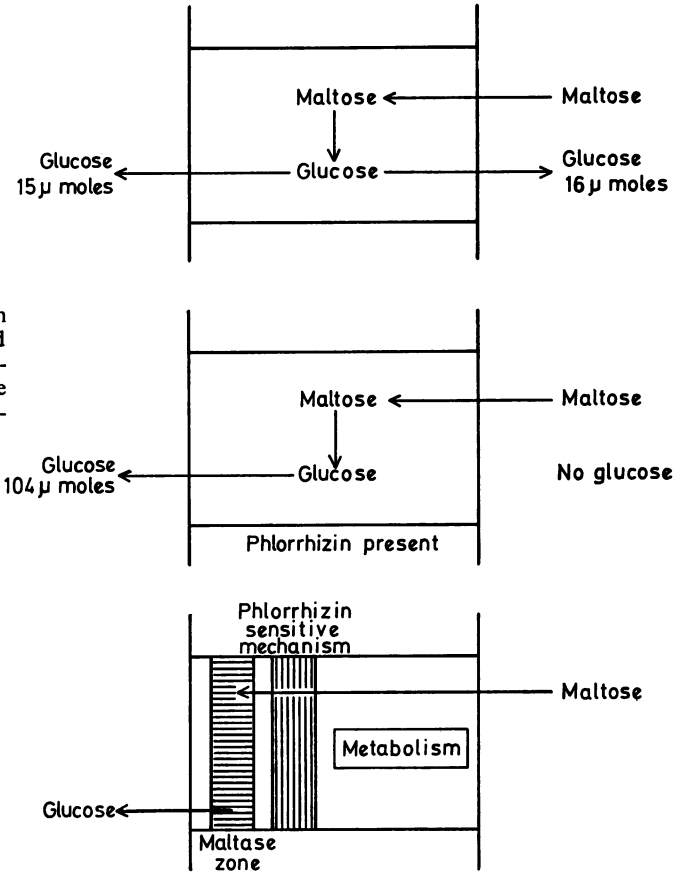


FIG. 14. Relative location of maltase zone and phlorrhizin-sensitive mechanisms by use of maltose and phlorrhizin. For explanation see Text.

in the serosal fluid can reach the maltase zone. The experiment is repeated but in the presence of phlorrhizin. It is now found that 104μmoles of glucose appeared in the mucosal fluid but none was present in the serosal fluid. Since glucose was formed maltose was still able to get into contact with the maltase zone. But it is clear that none of the glucose formed gets into the serosal fluid and furthermore, since much more passes into the mucosal fluid, it is probably also prevented from being metabolised. The only explanation for this must be that phlorrhizin-sensitive mechanism lies inside the maltase zone and we can therefore extend our topography to the picture shown in Fig. 14.

Let us now concentrate on this phlorrhizin-sensitive mechanism for entry of glucose into the cell. All cells are bounded by a membrane which is partly lipid, and some such membrane must separate the luminal contents from the inside of the epithelial cell. Substances which enter the cell must pass through the membrane, and the question arises how a hydrophilic substance like glucose diffuses through the lipid barrier. The simplest assumption would be the existence of aqueous pores in this membrane, i.e., pores filled with water, through which glucose is able to pass. The microscopical approach does not help us, as such pores could be too small for the degree of resolution even of the electron microscope. Again we use the functional approach. If pore size regulates entry, we should expect a relation between ease of entry and molecular weight. In fact, many substances have been tested[18], and the rates of entry studied. If we consider a few of these, glucose and galactose are readily absorbed, while mannose and sorbose are not, and yet all of these have the same molcular weight and roughly the same shape of molecule. This rules out the possibility of regulation of entry by pore size. It is in fact possible to get some idea of pore size expressed by the equivalent pore radius[19], and a simple method of determining this in the intestine[20], has shown that the pore size is too small to permit passage of glucose.

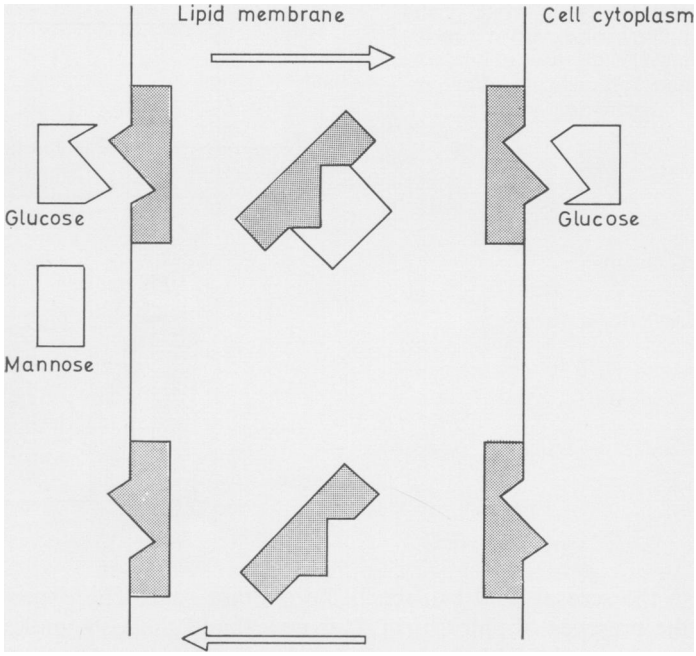


FIG. 15. The carrier concept in membrane transfer. The carriers are the shaded structures in the lipid membrane, which can cross the membrane either with attached molecule (glucose) or unattached. The specificity of the carrier is indicated by the geometric configuration which fits the molecule carried e.g. glucose but not mannose.

In order to explain the entry of substances in the cells through a lipid membrane the concept has been used of carriers, and this concept is useful not only because it explains how hydrophilic substances pass the lipid barrier, but also the high degree of chemical specificity in the process. The carrier concept has been extensively reviewed[21, 22, 23], and only a brief outline will be given here. We assume that there are substances in the membrane called carriers (Fig. 15). These have

the property of being lipid soluble so they can diffuse freely in the membrane but remain in the membrane and do not leave it. The carriers have also got specific sites to which other substances can have attached. These are analogous to the active centres of enzymes, which can give a high degree of specificity for particular subtrates. A number of carriers have been postulated in the intestine, and one of these can handle glucose. It is further assumed that when glucose is attached to the carrier the whole complex remains lipid soluble. When the carrier complex gets to the other side of the membrane glucose is set free, and the empty carrier can diffuse back across the membrane to take up more glucose. This carrier concept is however hypothetical. The carriers have never been identified or isolated, and their existence must depend on functional evidence. What sort of evidence exists for them? In the first place it might be possible to define chemically what substances are able to attach to the carrier, and it would be reasonable to expect a common structure in substances which can use the carrier. This has been done[18], and it is known that the glucose carrier also handles all substances with the basic

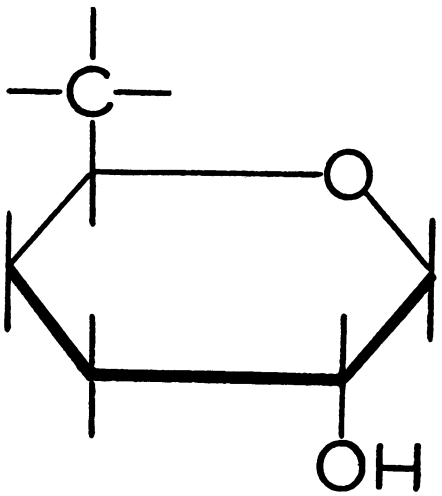


FIG. 16. Basic structure of hexoses which can be actively transferred by the intestine. From Crane, R. K. (1960). *Physiol. Rev.*, **40**, 789

structures shown in Fig. 16, i.e. a pyranose ring with a C attached to C_5, and the OH attached to C_2 in the same stereochemical position as in D-glucose. Another consequence should follow from this. Glucose and galactose both share the structure shown in Fig. 16, and can therefore use the same carrier. We might expect that if present together they might compete with each other for the carrier, and hence for intestinal transfer. This also happens. It was shown many years ago[24] in the whole animal, and more recently[25], in the *in vitro* intestine (incidentally a useful demonstration of the validity of the *in vitro* approach). Such experiments involving competition between two substances also show that while two different substances can use the site, one of them may be preferred, and in fact glucose has more effect in inhibiting galactose, than galactose has in inhibiting glucose. We say that the site has a greater affinity for glucose.

Another useful approach to the problem can be made with phlorrhizin. The formula of phlorrhizin (Fig. 8) shows that it contains a glucose residue. It there-

fore seems possible that phlorrhizin might act by this glucose residue attaching itself to the glucose site on the carrier. Furthermore, the affinity might be increased by the attachment of the lipid soluble phloretin, so that it attaches very firmly and prevents transfer of any sugars. It seemed to us[26] that there was one way in which

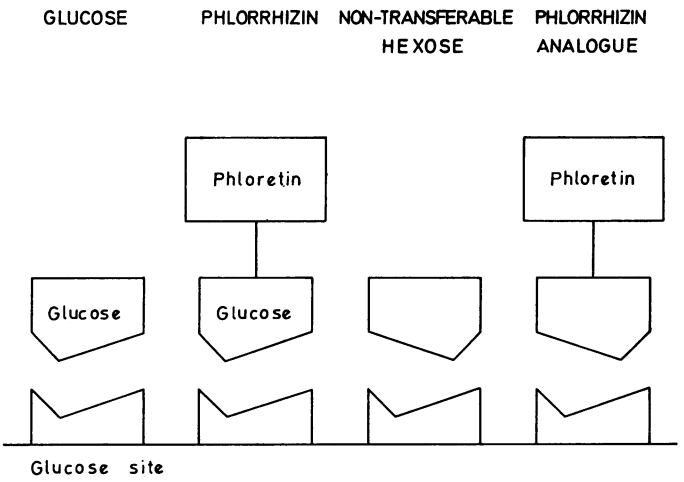


FIG. 17. Diagram to illustrate how phlorrhizin (with a glucose residue) could block glucose transfer, while a phlorrhizin analogue (with a different hexose residue) could fail to do so. The specificity of the carrier is indicated by the geometric configuration which fits glucose but not the other hexose residue.

this could be tested quite conclusively, and this is illustrated in Fig. 17. This shows the idea of phlorrhizin attaching to the glucose site, by means of the glucose residue it contains. Now supposing we could take another sugar which could not be transferred by the intestine and did therefore not fit the carrier site, and attach this to phloretin. We would then have a substance which was very similar to phlorrhizin and different only in the structure of the sugar residue. If our theory is right this phlorrhizin analogue should not be able to inhibit glucose transfer. All we required to test the theory was the suitable analogue of phlorrhizin. This however proved very elusive. It was not available commercially, and we were unsuccessful in persuading anyone to undertake the synthesis of the very small amount we required. The project was put aside until a solution turned up, and this in fact did happen from a very unexpected quarter. A chance meeting with Dr. A. H. Williams of the Long Ashton Research Station at Bristol revealed that he was classifying varieties of apple from the chemical substances which were present in the plant, and the substances he was using were different analogues of phlorrhizin. Among those he had already isolated was a rhamnoside – a phlorrhizin analogue containing rhamnose instead of glucose. Rhamnose does not have the basic structure shown in Fig. 16, it is not transferred by the intestine, and the rhamnoside was therefore the substance which we were looking for. Experiments were quickly carried out to test the effect of the rhamnoside on intestinal transfer of glucose, and these are seen in Table 1. It is evident that the rhamnoside has very little effect on glucose compared with that of phlorrhizin. These experiments supported the view of glucose entry by specific carriers.

Fig. 14 shows the picture we have built up of the intracellular topography of some of the functions. So far, however, we have said nothing of the relationship of

TABLE I

Effect of phlorrhizin analogues on absorption of glucose

Phlorrhizin or analogue	*Amount of glucose absorbed µmoles*	*Percentage inhibition*
None	250	—
Phlorrhizin 5 x 10^{-5}M	89	64
Phlorrhizin 5 x 10^{-4}M	16	94
Rhamnoside 5 x 10^{-4}M	244	2

metabolism to transfer, apart from the statement that the cellular machinery is able to convert metabolic energy into osmotic work. As an example we may consider transfer of hexose, which must be carried out at the expense of metabolic energy. It is difficult to study this problem with glucose, because it partakes in both activities – it is both transferred and metabolised. If, however, we use a sugar which can be transferred but not metabolised then we might throw some light on this problem. Galactose is such a sugar, for it is not metabolised appreciably by rat intestine, but it can be transferred against a concentration gradient. The energy for this process must come from the cell, and we assume it comes from the endogenous metabolism which takes place largely through the citric acid cycle – a process located in the mitochondrial compartment of the cell. We can represent this process

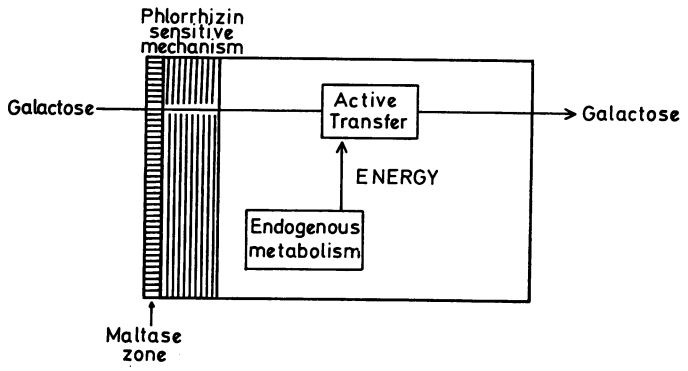


FIG. 18. Diagram to illustrate the endogenous source of energy for the galactose transfer mechanism.

by Fig. 18. Galactose enters by a phlorrhizin sensitive mechanism, and the energy for this is provided by endogenous metabolism. Previous experiments[9] had led us to believe that the supply of energy in the cell for transfer processes was limited, and it therefore seemed possible that we could increase the metabolism of the cell and hence the transfer of galactose by addition of glucose. If we put glucose in the mucosal fluid with galactose, there is a competition for the entry mechanism so that glucose will keep galactose from coming in. However, we can get around the difficulty by putting glucose on the other side, so that glucose can get into the cell without competing with galactose for the entry mechanism. The expectation would be that if glucose and galactose are present together in the mucosal fluid, galactose transfer would be inhibited, but that if galactose is present in the mucosal fluid

TABLE II

Effect of glucose in the mucosal or serosal fluid on the transfer of galactose

Initial condition		*Galactose transferred*
Mucosal fluid	*Serosal fluid*	*μmoles*
Galactose	—	117
Galactose Glucose	—	85
Galactose	Glucose	247

and glucose in the serosal, galactose transfer should be stimulated. Table II shows the results of such an experiment[27], which conforms entirely to the prediction. We thus add another complication to our cell, by putting in another metabolic com-

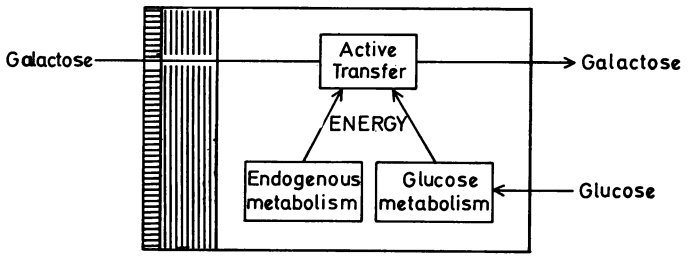


FIG. 19. Diagram illustrating the two sources of energy for galactose transfer, (a) from endogenous metabolism and (b) from glucose metabolism.

partment for glucose (Fig. 19). We know in fact that most of the glucose metabolised does not go through the citric acid cycle, but by the glycolytic pathway, and therefor we make two separate metabolic compartments.

At the beginning of the lecture, I said that if we made functional maps of the cell we might be able to assign these functions to definite structures. Is there any evidence that this can be done? Crane and his colleagues[28] have made a preparation of brush border of the epithelial cell and shown that this contains most of the maltase activity of the cell and our functional studies agree with this in placing the maltase zone close to the luminal border of the cell. Furthermore, histochemical evidence indicates that the enzymes for the citric acid cycle are in the mitochondria, while those for glycolysis are in the cytoplasm, and this agrees with the representation of separate metabolic compartments for endogenous metabolism and metabolism of added glucose.

I have run out of time, and have still only talked of one aspect of the functional topography of the cell, i.e. hexose transfer. There are many other aspects which can be studied in a similar way – amino acids[29, 30, 31], fatty acid and glycerides[32, 33], fluid and inorganic salts[34], and in each case we can make at least tentative maps of some of the processes involved in the intracellular transport. I hope however, I have achieved my main object which was not to give you an immense amount of detailed

information, but rather to illustrate one approach to the problem of cellular function.

In conclusion, could I remind you of the old biblical scholar who once said that the book we call the Acts of the Apostles was misnamed. It should have been "Some Acts of some of the Apostles". Perhaps the title of my lecture should have been "Some functions of some parts of some intestinal epithelial cells".

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ACCIDENTAL POISONING IN CHILDREN IN JAMAICA AND BELFAST: A COMPARATIVE STUDY

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IN EUROPEAN cities accidental poisoning has been a matter of increasing concern. The incidence has been steadily rising in recent years, and from figures supplied by the Medical Officer of Health for Belfast, accidental poisoning accounts for 15 per cent of all home accidents, and there has been an increase of approximately 300 per cent in the years 1963–66. Perhaps of more importance is that accidental poisoning accounts for 43 per cent of paediatric hospital admissions (Dodge 1966), and it is the child of the toddler age group that is the victim in the vast majority of instances. Fortunately death due to such poisoning is rare. The Royal Society for the Prevention of Accident reports that of 724 children accidentally poisoned in Northern Ireland, between 1960–63, only seven died.

In this report the children admitted to the Royal Belfast Hospital for Sick Children (R.B.H.S.C.) due to accidental poisoning are compared with children admitted to the observation ward of the University College Hospital (U.C.H.), Kingston, Jamaica. The observation ward in U.C.H. has 16 out of a total of 466 beds, while the R.B.H.S.C. has about 80 medical beds available out of some 230 beds.

METHODS

In Jamaica information on 113 children admitted to U.C.H. on account of accidental poisoning between September 1st 1963, and December 31st 1966, was obtained, either from the Casualty Observation Ward report books, or the admission records. The records of 293 children admitted to the R.B.H.S.C. as a result of accidental poisoning over the same period of time were examined for comparison. The age and sex of each child, date of admission, cause of poisoning, treatment and complications were recorded.

RESULTS

Age

In Kingston no child younger than 9 months was admitted and the oldest was 9½ years. The highest incidence fell between 1 and 2 years (69 per cent). In Belfast the youngest child admitted was 2 months old and the oldest, 12 years. The commonest ages were between 16 months and 3 years (59 per cent of total). In Figs. 1 and 2 each column represents intervals of three months of age from birth to 12 years of age. The figures show that the commonest age for accidental poisoning is a few months older in Belfast than in Kingston.

Sex

In Kingston there was a remarkable equality in the total poisonings for males and females (57: 56), while in Belfast males appeared to be more prone to the taking of poison than females (180: 116). (Table I).

Fig 1 Incidence of Poisoning With Age

Kingston - 113 Patients

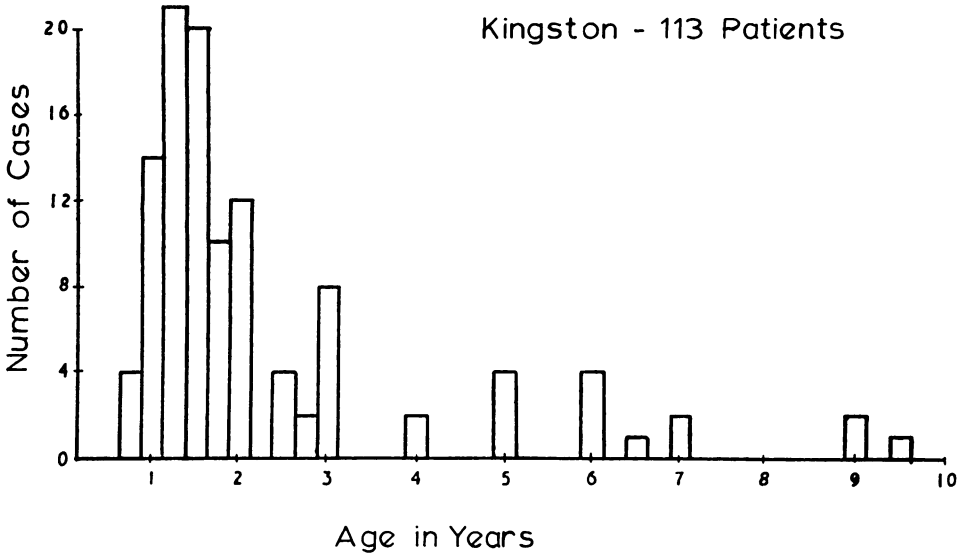

Fig 2 Incidence of Poisoning With Age

Belfast - 293 Patients

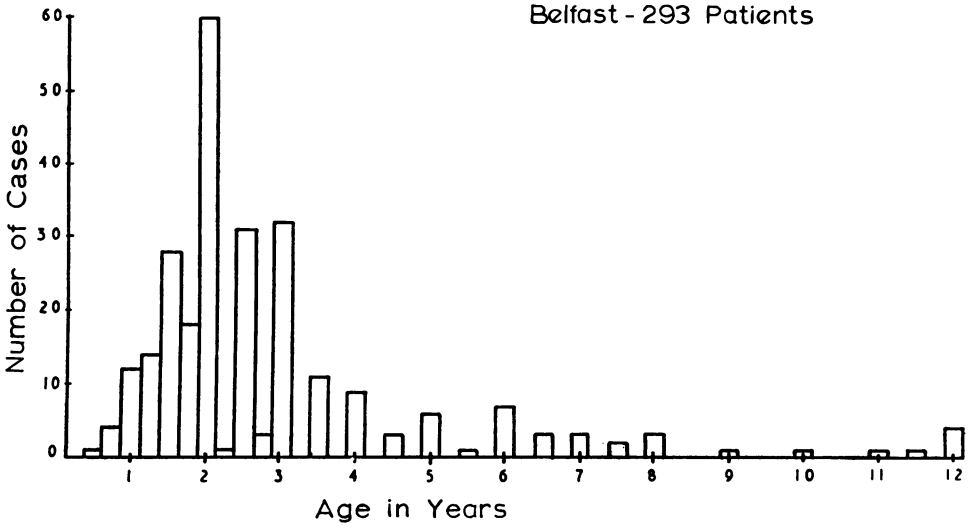

TABLE I

Sex and Poisoning

Kingston – U.C.H.	1963	1964	1965	1966	*Total*
Male	7	15	20	15	57
Female	7	27	12	10	56
TOTAL					113
Belfast–R.B.H.S.C.	1963	1964	1965	1966	*Total*
Male	19	46	60	56	181
Female	20	38	24	30	112
TOTAL					293

Seasonal fluctuations

In both Kingston and Belfast there is a higher incidence of poisoning during the summer. In Kingston the greatest numbers fell between August and September and in Belfast between May and August (Fig. 3 and 4).

Nature of the poison

In Jamaica, Kerosene was the cause of 65 per cent of all accidental poisoning, medicines and tablets of 19 per cent, and household materials, such as caustic soda and bleach, of 9 per cent. In Belfast the commonest cause of accidental poisoning was medicines and tablets, which accounted for 53 per cent of the total; household materials and petroleum products were each responsible for slightly over 20 per cent of the total. These difference are due to the widespread use of kerosene in Jamaica for lighting, for most of the poorer homes have no electricity supply. By itself kerosene is a less common cause of poisoning in Belfast, but when considered with other petroleum derivatives, turpentine and petrol, is more common than might be expected, the three causing some 21 per cent of all child poisonings in Belfast.

Table II shows that overt bronchopneumonia occurred in approximately 27 per cent of children after accidental poisoning with kerosene in Jamaica during the period 1963–65. In 1966 no cases of bronchopneumonia were reported, and this was thought to be due to the coinciding abandonment of stomach washout, which had hitherto been part of the routine treatment of such cases. In Belfast signs of pulmonary complications following poisoning by petroleum derivatives occurred in 64 per cent of patients. In Kingston only those children with clinical signs of bronchopneumonia were reported as such, while in Belfast, where there was more time for investigations, lung infiltrations were often found by chest radiography when the chest had been clinically clear. Behrer (1951) found by routine chest X-rays after kerosene poisoning that as many as 75 per cent of patients had lung infiltrations. Of the 38 Belfast patients who did have pulmonary complications 81 per cent had either vomited or had stomach washouts. Of the 31 children whose treatment included stomach washout, 20 developed complications, while of the 25 who vomited 17 developed pulmonary complications.

Fig 3 Seasonal Fluctuation

Belfast - 116 Patients

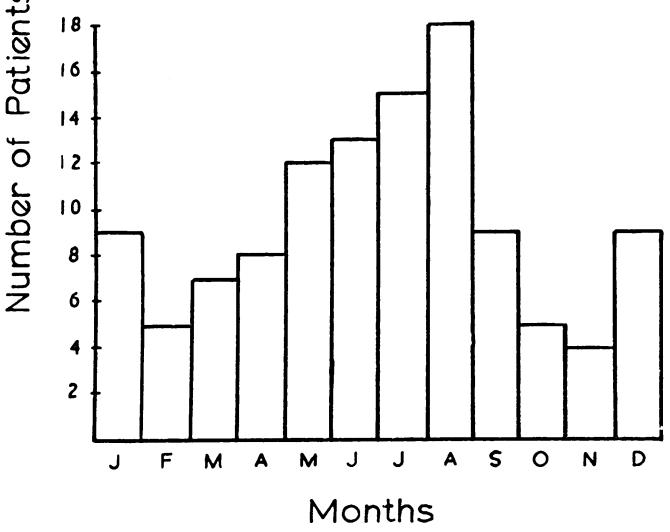

Fig 4 Seasonal Fluctuation

Kingston - 99 Patients

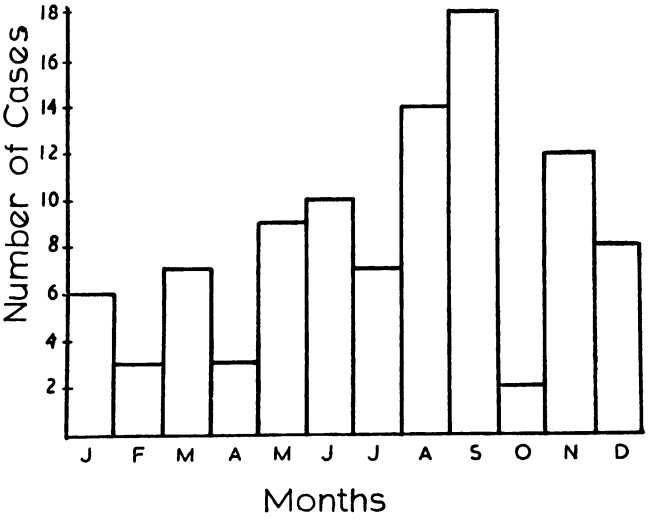

TABLE II

Type of Poison

Kingston–U.C.H.	1963*	1964	1965	1966	*Totals*	*Per cent*
Medicines and tablets	1	9	3	8	21	19
Kerosene	9	26	24	15	74	65
No. developing broncho-pneumonia	2	6	4	0	12	—
Household materials	3	3	3	1	10	9
Plants	0	2	1	0	3	—
Others	1	2	1	1	5	—
TOTALS	14	42	32	25	113	100

Belfast–R.B.H.S.C.	1963*	1964	1965	1966	*Totals*	*Per cent*
Medicines and tablets	22	36	51	45	154	53
Petroleum distillates	6	24	15	17	62	21
No. developing broncho-pneumonia	4	15	8	11	38	—
Household materials	10	18	16	21	65	22
Plants	—	1	2	3	6	—
Others	1	5	—	—	6	—
TOTALS	39	84	84	86	293	100

*Only September-December inclusive considered

DISCUSSION

Age

It is well known that accidental poisoning is most common in the 1–3 year age group. At this age the child explores its surroundings with his mouth as well as his hands, and has not yet learnt to distinguish between 'good' and 'bad' food and drink. The American Pediatric Association (1962) reported 83 per cent of kerosene poisonings occurred in children between 1 and 3 years old. Why the Kingston children should tend to poison themselves at an earlier age than those in Belfast is uncertain; possibly it is due to maturity occurring at an earlier age in the Caribbean, so that the child learns to toddle earlier than his Irish counterpart, who is still pram-borne but safe.

Sex

Male and female were equally liable to accidental poisoning in Kingston, in contradiction not only to the Belfast figures, but also to findings elsewhere. The Register General's reports for England and Wales (1962, 1963, 1964) indicate that accidental poisoning in the home in the 0–5 age group is more than 1½ times as common in males as in females. However, the Kingston ratio may be distorted by the 1964 figures (Table I).

Seasonal Fluctuations

The higher summer incidence is probably due to these months being the hottest, so that the thirsty child is more likely to reach for the lemonade bottle unwisely filled with some other material. Older children being at home due to the summer holidays from school may result in mother being less able to give adequate supervision to the young ones. The findings are in accordance with other reports. An American study found 47 per cent of its cases of kerosene poisoning occurred in the three months, June, July and August, and blamed the hot weather (1964). In Figs. 3 and 4 household materials and petroleum distillates only were considered.

Type of poisoning

The reason for the prevalence of kerosene in Kingston has already been mentioned, and a great reduction in the overall number of poisonings could therefore be achieved by the provision of electric lighting in the poorer homes. However, medicines and drugs might be a higher percentage of the total poisonings than 19 per cent if Jamaicans obtained their drugs free, for cash payment prevents the uncontrolled hypochrondiac drug deluge that occurs in this country. The frightening number (53 per cent) of accidental poisoning due to medicines and drugs in Northern Ireland is probably an indication of the greater affluence of the community and of the readier availability of drugs due to the National Health Service. The incidence will continue to rise if these drugs continue to be left lying about in the home, instead of being locked in proper cupboards. Too often the unused drugs are not destroyed. As for household materials such as caustic cleaners and petroleum distillates, these will remain a major cause of poisoning while the common practice of leaving dangerous liquids in inviting lemonade or other bottles, persists.

Incidence of bronchopneumonia in kerosene poisoning

It is tempting to put too much significance on the fall in the incidence of bronchopneumonia in Kingston following the abandonment of gastric lavage; a continuation of the survey is needed to confirm these results. In Belfast, stomach washout has been given at the discretion of the House Officer attending the patient, and the findings would suggest that vomiting and gastric lavage are equally implicated in the development of any subsequent lung infiltrations. As there is some controversy as to the correct treatment of hydrocarbon poisoning it is useful to review the literature on this subject.

Olstad and Lord (1952) and George (1960) recommended gastric lavage irrespective of the amount of kerosene ingested, due to its possible toxic effects. But it has been shown that the oral toxicity of kerosene is low, and Richardson & Pratt-Thomas (1951) have estimated that a 50 lb. child would have to ingest more than a pint of kerosene to develop severe toxic complications. Yet, due to its unappealing taste, the amount swallowed is probably seldom more than 1 or 2 teaspoonfuls (Cachia and Fenech 1964). The American Co-Operative Study of Accidental Poisoning (1962) concluded that while gastric lavage was not harmful, there was no conclusive evidence that it was beneficial. A more definite conclusion was reached by Cachia and Fenech (1964) who showed that complications were more common in patients who had gastric washout. They recommended that gastric

washout should not be given routinely in cases of kerosene poisoning, but should be reserved for patients who had swallowed large amounts of kerosene. It is uncertain whether lung infiltrations result from kerosene circulating in the blood after being absorbed from the gastrointestinal tract, or are due to its inhalation into the respiratory system. It has been shown that pneumonitis can follow gastrointestinal absorption of kerosene (Ashkenazi and Berman, 1961 and Deichmann et al, 1944), but both the American Co-Operative Study (1962) and Coruh and Inal (1966) felt that pulmonary complications were related to vomiting, and the latter reported that of patients who vomited (whether gastric lavage was carried out or not), 45 per cent developed lung complications as opposed to 10 per cent of those who did not vomit. It is thought that small amounts of kerosene are aspirated while vomiting and the ensuing pulmonary complications are due to its low viscosity and surface tension (Gerarde 1963).

To put such poisoning in perspective it is important to appreciate other complications. Lung complications, in one study (Coruh and Inal, 1966) occurred in 45 per cent of cases (Reed 1950, put it as high as 86 per cent), symptoms of damage to the central nervous system in 34 per cent and of damage to the gastrointestinal system in 33 per cent. The cardiovascular system showed signs of involvement, such as tachycardia, in 26 per cent of cases. The neurological symptoms are important, and can vary from drowsiness through coma to convulsions. These complications seem related to the quantity of kerosene ingested, and have been reported as being less frequent when no gastric lavage was performed.

Conclusions

Accidental poisoning is commonest in the toddler age group, 71 per cent of the combined Kingston and Belfast cases being between 1and 3 years, with the greatest incidence a few months earlier in Kingston than Belfast. It is during this period that the child may frequently put things in his mouth and early recognition of this by mother, and with warnings from the family doctor, might reduce the likelihood of poisoning in childhood.

In Kingston either sex is equally susceptible to accidental poisoning, but in Belfast and elsewhere males are more at risk.

There is a tendency both in Jamaica and Belfast for liquid poisons to be taken more frequently during the hotter summer months coinciding with the school holidays.

Kerosene is the most common cause of accidental poisoning in Kingston (65 per cent) followed by medicines and drugs (19 per cent). A marked reduction in the total poisonings could therefore be achieved by the provision of electric lighting in the poorer homes.

In Belfast most accidental poisoning is due to medicines and tablets (54 per cent) and this ever increasing problem can only be countered by educating the public of the dangers of a casual attitude towards drugs, and of hoarding unused and unknown past remedies. Petroleum derivates account for 23 per cent of the total.

Routine stomach lavage is not recommended for patients with hydrocarbon poisoning; it should be reserved for those few who ingest large quantities, and if possible patients should be restrained from vomiting.

Acknowledgements

I would like to thank Dr. Minot and Dr. M. Geuri of the Casualty Department, U.C.H., and the Records Department of U.C.H. for their assistance in Kingston, Mrs. Burns of the Records Department of R.B.H.S.C. for helping me collect data in Belfast and Professor O. L. Wade for assistance with presentation.

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HONORARY FELLOWSHIP OF THE ULSTER MEDICAL SOCIETY

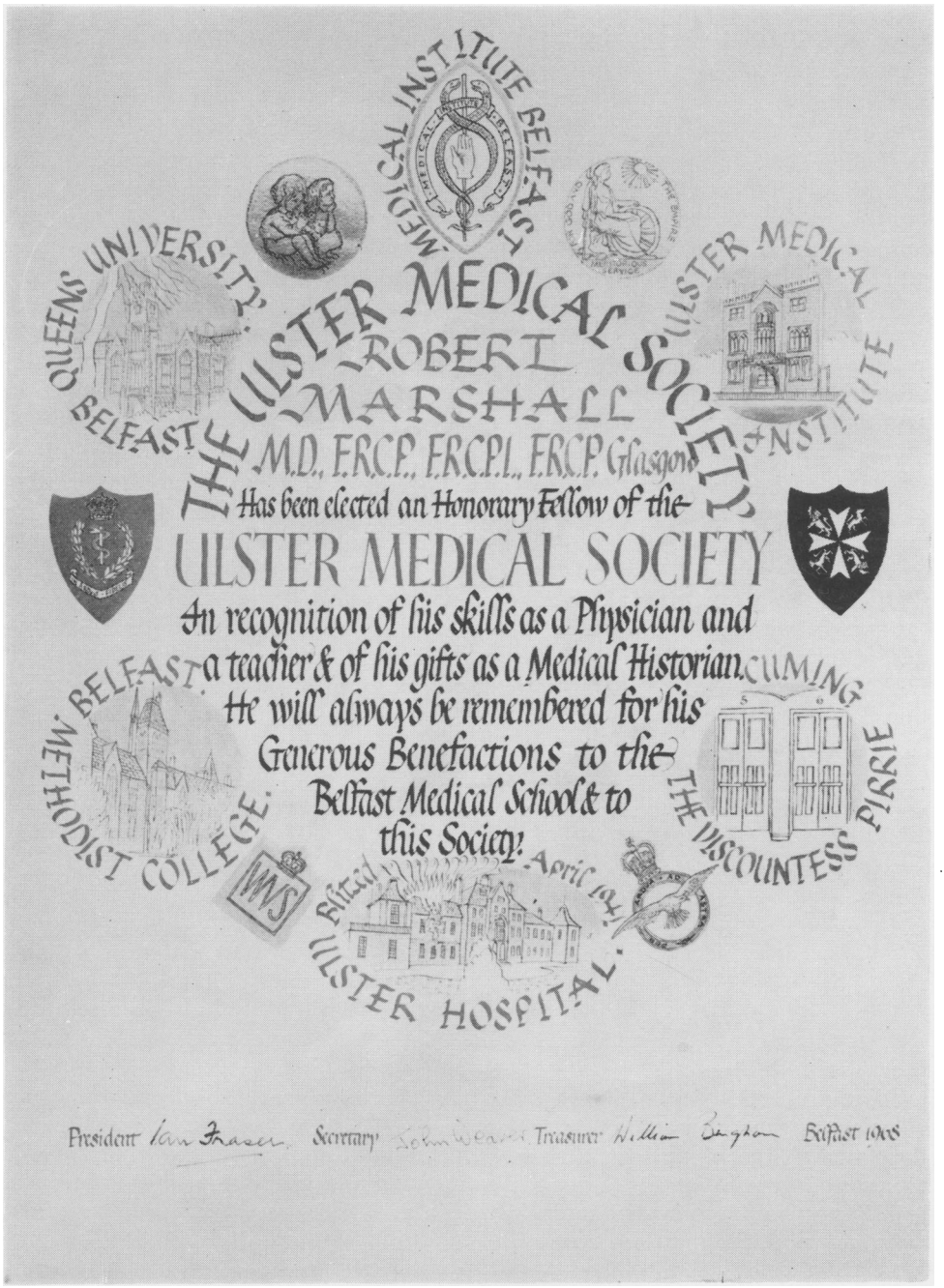
At the Annual Dinner of the Ulster Medical Society on 8th February, 1968, an opportunity was made to present Dr. Robert Marshall with the Honorary Fellowship of the Society.

In making the presentation the President pointed out that it was over twenty-two years since an Honorary Fellowship had been given, and it was the unanimous wish of the Council that Dr. Marshall should be so honoured. It was pointed out that his loyalties embraced many of the leading institutions of Ulster. Although now Chairman of the Governors of Methodist College it was just over seventy years ago that he had gone there first as a very small boy.

To the Ulster Hospital for Children and Women his service in various capacities had extended over 45 years, and at the Royal Victoria Hospital he had held every relevant position from resident pupil to consulting physician and honorary governor. With the Queen's University, of which he is now a senator, he has had close ties for over 60 years, and with the Ulster Medical Society he had in succession filled the posts of Honorary Secretary, Editor of the Journal, and President.

The artist responsible for the illuminated address was able to bring illustrations of all of these places, and with the Ulster Hospital he has shown the flames which marked the blitz of 1941. This hospital, like Malta, G.C., will always be remembered for its gallantry. As the Royal Victoria Hospital is difficult to reproduce as an artistic drawing it was felt that the corridor with the wards V and VI would bring back the happiest memories. The artist was able to bring in a few personal notes showing the Gold Medal of the Ulster Hospital given to Dr. Marshall by the Board of Management when he was elected an Honorary Governor. The badge of the W.V.S. and the British Empire Medal can be seen commemorating the work done at the docks during the war by Dr. Marshall's wife and in the war hospitals by his daughter. In another corner we see the wings of the R.A.F. – in memory of Squadron-Leader R. W. S. Marshall. The Maltese Cross of St. John and the Crest of the R.A.M.C. complete the embellishments.

The citation itself is short. "Robert Marshall, M.D., F.R.C.P., F.R.C.P.I., F.R.C.P. Glasgow, has been elected an Honorary Fellow of The Ulster Medical Society in recognition of his skills as a physician and a teacher and of his gifts as a medical historian. He will always be remembered for his generous benefactions to the Belfast Medical School and to this Society."


THE ULSTER MEDICAL SOCIETY
MEDICAL INSTITUTE BELFAST
QUEENS UNIVERSITY BELFAST
ULSTER MEDICAL & INSTITUTE
ROBERT MARSHALL
M.D., F.R.C.P., F.R.C.P.I., F.R.C.P. Glasgow
Has been elected an Honorary Fellow of the
ULSTER MEDICAL SOCIETY
In recognition of his skills as a Physician and a teacher & of his gifts as a Medical Historian.
He will always be remembered for his Generous Benefactions to the Belfast Medical School & to this Society.
METHODIST COLLEGE BELFAST
CUMING MUSEUM
THE VISCOUNTESS MASSEREENE
ULSTER HOSPITAL
April 1st
President
Secretary
Treasurer
Belfast 1968

CERVICAL CANCER SCREENING IN NORTHERN IRELAND

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IN 1965 a screening programme for the detection of cervical cancer was extended throughout Northern Ireland. The laboratory service for this programme was largely centralised and during the past three years this department has examined cervical smears from over 54,000 women, submitted by a variety of sources from all parts of the Province. This constitutes almost 11 per cent. of the female population of Northern Ireland over 20 years of age. So that the future development of community screening can be properly planned, it was felt necessary to review the pattern of growth of the service in these initial years. It is also of interest to determine what results have been obtained and to attempt to assess the present effectiveness of the programme.

Development of the Service

In Table I is shown the sources which submitted cervical smears and the number of women, over 20 years of age, screened by each from 1965–1968. Equipment for taking cervical smears was supplied by the laboratory to general practitioners on request, other clinics obtaining their own. The equipment included glass slides, Ayre spatulae, laboratory forms and cardboard containers with printed labels for posting the smears back to the laboratory. Also in each kit was a description of the technique of taking and fixing a cervical smear. Fixation in industrial methylated spirit (74 O.P.) was advised but fixative could not be supplied because of postal regulations. After fixation the smears were allowed to dry without appreciable loss of

TABLE I

Source	*Number of Women Screened* 1965-1968
Gynaecological Clinics	22,232
Antenatal Clinics	9,147
Local Authority Clinics	9,886
General Practitioners	8,702
Family Planning Clinics	4,869
Total	54,836

staining properties. Instruction in the taking of smears was also offered by gynaecologists to general practitioners and medical officers of local authority clinics in their area. A record card for each patient screened was kept in the laboratory. In the case of those patients with positive smears, it was possible to compare the smear and biopsy appearances in most instances as the biopsy specimens were also examined at this laboratory.

In the early stages of development of the screening programme it was feared that there might be overload of the laboratory before sufficient staff had been trained

with a danger of collapse of the service. At first therefore, the service was offered only to hospital clinics and also restricted to certain age groups, unless of course, there was a clinical indication for taking a smear. These age restrictions were then removed and later the service was extended to general practitioners throughout the Province and also to family planning and local authority clinics, the number of these clinics submitting smears gradually being increased as laboratory facilities allowed.

The increase in the number of smears was in fact slower than expected and, since the middle of 1967, the total number of women being screened has shown no further rise (Fig. 1). Smears from hospital clinics showed their biggest increase during the first part of 1966. This was due to the removal of age restrictions for routine screening and because screening of antenatal patients was started at this

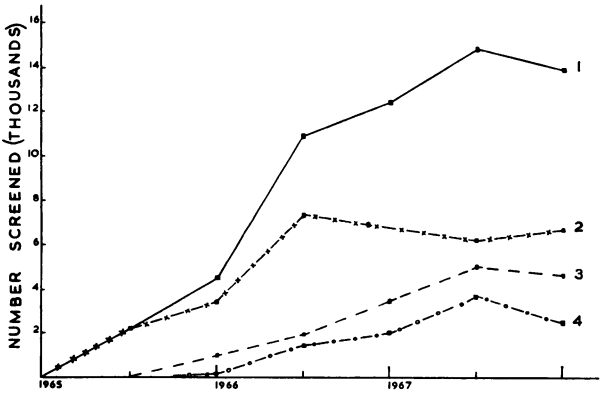

FIG. 1
Development of the screening programme
1. *Total number of women screened.*
2. *Patients attending hospital gynaecological and antenatal clinics.*
3. *Women attending local authority and family planning clinics.*
4. *Women screened by general practitioners.*

time. Since then there has been a slight decrease in the number of smears submitted from these clinics. It is difficult to determine accurately what proportion of patients attending the hospital gynaecological clinics of the Province are being screened for cervical cancer. During 1967 13,665 new patients were recorded as attending clinics served by this laboratory, although due to the method of registration some of these patients were probably recorded more than once. In this year these clinics submitted smears from 7,666 women, or 56 per cent. of the new patient attendance. A survey was also made of 548 consecutive gynaecological patients from whom biopsy or surgical specimens were submitted for histological examination. The laboratory records showed that less than half of these women had had a cervical smear examined during the previous eighteen months.

Screening by local authority and family planning clinics and also by general practitioners increased steadily until the middle of 1967 when the increase stopped and indeed was followed by an appreciable decrease in smears taken in general practice. It was at this time that the Ministry of Health made a fee payable to general practitioners for the smearing of women aged 35 years and over. Comments from general practitioners indicate that this fee has been insufficient to promote the active encouragement of older patients in practices to have a smear taken but has merely served to discourage the screening of younger women. Since the middle of 1967 there has also been a lull in the nation-wide publicity which was given to

cervical cytology in the earlier part of that year. Individual general practitioners and medical officers of health have remarked on the smaller number of women who now request screening and of resistance encountered by health visitors when canvassing women to undergo the test.

Reporting of Smears

Papanicolaou's classification was not used when reporting smears containing cells indicative of a dysplasia or malignancy of the cervical epithelium. It was felt that the classes "suggestive of malignancy", "strongly suggestive of malignancy" and "conclusive for malignancy" were too imprecise, giving no indication of the anticipated severity of the epithelial abnormality. In an attempt to obtain more precision in diagnosis, reports on positive and suspicious smears described the cytological abnormality relating it to the probable histological lesion in a manner similar to that described by Koss and Durfee (1961). Thus, positive smears fell into one of four categories :

(a) Dyskaryosis which affected only the superficial and intermediate squamous cells were considered to reflect a probable dysplasia of the cervical epithelium.

(b) Dyskaryosis affecting also the parabasal squamous cells were reported as suggesting either a marked dysplasia or carcinoma-in-situ of the cervix.

(c) Malignant cells suggested the presence of a carcinoma and invasive change could not be excluded.

(d) Malignant cells, frequently of pleomorphic appearance, in a smear containing much blood and inflammatory debris were considered suggestive of an invasive carcinoma.

Patients having a smear pattern suggesting epithelial dysplasia were followed by repeat smears provided that there was no clinical indication for biopsy. A cone biopsy was advised only if the abnormality was persistent or the smear appearances worsened. Cone biopsy was advised in all other patients having evidence of a severe dysplasia or a malignant epithelial change, unless a suspicious lesion was present in the cervix when a local biopsy was performed.

Some smears could only be reported as containing atypical cells about which no decision could be reached. In most instances a repeat smear was obtained which was more helpful, in some, immediate biopsy was indicated on clinical grounds.

Relation of Cytological Changes to Histological Lesion

The biopsy findings were available for 243 patients whose smear pattern suggested a dysplasia or malignant change in the cervical epithelium. In Table II the nature of the cytological abnormality is compared with the histological diagnosis made in most cases after cone biopsy or hysterectomy. In patients with a positive smear it has been our practice to obtain a further smear before biopsy to ensure that there has been no misidentification of the patient. Consequently, most patients were smeared at least twice and when the two smears differed in appearance, the one showing the most marked abnormality appears in the Table. Not included are nine patients with invasive carcinoma, seven with carcinoma-in-situ and two with dysplasia. These patients had smears which could not be accurately assessed but which contained atypical cells.

TABLE II. *Correlation of smear pattern with biopsy findings*

	Histology					
Smear pattern	*Invasive Carcinoma*	*Carcinoma in situ*	*Dysplasia*	*Chronic Cervicitis*	*Histology Not Known*	*Total*
(a)	0	3	16	4	38	61
(b)	2	20	11	4	8	45
(c)	31	76	8	0	4	119
(d)	43	25	0	0	0	68
Total	76	124	35	8	50	293

(a) Dyskaryosis of superficial and intermediate squamous cells
(b) Dyskaryosis of parabasal squamous cells
(c) Malignant cells present
(d) Malignant cells present. Smear pattern suggestive of invasive carcinoma

Table II shows that the classification of smear pattern used does correlate to a useful extent with the severity of the histological lesion. In patients whose smear shows only a dyskaryosis affecting the parabasal squamous cells invasive cancer is infrequent and in many cases the lesion is a dysplasia (b. in Table). In the case of smears containing malignant cells (c. and d.) it was not possible to predict accurately the presence of invasive lesions but the classification used does divide such smears into two categories with quite different probabilities of invasion. Dysplasia is uncommonly associated with both these types of smears. In contrast, smears showing a dyskaryosis of only the superficial and intermediate squamous cells (a) are mainly associated with a dysplasia and no invasive lesions were found in this group.

In eight patients biopsy showed only inflammatory changes in the cervix despite a smear which suggested epithelial dysplasia or carcinoma. Assessment of these patients is difficult as in some the biopsy consisted only of a small fragment of tissue and in others the pathology department was unaware of the smear result so that the tissue was incompletely blocked. Also, in some patients a biopsy which showed no abnormality was delayed about six months after a smear showing superficial dyskaryosis. This may merely reflect regression of an epithelial dysplasia in the interval.

RESULTS OF THE SCREENING PROGRAMME

The results obtained by screening 22,232 women who were attending hospital gynaecological clinics are shown in Fig. 2. In Fig. 3 are the results from 32,604 women who were screened by local authority and family planning clinics or by their general practitioner. Most of these were well women. This last group also includes those smeared at antenatal clinics as these patients were found to have a prevalence of epithelial abnormality similar to that of the well women. The prevalence rates are based mainly on the histological changes found in a cone biopsy or hysterectomy specimen. Patients shown as having a dysplasia, but who have not had a biopsy, had smears showing dyskaryosis of only superficial and intermediate

squamous cells suggestive of this lesion (Table II). These patients are for the most part still being followed by repeat smears or their smears eventually became normal so that biopsy has not been required. The number of these unconfirmed dysplasias has been corrected to allow for the proportion of those suspected of having this lesion on their smear but who showed no evidence of it on biopsy (Table II). The small number of women in the "carcinoma-in-situ" category for whom biopsy findings are not available showed either parabasal dyskaryosis or malignant cells in their smear to justify this grouping.

The pattern of Figures 2 and 3 are similar. Evidence of dysplasia was most commonly found in the 20–29 year age group, the frequency of this lesion thereafter declining. In both groups of patients carcinoma-in-situ reaches its highest prevalence between 40 and 49 years, being 4.4 per 1,000 in patients attending gynaecological clinics and 3.4 per 1,000 in patients smeared elsewhere.

Invasive cancer had a high prevalence in both groups of women, especially in those over 50 years of age and attending gynaecological clinics. This high frequency reflects the smaller number of women screened in these age groups and the occurrence of symptoms which prompted the taking of a smear. Nevertheless, of the total of 85 cases of invasive carcinoma, nine were only micro-invasive and in a further nineteen the cervix was described as "benign" on clinical examination.

Patients attending hospital gynaecological clinics show a higher frequency of all three types of lesion at each age group than women screened elsewhere. In the case of invasive carcinoma this can be attributed to selection at hospital clinics because of the presence of symptoms. However, it is more difficult to relate the presence of symptoms directly with dysplasia or carcinoma-in-situ.

It was felt that better smear taking technique at hospital clinics might account for the higher prevalence rates among gynaecological patients. However, this was not supported by a review of the frequency of unsatisfactory smears as 4.7 per cent. of smears from gynaecological clinics and 4.1 per cent. submitted by other practitioners had been considered unsuitable for reporting. Also, it has been previously noted that patients attending hospital antenatal clinics had a prevalence of pre-invasive lesions no higher than that found in women attending other clinics, the prevalence also being appreciably lower than that found in gynaecological patients of similar age. This also suggests that factors other than smear taking technique is responsible for the higher rates of abnormality in gynaecological patients.

Age Distribution of Well Women Screened

In Figure 4 is shown the age distribution of the 32,604 women smeared by all sources except gynaecological clinics between 1965 and 1968. This group comprises largely the well women who have been screened by this laboratory. It can be seen that only 28.6 per cent. of these women have been older than 39 years of age and thus in those decades in which both carcinoma-in-situ and invasive cancer are most prevalent (Figs. 2 and 3). Indeed, women in their twenties make up as much as 30 per cent. of all those screened mainly because a relatively large number were patients attending antenatal or family planning clinics.

If only those women smeared by general practitioners and local authority clinics in these years are considered, it is found that just over 42 per cent. were older than

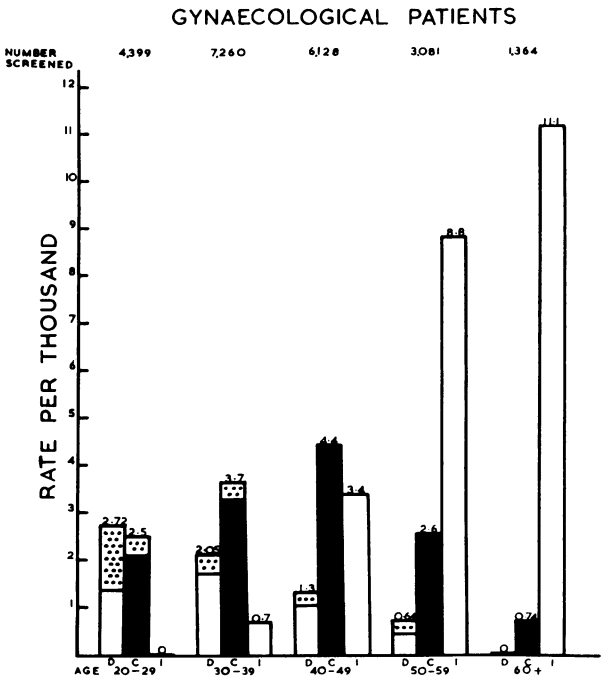

FIG. 2
Age-specific prevalence of dysplasia (D), *carcinoma-in-situ* (C) *and invasive carcinoma* (I) *among gynaecological patients. The dotted parts of the columns indicate patients who have not been biopsied.*

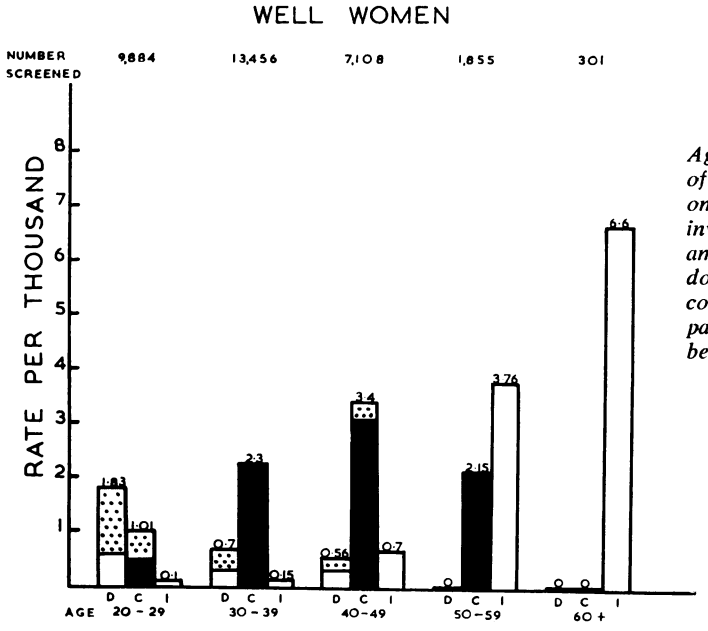

FIG. 3
Age-specific prevalence of dysplasia (D), *carcinoma-in-situ* (C) *and invasive carcinoma* (I) *among well women. The dotted parts of the columns indicate patients who have not been biopsied.*

39 years. During 1967 the Ministry of Health advised that screening of the population should be concentrated initially on women aged 35 and older and a fee was made payable to general practitioners for screening patients over this age. Our records show that this was followed later in that year by an increase of about 5 per cent. in the proportion of women over 39 years of age screened by general practitioners and local authority clinics. However, when this increase is related to the appreciable fall at this time in the number of women screened, especially by general practitioners (Fig. 1), it appears that payment of a fee did not result in increased screening of older patients, but merely in a bigger decrease in the number of younger patients screened. This supports a similar conclusion reached previously in this paper.

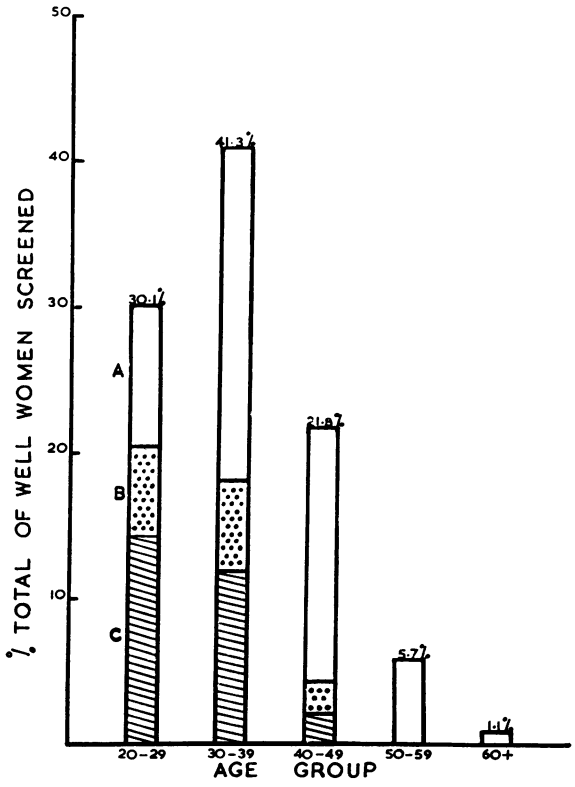

FIG. 4
Age distribution of well women screened from general practice and local authority clinics (A), *family planning clinics* (B), *and antenatal clinics* (C).

DISCUSSION

In this survey carcinoma-in-situ of the cervix has been found to be most prevalent between the ages of 40 and 49 years. It occurred in 4.4 per thousand of gynaecological patients of this age, whereas in the group composed largely of well women its prevalence was 3.4 per thousand in this decade. Dysplasia occurs most frequently in a younger age group consistent with the view that it is a precursor of carcinoma-in-situ.

When the prevalence rates for gynaecological patients and for well women are

compared, a striking feature is that although dysplasia, carcinoma-in-situ and invasive cancer show a similar rise and fall in frequency throughout the decades, the prevalence of all three lesions is appreciably higher among gynaecological patients in any given decade. Hospital clinics will clearly select patients with symptomatic invasive cancer. However, it is more difficult to understand how a dysplasia or carcinoma-in-situ can give rise to symptoms which will cause a similar selection. We have found no evidence to suggest that better smear taking in hospital clinics determines a higher rate of detection of these lesions. It seems probable that factors such as higher parity among hospital patients have favoured the occurrence of gynaecological complaints and, as is well established, an increased incidence of cervical neoplasia. It is also likely that hospital clinics see more women from the lower social classes, in whom cervical cancer is also more prevalent, than do local authority clinics.

The prevalence of carcinoma-in-situ varies widely in different surveys (Ashley 1966). This can be attributed partly to differences in the social class of the women studied and to ethnic differences in the incidence of invasive carcinoma of the cervix. There is also considerable variation in histological interpretation among pathologists and in surveys which make little or no mention of epithelial dysplasia it is difficult to be certain whether these lesions have been distinguished from carcinoma-in-situ. Thus, although the prevalence of carcinoma-in-situ among well women in the present survey is similar to that found by Stern (1958) in California, it is lower than that found by Boyes (1964) in British Columbia. Comparison is difficult however, as the mortality rate for carcinoma of the cervix in British Columbia (Boyes and Fidler 1963) is appreciably higher than in Northern Ireland.

Cervical smears are still reported by many laboratories using the system devised by Papanicolaou or some modification of it. In this classification smears are graded into five classes and those showing evidence of a pre-malignant or malignant lesion are graded as class III, IV or V, indicating suggestive, strongly suggestive or conclusive evidence or a malignant tumour. The continued use of this system, or "numbers game", has been criticised as being imprecise and sometimes of concealing poor standards of cytologic diagnosis (Reagan 1965, Frost 1966). It gives no indication as to whether a dysplasia or malignant change is expected in the cervical epithelium and, if the latter, the likelihood of invasion. It also suffers from the drawback that its classes are variably interpreted by different laboratories (Dunn and Martin 1967).

Diagnosis of the epithelial abnormality must depend finally upon histological examination of the tissue. Nevertheless, it is felt that a useful indication of the nature of the epithelial atypia can be given if smears are reported on the basis of their morphological abnormality as advocated by Koss & Durfee (1961). It is possible to define more clearly those patients who are likely to have only a dysplasia, who do not require early cone biopsy and in whom the epithelial abnormality frequently regresses if they are followed by repeat smears (Koss and Durfee 1961). It also serves to distinguish a group of patients in whom an invasive lesion is probable and urgent biopsy is indicated. This is of value when it is considered that of 85 patients with invasive lesions in the present review, in 28 the cervix was not thought to be malignant on clinical examination.

During the first two years of the screening programme in Northern Ireland there was, as elsewhere in the United Kingdom, a lack of laboratory facilities which slowed the rate of expansion of the programme. In recent months however, the laboratory has been able to deal with smears from all those who are anxious to be screened. This has resulted in a waning of parliamentary, newspaper and television publicity about "the smear test" which was previously largely focused on complaints of inadequate laboratory facilities. Paradoxically therefore, as facilities have increased the rise in the number of women being screened has ceased and has even shown signs of falling. Further development of the screening programme in Northern Ireland is now as much dependent upon effective publicity to persuade women to be screened as upon the provision of laboratory facilities. Much more active promotion of the screening programme by the medical profession is also required. The payment of a fee to general practitioners for taking smears has had the negative effect of reducing the number of younger women screened without increasing the screening of older women. It is also disappointing to find that of patients undergoing gynaecological surgery, less than half were found to have had a cervical smear in the previous eighteen months. Not infrequently, the gynaecologist's "screening" for cervical cancer consists solely of a small snippet of tissue taken from the cervix during the course of a curettage or other procedure.

In order to produce an appreciable fall in the mortality from invasive cervical cancer as soon as possible a screening programme should concentrate on those women at highest risk. So far in the present programme less than 29 per cent. of the women screened from all sources except gynaecological clinics, have been over 39 years of age. It is after this age that carcinoma-in-situ becomes most prevalent and that there is the best prospect of detecting many cancers at an early stage of invasion. Many of the younger women screened were attending antenatal or family planning clinics. Although it is clearly desirable to screen women in these age groups eventually, their priority is low, and we feel that it was a mistake to devote so much of limited laboratory facilities to their examination in the early stages of the screening programme. Certainly, all gynaecological patients, especially those undergoing surgery, should be screened before antenatal screening is attempted.

We believe with others (Smith *et al* 1965, McInroy 1966) that to maintain quality in interpretation it is necessary to develop cytology as a centralised laboratory service. Reliable cytology requires a laboratory to have a nucleus of well trained staff engaged full-time at cytology as well as a work-load which is sufficient to maintain interest and experience and to provide adequate training for others. Close liaison with the histology laboratory is also essential. Further, to assess the results being obtained by a community screening programme some uniformity in methods of record-keeping and reporting of smears is necessary. It will become difficult or impossible to achieve these objectives if cytology is developed at numerous small laboratories throughout the country.

Summary

The development of a cervical cancer screening programme in Northern Ireland is described. After the first three years expansion of the programme has ceased and more effective methods will be required to persuade women to undergo screening. Payment of a fee for cervical smears has not increased the number of smears

taken by general practitioners. There is also evidence that gynaecologists take a cervical smear from a surprisingly small proportion of their patients.

The correlation between smear pattern and the histological findings on biopsy is described. It is considered more useful to report smears on the basis of their morphological abnormality rather than on a classification based on degrees of suspicion of malignancy.

The results of the screening programme are described. It is felt that at present young women constitute too high a proportion of those being screened to make the programme most effective in reducing the incidence of cervical cancer.

We wish to thank Dr. J. E. Morison who reported the biopsies and gave helpful advice and criticism. We are also grateful to Mrs. Barbara Harper, B.Sc., for her assistance in the preparation of the paper.

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THE RAPID RECOGNITION OF STAPHYLOCOCCUS AUREUS :
Desoxyribonuclease and Coagulase Tests in Correlation with Sensitivities and Other Properties

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WHEN. in a routine laboratory, large numbers of cultures have to be made, many of them are incubated late in the afternoon and examined the next morning. When colonies of *Staphylococcus aureus* grow after a short incubation period few produce pigment, and it is impossible to say definitely if they are, in fact, *Staph. aureus* or *Staph. albus*. It is usual to test these organisms for coagulase but it may be necessary to come to a preliminary conclusion before the coagulase test can be done. They can be tested for desoxyribonuclease, and this may be quicker and more convenient than the coagulase test; but a simpler aid to a preliminary opinion is a selective indicator medium, and such a medium has been described by Davis and Davis (1965). It was decided to try this, and at the same time compare the coagulase test and the test for desoxyribonuclease on each *Staph. aureus* isolated. The opportunity was also taken to test the organisms for their sensitivity to antibiotics and their resistance to mercury salts, to phage type them, and to enquire into the source of infection in each case.

Investigation and Methods

Working in a routine laboratory attached to a large hospital, there was no difficulty in getting material, and organisms from 55 patients were studied. These organisms were isolated from post-operative wound infections, from abscesses, boils, ulcers, infected cords and cases of blepharitis, and from patients with chronic ear infections. A few were from members of the staff in the hospital who acquired their infections in the hospital. Seven of the 55 organisms were from patients seen in the casualty department.

Selective Indicator Medium

This consists of oxoid nutrient broth (C.M.1.) 1.5% oxoid agar, pH 7.4, and 500 units of polymyxin, 1% mannitol, and 0.004% bromocresol purple. Mannitol fermenting *Staph. aureus* growing on it produces yellow colonies with a yellow zone around the colonies. *Staph. albus* usually do not grow, but if they do they are not yellow, and there is no yellow zone. *Staph. aureus* usually grows on this medium at 37°C in 24 hours or less, but some strains may need an incubation period of 30 to 36 hours.

Coagulase Tests

The organisms were tested for bound coagulase by the slide test (Loeb, 1903), and for free coagulase by the tube test (Fisk, 1940).

Desoxyribonuclease Test

The desoxyribonuclease test (Jeffries, Holtman and Guse, 1957) was done using 'Bacto-D-Nase' test agar. Plates were inoculated heavily with the test cultures in

streaks, incubated for 24 hours, and then flooded with N/1 HCl. The clearing when desoxyribonuclease was present was easily seen. A coagulase negative *Staph. albus* was used as a negative control and the 'Oxford' staphylococcus as a positive control.

Antibiotic Sensitivity Tests

The organisms were inoculated on each half of the blood agar plate with the 'Oxford' staphylococcus in the centre (Stokes, 1960) and the zones of inhibition compared after incubation at 37°C overnight. The discs used were penicillin four units, tetracycline 25 *u*g, streptomycin 25 *u*g, neomycin 30 *u*g, kanamycin 30 *u*g, erythromycin 10 *u*g, fucidin 10 *u*g, and methicillin 10 *u*g.

Production of Penicillinase

The method of Cooper, Brown and Vesey (1966) was used.

Resistance to Mercury Salts

These tests were done by Moore's (1962) method as modified by Green (1962).

Phage Type

Most of the organisms were phage typed (Blair and Williams, 1961).

Results

Fifty-five strains were examined, 48 from the hospital and seven from the casualty department of the hospital. All except one were easily recognised on the selective indicator medium for they grew in twenty-four hours as yellow colonies with yellow zones. The exception was an organism which was not definitely yellow, and did not produce a yellow zone. Growing on blood agar it appeared to be a *Staph. aureus*, and in fact proved to be coagulase positive, and it produced desoxyribonuclease. On subculture it fermented 1 per cent mannitol after four days incubation at 37°C. All the strains produced free coagulase, seven were negative when tested for bound coagulase. All produced desoxyribonuclease.

Strains Resistant to Penicillin and no other Antibiotic

Twenty-eight (58.3 per cent) of the 48 strains received from the hospital were resistant to penicillin only. Two of these were resistant to mercury salts; 24 produced penicillinase, and two did not. (Two were not tested for penicillinase). Eighteen of these, all mercury sensitive, belonged to phage group 1, namely types 29(7*), 79/81(1), 29/52/80(3), 52A(1), 29/52(3), 29/80/81(1), 52A/80/81(1), and 29/52/52A/80(1). Three belonged to group II, namely 3c/55/7(1), and 3c/55(2), and these were also sensitive to mercury salts. Four belonged to group III, namely 43E/47/54/81(1)(MS)†, 6/47/54/75/83A(1)(MS), 6/47/53/77/83A(1)(MR) and 7/47/54/75/83A(1)(MR). There were two other mercury sensitive strains which did not belong to any group, and an untypable strain which was also sensitive to mercury salts.

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* Indicates the number of strains.

† MS=Sensitive to mercury salts.
MR=Resistant to mercury salts.

Strains Resistant to Penicillin and other Antibiotics (Multi-resistant Strains)

Ten (20.8) per cent of the 48 hospital strains were resistant to penicillin and other antibiotics (see table). Six (12.5 per cent) of these were resistant to mercury salts and also to tetracycline. Of the 10 multi-resistant strains four were sensitive to mercury salts, and two of these were resistant to tetracycline. Of the two tetracycline sensitive strains, one was resistant to penicillin and erythromycin, sensitive to mercury salts, and produced penicillinase, and the other was resistant to penicillin, methicillin, streptomycin and fucidin. This strain was sensitive to mercury salts also, but was not tested for penicillinase. Four of these organisms belonged to phage group I, namely phage types 29(1)(MR), 80(1)(MS), 52A/80(1)(MS) and 29/52(1)(MS). The other six strains were 84/85(4)(MR), 83A/85(1)(MR) and an untypable mercury sensitive strain.

TABLE

Cult. No.	*Pen.*	*Tetra.*	*Strep.*	*Neo.*	*Kana.*	*Eryth.*	*Fucid.*	*Meth.*	*Merc. resistant*	*Phage*
38	R	R	R	R	R	R	S	S	R	
34	R	R	R	R	R	R	S	S	R	84/85
31	R	R	R	R	R	R	S	S	R	
23	R	R	R	R	R	R	S	S	R	
56	R	R	R	S	S	R	S	S	S	Untypable
58	R	R	R	S	S	R	S	S	S	29/52
27	R	R	R	S	S	S	S	S	R	83A/85
5	R	R	R	R	R	R	R	S	R	29
40	R	S	S	S	S	R	S	S	S	80
17	R	S	R	S	S	S	R	R	S	52A/80

Strains Sensitive to all Antibiotics

Eleven (22.9 per cent) of the 48 strains were sensitive to all the antibiotics. All were sensitive to mercury salts, and none produced pencillinase. Three belonged to group I, namely phage types 29/81, 29/52/52A/80/81 and 81. Three belonged to group II, namely phage types 3c55/71, 55 and 3c. Two belonged to group III, namely phage types 7/42E/47/75 and 42E/53/54. There was one untypable strain and two which were phage type 187.

Strains received from the Casualty Department

Seven strains were examined. Four were resistant to penicillin and no other antibiotic, and these all produced penicillinase. One belonged to phage group 1, phage type 29/52(MS), two to group II, phage type 3c/55/71(MS) and phage type 77(MS) and one belonged to group III, phage type 42E(MS). Three were sensitive to all the antibiotics; two of these belonged to group I, phage type 42E/47/53/54/81(MS) and 29/81(MS), and the third to group II, phage type 55/71(MS). Six of the seven were from abscesses or boils and the seventh (phage type 77(MS)) pus from an old mastoidectomy.

Discussion

The selective indicator medium worked well. Even when there were only a few colonies on the plate it was possible to make an immediate decision and say with confidence that the organism was a *Staph. aureus* although the colony growing on the blood agar plate appeared to be a *Staph. albus*. Time was not wasted, nor the flow of work held up while unnecessary coagulase tests were done. In mixed cultures it was easy to see the yellow colony of *Staph. aureus*, and its yellow zone, and in many of these the staphylococcus was not seen on the blood agar plates. The only exception was the one *Staph. aureus* which required prolonged incubation to ferment mannitol, and no doubt non-mannitol fermenters will be encountered occasionally. Enterococci were frequently seen, and these grew as yellow colonies also with yellow zones, but they cannot be mistaken for *Staph. aureus* because they are smaller than *Staph. aureus*, and transparent, whereas the *Staph. aureus* is opaque. Proteus, coliforms and *Staph. albus* were also seen, but the latter was rarely seen and never as a yellow colony. Coliforms and proteus are easily recognised, but proteus can cause confusion by interfering with the development of the yellow zones around the staphylococci growing on the same plate. The desoxyribonuclease test was simple to do, and the results easily read provided there were not too many organisms streaked or spotted on the plate. Three streaks per four inch plate is the maximum which should be used. The test is more convenient to do than the coagulase test.

The antibiotic patterns and the phage types reflect the diversity of antibiotic resistance and phage types seen in a general hospital. The majority (24 of 28) of the organisms resistant to penicillin alone produced penicillinase, and were sensitive to mercury salts (22 of 24 – two were not tested). The majority (8 of 10) of the tetracycline resistant strains were resistant to mercury salts (6 of 8) and these also produced penicillinase.

This was to be expected because those staphylococci which survive in a hospital environment are usually resistant to one or more antibiotics, and those resistant to more than one antibiotic are usually resistant to tetracycline and mercury salts. Also those which are resistant to mercury salts are often more virulent (Moore 1960). Most of the organisms in this series produced penicillinase, and while the amount produced was not estimated, this finding is in keeping with conclusions of Richmond, Parker, Jevons and John (1964) who consider that the production of large amounts of penicillinase is necessary for the survival of antibiotic resistant organisms in hospitals. The majority of the multi-resistant and mercury resistant strains belonged to phage type 84/85 or 83A/85, phage types associated with epidemics of staphylococcal infections in this hospital in the past.

Enquiries were made as to how many of these patients arrived in the hospital with infections, and it appeared that eight (72.7 per cent) of the 11 fully sensitive strains were acquired outside the hospital, and that 12 (42.8 per cent) of the 28 strains resistant to penicillin only, and two (20 per cent) of the 10 multi-resistant strains, were also acquired outside the hospital, but some of these were originally acquired in other hospitals in the province and one was acquired in a hospital in England.

Summary

By including polymyxin-mannitol bromocresol agar in the culture media for the isolation of *Staph. aureus* it was found that the organisms could be recognised quickly as an aureus strain, and seen amongst mixed growths.

The desoxyribonuclease test was simple to do, and suitable for use in a routine laboratory. It was probably more convenient than the coagulase test.

The antibiotic patterns and the phage types were what would be expected in organisms found in a general hospital, but some of the infections were, it appeared, originally acquired outside it.

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THE USE OF L.S.D. 25 IN PSYCHIATRY

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MUCH PUBLICITY in the national press, most of it adverse in the past two years, has been attached to lyseric acid diethylamide (L.S.D.25) and, therefore, it seems essential to review cases and publish the findings about the results of treatment with this drug. It would appear that in the British Isles only about 25 psychiatrists, including the author, have been enquiring into the uses and dangers of the drug.

L.S.D. 25 was first prepared in 1938 by Stoll & Hofmann, and was for a few years of interest to research workers only because of its hallucinogenic properties, and its abilities to distort the sense of perception and of orientation in time, place and person. Only later was its therapeutic potential explored in the treatment of psychiatric disorders. Sandison, Spencer & Whitelaw (1954) reported its use in a wide variety of psychiatric patients, and reports appeared more frequently until tranquillisers and anti-depressant drugs became popular.

Its use by the present author has been at dosage level of 25 μg-100μg per sessions and generally at weekly intervals, and varying in number from 1 to 8. This dosage is about one-tenth of that used in illicit psychedelic sessions. Three-quarters of the subjects were out-patients, a practice carried out successfully for a number of years at, for example, day hospitals (Martin 1957), (Long & Buckman 1960).

Where insightful psychotherapy has been indicated the author for some years has followed the general pattern elaborated by Finesinger (1948), but even this short-cut to analytical procedure is too time-consuming for National Health Service practice. L.S.D. 25 was used in the hope of accelerating the treatment of those patients in whom a poor prognosis was predicted as regards recovery with other methods of treatment. In practically all other reported studies where the drug has been shown to be useful, the patients selected were those who would have responded equally well to other forms of treatment.

The patients, in single rooms throughout each session, were given the drug orally at 9 a.m. A nurse was immediately available. The author visited the patients at intervals and also if they complained of anxiety or any peculiar sensations. At the end of 4 hours each patient received Chlorpromazine 100 mgm. orally to terminate the session. They were instructed to record any memories, ideas or "insights" which occurred to them during sessions and in the days between sessions. It was hoped that this would enhance their desire for improvement.

It was decided to follow up the cases treated in the 3-year period commencing June 1961. Cases after June 1964 have not been followed up for a long enough period. Later cases were upset by the press outcry against illegal abuse of L.S.D. 25, so that temporarily this type of treatment had to be stopped. In the 3-year period under review 24 patients were treated. There were five female patients with psycho-sexual disorders. All showed marked improvement. In another group there were five unstable psychopaths, none of whom responded to treatment. The remaining 14 cases showed no pointing pattern of response for future studies, but then they were

a medley of types including chronic hysterical conversion syndromes, incapacitating anxiety states, obsessive compulsive disorders, and housebound housewives. Short case summaries of the 10 cases with definite responses are presented :

Female Psychosexual Cases

Case 1. Female, aged 23. Non-consummation after 3 years of marriage. Happy childhood and married life, apart from frigidity. After three L.S.D. 25 sessions some degree of sexual intercourse possible. Two further sessions given after an interval of 2 months. Patient became pregnant one month later with satisfactory relationships since then.

Case 2. Female, aged 32. Married 9 years. 1 child aged 7½ years. Could not tolerate idea of sexual intercourse since stillbirth 3 years previously. Rows with husband, depressed and beginning to have delusions of infidelity about husband. Three L.S.D. 25 treatments led to resumption of normal sexual relationships with pregnancy 5 months later. Remains well.

Case 3. Female aged 34. Married 14 years, 13-year old child. Acutely depressed, headaches. Separated from husband 4 years. Indecision about proceeding with impending divorce. She had allowed sexual intercourse for several years before separation. Under L.S.D. 25 revealed her disgust for husband's increasingly perverted sexual behaviour. Gained confidence in making necessary decisions followed by disappearance of symptoms. No longer a distorted viewpoint about men in general.

Case 4. Female aged 26. Married 3½ years. Miscarriage, three months after marriage, followed by fear leading to aversion from sexual intercourse. After six L.S.D. 25 sessions sexual relations resumed, although with some lack of interest on the patient's part. This degree of recovery persists.

Case 5. Female, aged 37. Married 10 years. Two sets of twins within 18 months of marriage. Four periods of hospitalization with psychiatric illness before admission for L.S.D. 25 in 1964. Two of the admissions had followed definite suicidal attempts. She had felt that she was a sex maniac and she said a voice was instructing her on sexual misdemeanours, and had also instructed her to commit infanticide and suicide. L.S.D. 25 revealed background of illegitimate pregnancy in an older sister in her early teens and the equation sex=pregnancy=shame became instilled into her. She had withdrawn into a schizophrenic aloof state having infrequent sexual intercourse but with florid symptomatology when thought pregnant. Now well balanced on oral contraception with normal married life.

Psychopathic Personality Cases

Case 6. Male, aged 38. Married 14 years. Record of instability, debts, frequent job changing and unemployment, gambling, impulsive behaviour, admitted following suicidal overdose. Four L.S.D. 25 treatments given in attempt to help him have a proper review of his maladaptation to life, so as to change his ways. Still as unstable as ever. Made another suicidal attempt shortly after discharge.

Case 7. Female, aged 23. Married 6 years. Unstable record, Atrocious upbringing. Parents separated and patient shuttled between relays of relatives. Sexual

morality practically non-existent. Claimed depressed on admission, but proved to be escaping debts. Three L.S.D. 25 treatments produced no change in outlook or behaviour. Has returned several times, has separated from husband and made a couple of suicidal gestures.

Case 8. Male, aged 39. Single. Has succeeded for years being a parasite on his mother and brother, living the life of a gentleman whilst they slave. L.S.D. 25 (2) may temporarily have made him more plausible, which may have "helped" him in his ability to scrounge more free alcohol.

Case 9. Female, aged 30. Married 8 years. Admissions here have been escapes from more difficult positions in a frequent series of domestic upheavals. Three L.S.D. 25 treatments, although appearing to produce insight, did nothing to help, and marital disharmony remains in a very unstable household.

Case 10. Male, aged 53. Married 20 years. Irresponsible behaviour for years with frequent invalidism and hospitalisation for trivial complaints. Of borderline intelligence. L.S.D. 25 (2) did not affect his subsequent behaviour.

Comment and Discussion

Female psychosexual disorders of long duration have been considered to be intractable to treatment. It is obvious from results in the first five cases that treatment by L.S.D. 25 has been an advance by any measure. Two of these patients had had schizophrenic breakdowns. From this study the use of L.S.D. 25 would seem to be not necessarily contraindicated where there is a history of schizophrenia, as has been formerly held to be the case (Sargant & Slater 1963).

The psychopathic cases have not been changed by this method of treatment. They continued in their irresponsible ways. Spencer (1963) would appear to have been the only other author to have reported on studying patients selected because of poor prognosis, and evidently some of his 10 cases fell into the psychopathic category. He commented on the responsibility and load felt by the doctor when L.S.D. 25 was used to treat this group.

It is of course mainly the psychopathic and immature individuals in the community who are indulging in illicit L.S.D. 25 ingestion. It is not unexpected, as the results of the present study show, that their behaviour becomes more obviously antisocial and irresponsible, and one must remember that illicit dosage is about 10 times what has been used here. It is a pity that abuse by this psychopathic group, the results of which have led to a national outcry, should result in the drug itself being blamed for what it is – a potent drug but useful in certain circumstances. If morphine had been banned, instead of being made subject to regulations, because of its dangers in certain individuals, doctors would not have had at their disposal a powerful therapeutic agent. There is no agreement amongst psychiatrists regarding the mode of action of L.S.D. 25. Most commonly it has been thought of as an abreactive agent (Sanderson et al 1954), capable of summoning up deeply repressed memories (Spencer 1963), but Robinson et al (1963) felt that "abreaction alone is not essential for recovery." The present author feels that the following two events happen as the result of the chemical influence of the drug (a) the patient is able to see simultaneously a panoramic viewpoint of his past life, and in contra-distinction

to other drugs, L.S.D. 25 does not allow him to reject those memories, no matter how unpleasant and (b) there is markedly increased suggestibility – much more so than with hypnosis, without the patient feeling in the same way that he has been influenced by the therapist.

Summary

The results of a 3-year enquiry using L.S.D. 25 are reported. Only patients with poor prognosis were studied. A three-year follow-up indicated that L.S.D. 25 is a useful drug in the treatment of psychosexual disorders in the female, whilst it is at least useless if not dangerous in the case of psychopaths. The latter group is liable to abuse any potent drug with catastrophic results. An explanation is offered of how L.S.D. 25 may produce beneficial therapeutic effects in certain female patients with psychosexual disorders.

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BOOK REVIEW

PAUL WOOD'S DISEASES OF THE HEART AND CIRCULATION. Revised and Enlarged by his Friends and Colleagues. Third Edition. (Pp. xlvii+1164; Illustrated; 210s.). London: Eyre and Spottiswoode, 1968.

THE latest edition of this book makes its appearance after almost twelve years since the second edition written by Paul Wood. His name remains in the title as a lasting tribute by the participants of the new edition, twenty-four in all, headed by Somerville. Advances in cardiology carry on apace and the authors have done well in keeping up to date with recent ideas and techniques, although inevitably most recent advances in the field of intensive care could not be included. However, this book will be of most value for physicians wishing to have a clear exposition of heart disease correlated with physiological data and routine technical investigations. It is conveniently arranged into sections dealing with difference topics, congenital heart disease, congestive heart failure, cardiac arrhythmias, etc., with terse accounts of relevant data. The sections of special investigations are good and will help the general physician to gain a grasp of what the specialist cardiologist refers to. Each section has its list of references which make a comprehensive bibliography useful for those wishing to study the subject more thoroughly in the literature. The illustrations are profuse and produced on full art paper. There is a good index at the back of the book. This book should be in the possession of those wishing to acquire a sound knowledge of cardiology. The more specialist cardiologist will still find items of interest in topics with which he may be concerned at any time. It can be recommended as a standard text book of general cardiology. E.F.

to other drugs, L.S.D. 25 does not allow him to reject those memories, no matter how unpleasant and (b) there is markedly increased suggestibility – much more so than with hypnosis, without the patient feeling in the same way that he has been influenced by the therapist.

Summary

The results of a 3-year enquiry using L.S.D. 25 are reported. Only patients with poor prognosis were studied. A three-year follow-up indicated that L.S.D. 25 is a useful drug in the treatment of psychosexual disorders in the female, whilst it is at least useless if not dangerous in the case of psychopaths. The latter group is liable to abuse any potent drug with catastrophic results. An explanation is offered of how L.S.D. 25 may produce beneficial therapeutic effects in certain female patients with psychosexual disorders.

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THE LONG TERM PROGNOSIS OF ATRIAL FIBRILLATION FOLLOWING DIRECT CURRENT CONVERSION

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Introduction

WITH the introduction of direct current countershock (Lown et al. 1962) a simple, safe and effective method of converting atrial fibrillation to sinus rhythm became available. A detailed account of the technique used here, the indications for its use, the success rate achieved and the hazards encountered has been published (Pantridge and Halmos 1965). While the immediate results of D.C. conversion make it the method of choice in removing atrial fibrillation, few long term follow-up studies have been made (Charms et al. 1966, Radford and Evans 1968). It is clear that unless a patient is likely to remain in sinus rhythm for a reasonable period, D.C. conversion is pointless.

Patients and Methods

Direct current conversion of chronic atrial fibrillation was attempted on one or more occasions in 356 patients between October, 1963, and March, 1967. Initially all patients in whom chronic atrial fibrillation was diagnosed had an attempted D.C. conversion, with the exception of those awaiting mitral valvotomy. Following analysis of the results obtained in the first 175 patients, D.C. conversion was usually not attempted in patients with atrial fibrillation of more than five years' duration, or in those with gross mitral incompetence and marked cardiac enlargement.

Full clinical records were obtainable in 330 of the 356 patients. This group was studied to assess the immediate success rate of attempted D.C. conversion. The prognosis with regard to relapse of atrial fibrillation was obtained by reviewing 278 patients between 3 and 42 months after the initial D.C. conversion.

The methods of conversion and of anaesthesia in the first 175 patients were as described by Pantridge and Halmos (1965). Since 1965, Brietal Sodium (Eli Lilly) 1 mg./Kg. body weight, has been used to induce anaesthesia and the electrode paddles have been placed antero-posteriorly. Initially a direct current shock at an energy level of 50 watt seconds was used. If atrial fibrillation persisted, three further shocks were delivered up to a maximum of 400 watt seconds. If atrial fibrillation still persisted no further attempt was made. Since 1964, digitalis has been discontinued 48 hours prior to conversion, as it has been shown that digitalis adversely affects the chances of successful conversion and increases the risk of post-conversion arrhythmias (Pantridge and Halmos 1965).

Immediate Success Rate

Sinus rhythm was restored in 268 (81 per cent) of 330 patients. Before any attempt to select patients for conversion was made, 130 of 175 (74 per cent) had successful conversion. Following the exclusion of patients with very long-standing atrial fibril-

TABLE I

Immediate results of D.C. Conversion in 330 Patients

	No. of Patients	*No. Converting*	*Percentage Converting*
Male	117	103	88
Female	213	165	77
Under 50 years	164	136	83
Over 50 years	166	132	79
Rheumatic	241	192	80
Ischaemic	43	37	86
Thyrotoxic	20	18	90
Miscellaneous	26	21	81
Total	330	268	81

lation and those with gross mitral incompetence and cardiac dilatation from attempted conversion sinus rhythm was restored in 137 of 155 patients (89 per cent).

Table I shows the conversion rate according to age, sex and the aetiology of the atrial fibrillation. The immediate success rate was little influenced by age but was higher in males than in females. More than 80 per cent of patients were converted irrespective of the aetiology of the atrial fibrillation, but patients who had formerly had thyrotoxicosis had a slightly higher conversion rate (90 per cent) than patients in the ischaemic (86 per cent) rheumatic (80 per cent) or miscellaneous (81 per cent) groups.

Anticoagulants were not given routinely before D.C. conversion. Eighteen patients who had been receiving anticoagulants following a myocardial infarction or a recent embolus, continued on this therapy. Among 450 successful conversions in 330 patients, 2 patients developed transient hemiparesis in the week following conversion, presumably due to cerebral emboli. Both recovered completely. Another patient had a major cerebrovascular accident on the eighth day after conversion. Thus the incidence of clinically detected emboli was less than 0.7 per cent.

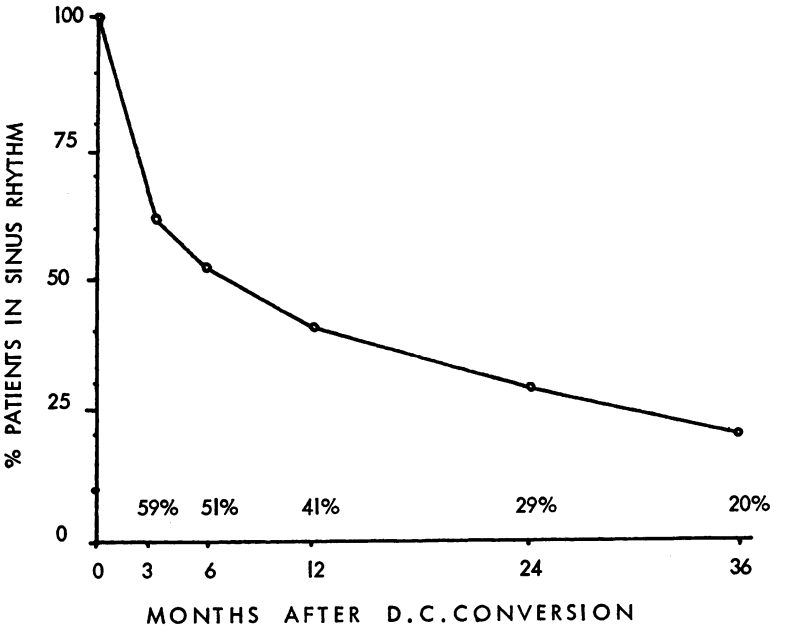
Among the patients in whom sinus rhythm could not be restored or maintained, seven major embolic episodes are known to have occurred. Two patients who remained for long periods in sinus rhythm were admitted following embolic episodes and were found to have relapsed to atrial fibrillation since their previous visit. In these patients it was impossible to determine whether emboli had occurred before or after relapse. Three other patients died suddenly at home, possibly as a result of emboli. No episode of ventricular fibrillation occurred following D.C. conversion in this series. One patient developed pulmonary oedema several hours after D.C. conversion, and was successfully treated with diuretics.

LONG TERM RESULTS

Two hundred and twenty-two patients had successful conversions and were followed up for 3 months or more. The percentage of these remaining in sinus rhythm after various intervals is illustrated in the Figure. The relapse rate was highest soon after D.C. conversion and thereafter the risk of reversion to atrial fibrillation decreased. Forty-one per cent of those followed up for one year, and twenty per cent of those followed up for three years remained in sinus rhythm.

In assessing the effect of various factors on the maintenance of sinus rhythm, the percentage of patients remaining in sinus rhythm one year after D.C. conversion has been taken as an indication of the long-term trend of relapse. One hundred and sixty-eight patients were reviewed one year or more after the first conversion.

Age, sex and blood pressure did not have a significant influence on the percentage of patients remaining in sinus rhythm one year after D.C. conversion (Table II).



Maintenance of Sinus Rhythm after D.C. Conversion

TABLE II

Long term results of D.C. Conversion

		Number of Patients	*Number in Sinus Rhythm after 1 year*
Age	<50 years	97	38 (42%)
	>50 years	77	31 (40%)
Sex	Male	59	26 (44%)
	Female	109	43 (39%)
Diastolic	<90mm. Hg.	116	49 (42%)
Blood Pressure	>90mm. Hg.	52	20 (38%)
Aetiology	Rheumatic	131	55 (42%)
	Ischaemic	15	4 (27%)
	Thyrotoxic	10	6 (60%)
	Miscellaneous	12	4 (33%)
Total		168	69 (41%)

The percentage of the large group of patients with rheumatic heart disease remaining in sinus rhythm at one year (42 per cent) was similar to that for the total. Six of 10 patients with treated thyrotoxicosis maintained sinus rhythm for a year, compared with only 4 of 15 with ischaemic heart disease.

Repeated D.C. Conversion

One hundred and fourteen patients had an attempted second D.C. conversion. The immediate conversion rate (92 per cent), and the percentage of patients remaining in sinus rhythm 1 year after conversion (20 per cent) are presented in Table III. They have been divided into two groups according to whether the sinus rhythm established on the first occasion persisted for more or less than 6 months. Thirty-two per cent of those who had maintained sinus rhythm for 6 months or more on the first occasion were still in sinus rhythm 1 year after a second conversion. But only 14 per cent of those who had relapsed within 6 months, remained in sinus rhythm 1 year after a second conversion.

Table III

Immediate and Long Term Results of a Second D.C. Conversion

Duration of S.R. after first D.C.C.	*No. of Patients*	*No. Converted*	*Percentage of those converted still in sinus rhythm*	
			3 mths. later	*1 year later*
Less than 6 mths.	58	51 (88%)	47	14
More than 6 mths.	28	28 (100%)	71	32
Total	86	79 (92%)	56	20

Twenty-four patients had an attempted third conversion. All but three were successfully converted again. Twenty patients were examined after three months. Nine (45 per cent) remained in sinus rhythm.

Relapse was commonly associated with return of palpitations and diminished exercise tolerance. Seven patients required re-admission shortly after relapse because of acute left heart failure associated with rapid ventricular rate.

Discussion

In most reports on the effectiveness of the D.C. conversion, the immediate conversion rate has been high (Killip 1963, Hurst et al. 1964, Lown 1964, McDonald et al. 1964, Oram and Davies 1964, Duchelle 1966). This is confirmed by the present study. Our overall conversion rate of 81 per cent is slightly lower than that of several other authors. The fact that the conversion rate rose from 74 per cent to 89 per cent when attempts were no longer made in the presence of very long-standing atrial fibrillation or gross mitral incompetence with marked cardiac enlargement, indicates that patients with atrial fibrillation can be selected with regard to likelihood of successful conversion. Stricter criteria for selection of patients would increase the percentage of successful attempts, but would deny long periods in sinus rhythm to a minority of the excluded patients.

The success rate is relatively little affected by age or sex. It has been shown to be principally dependant upon the time for which atrial fibrillation has been present

(Halmos 1966). This probably reflects the greater degree of atrial dilatation in the presence of long-standing fibrillation (Lown 1967). Patients with atrial fibrillation of long duration also tend to have fine fibrillation (f) waves in the electrocardiogram. This has been shown to decrease the chances of successful conversion (Halmos 1966, Lown 1967). These facts could account for the lower incidence of success in those with long-standing rheumatic heart disease. The lower success rate in women in this series is related to the higher incidence of rheumatic heart disease in this sex.

The risk of systemic embolism following conversion has been stressed, and anticoagulants have been given by some authors in an attempt to lessen this risk (Lown 1964, Duchelle 1966). Killip (1963) did not find any difference in the incidence of embolism in two groups of patients, when only one group received anticoagulants. Both groups were rather small. No emboli occurred in the 94 patients converted without anticoagulation, who were reported by Radford and Evans (1968). Cerebrovascular accidents may occur shortly after D.C. conversion even in patients treated with anticoagulants (Charms et al. 1966). In the present series the incidence of embolism was very low in patients not so treated. It is very doubtful whether routine anticoagulation, with its own attendant risks, would have lowered the incidence of emboli further. Attempted D.C. conversion would not appear to call for anticoagulation therapy in patients in whom other indications for its use are absent.

There is still little information regarding the long-term maintenance of sinus rhythm once it is re-established. Lown (1967) reported that 50 per cent. of his patients maintained sinus rhythm for a year. But Killip and Yormak (1965) found that only 27 per cent, and Radford and Evans (1968) only 18 per cent of their patients were in sinus rhythm one year after D.C. conversion. In the present study in which some patients were followed up for more than 3 years, the decreasing likelihood of relapse with time is demonstrated. The patients reviewed at 3 years all came from the unselected group, wheaeas many of those reviewed after only 1 year came from the group selected to exclude patients with several factors predisposing to early relapse (Halmos 1966). This probably accounts in part for the fact that whereas 41 per cent of those reviewed at 1 year maintained sinus rhythm, the figure was only 20 per cent for those reviewed after 3 years. It is likely that the relapse rate between 1 and 3 years is lower than that indicated in the figure.

The rate of relapse was apparently unaffected in this series by age, sex or blood pressure. From the series of Radford and Evans (1968) as from the present series, patients with atrial fibrillation persisting after control of thyrotoxicosis seem to have a better chance of maintaining sinus rhythm for long periods after D.C. conversion, than patients in other aetiological groups. On the other hand, patients in whom chronic atrial fibrillation is associated with ischaemic heart disease are unlikely to remain in sinus rhythm for very long. Within the large group with rheumatic heart disease, the patients with atrial fibrillation of short duration who were converted following a first mitral valvotomy, had a relatively low risk of early relapse. A more detailed study of this group is in progress.

Most workers give their patients oral quinidine (1.0–1.6 grams daily) in an attempt to reduce the relapse rate (Hurst et al. 1964, Duchelle 1966, Rossi and Lown 1967). However, Pantridge and Halmos (1965) found that neither quinidine

(1.2 grams daily) nor potassium (50 mEq. daily) lowered the relapse rate significantly. Likewise, Hall and Wood (1968) found no significant difference in relapse rate between patients receiving 1 gram of quinidine daily and those receiving none. Only 15 per cent of our patients were given quinidine at any time. The overall relapse rate was not markedly different from those reported by workers using quinidine.

In spite of the high incidence of relapse, we feel that since more than 40 per cent of patients remained in sinus rhythm for a year or more, D.C. conversion was worth while. Most patients not only felt better but were shown to have higher cardiac outputs following conversion (Scott and Patterson, 1968). The place of repeated conversions is less clear. The relapse rate following second conversions is somewhat higher than after first. However, all attempted second conversions in patients who maintained sinus rhythm for six months or more after the first conversion were successful, and the percentage of these remaining in sinus rhythm for a year (32 per cent) was only 9 per cent less than the one year figure after the first conversion.

The results of attempted third D.C. conversion were similar to those of the second. The number of patients available for follow-up has been small but the tendency to relapse seems even greater than that following the first and second conversions. In the few patients in this series who have had four or more conversions, the duration of sinus rhythm has tended to become progressively shorter after each procedure. This is in keeping with the findings of other workers (Radford and Evans 1968).

Though exceptions occur (Oram and Davies 1965), it would appear that patients who relapse soon after the first D.C. conversion, rarely maintain sinus rhythm for long after second or subsequent conversions. If sinus rhythm persists for six months or more on the first occasion, repeated D.C. conversion would appear to be justified. A few patients who relapse repeatedly at intervals of more than six months may be kept in sinus rhythm for years by repeated D.C. conversions.

Summary

The results of attempted D.C. conversion in 330 patients with atrial fibrillation are reported. Sinus rhythm was restored in 81 per cent. The incidence of embolism was less than 0.7 per cent in non-anticoagulated patients.

Two hundred and twenty two patients were reviewed between three and forty-two months after successful D.C. conversion. After one year 41 per cent, and after three years 20 per cent of patients remained in sinus rhythm without further conversions.

Maintenance of sinus rhythm was unaffected by age, sex or blood pressure. Patients with treated thyrotoxicosis tended to maintain sinus rhythm better than those with ischaemic heart disease. Those with rheumatic heart disease had an intermediate prognosis.

The immediate success rates in attempted second and third D.C. conversions were high. Patients who relapsed rapidly on one occasion usually did so again. It is suggested that repeated D.C. conversion is useful in the management of patients who have maintained sinus rhythm for more than six months.

Acknowledgements

We are grateful to Dr. J. F. Pantridge for permission to study these patients who were under his care. Our thanks are also due to the anaesthetists who anaesthetized the patients, and the general practitioners who helped in the follow up of patients living some distance from Belfast. Dr. Scott was in receipt of a Royal Victoria Hospital Research Fellowship while the follow-up was conducted.

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RIB PAIN – A NEGLECTED DIAGNOSIS

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INTRODUCTION

THE DIAGNOSIS of pain in the chest is one of the important problems met with in medical practice, and is usually considered by the patient and doctor to be of ominous significance until otherwise explained. In the upper chest, disease of the heart, lungs and pleura is usually suspected; while in the lower chest, disorders of gallbladder, kidney or stomach may be incriminated. In presenting this paper we wish to draw attention to pain arising in the wall of the chest, and describe our experience in a group of patients in whom this diagnosis was made. A previous series with similar clinical features has already been reported by one of us (Grant 1966) with suggestions as to treatment. The reasons for referral in the present series confirm the opinion that chest wall pain is seldom thought about, and that a more general recognition might save unnecessary worry and invalidism. We recognise our diagnosis is a clinical one lacking technological confirmation, a fact which may partly explain both its neglect and the confusion in nomenclature. It is not possible to make what are unsubstantiated claims, but research reading would suggest that what we describe has been called by different names, and in many instances attention has been focused only on the front part of the chest. We suggest that chest wall pain is often associated with a rib which examination will reveal to be tender along its length, and on this basis we attempt to clarify the literature. As a working hypothesis minor mechanical derangements of the ribs, and in some instances the associated dorsal vertebrae, would explain the clinical picture met with in our patients.

PATIENTS AND FINDINGS

A general account is given of the clinical features in a series of 41 patients with rib pain, who presented in a general medical unit in the course of one year. The diagnosis was limited to pain in the thoracic cage which was not caused by any obvious inflammatory or neoplastic process. Fractured ribs and underlying chest disease were excluded by X-ray of the chest and dorsal spine. Where necessary, cardiography and enzyme tests were used to exclude angina.

SYMPTOMS

The diagnosis was that of pain in the chest. This was described by the patients in many different ways and could be easily misinterpreted except for certain fairly constant features :

(1) Reasonably accurate localisation.
(2) Accentuation by movements of the thoracic spine – twisting and bending or turning in bed.
(3) Exacerbation by breathing, coughing or straining.
(4) Association with posture and position.

(5) A history of twist or muscular stress sometimes requiring questioning to elicit.

Our patients used different qualifying adjectives – cramp-like, rheumatic, darting, sharp, a catch, and occasionally dull or burning. They often felt the pain in the front of the chest but sometimes it was associated with discomfort in the back or around the axilla.

Physical Signs

Tenderness on pressure over the rib was the diagnostic criterion. Compression at the localisation reproduced or accentuated the patient's discomfort.

Localisation of Tenderness (Tables I and II)

In all patients there was tenderness on pressure involving one or several ribs, but in a third of the cases there was also tenderness over the associated dorsal spines. On this clinical criteria the series was divided into a larger group in whom only the ribs were tender – the 'costal syndrome', and a smaller group in whom there was also tenderness of the dorsal spine – the 'vertebro-costal syndrome'.

Table I

Sites of Tenderness Vertical Plane

		Right	*Left*	*Bilateral*
Costal Syndrome=31 *cases*				
Single Ribs Tender=20 cases				
2 or 3		1	1	–
4 or 5 or 6		3	7	–
7 or 8 or 9 or 10		1	3	–
11 or 12		3	1	–
Multiple Ribs Tender=11 cases				
2/3		1	1	–
3/4 or 3/4/5 or 4/5 or 5/6		2	3	–
6/7/8		–	1	–
10/11 or 11/12		2	1	–
		13	18	–
Vertebro-Costal Syndrome=10 *cases*				
Single Spines Tender=7 cases				
T.3	3	–	1	2
T.4	2	–	–	2
T.7	1	–	–	1
T.8	1	–	–	1
Multiple Spines Tender=3 cases				
3/4	1	–	1	–
3/4/5	1	–	–	1
5/6	1	1	–	–
		1	2	7

TABLE II
Sites of Tenderness Horizontal Plane

No. of Cases		*Rib*		*Dorsal Spine*	
		Costo-Chondral Jn.	*Shaft*	*Costo-Vertebral Jt.*	
3	Costal Syndrome	+	+	—	—
9		—	+	+	—
1		—	—	+	—
18		+	+	+	—
2	Vertebro-Costal Syndrome	—	—	+	+
8		+	+	+	+

In the 'costal syndrome' no instance of tenderness of the first rib was found and involvement of ribs below the third was more usual. The most common complaints were of apparent involvement on the 4th to the 8th ribs on the left side and after this of the 10th to the 12th ribs on the right side. In most instances single ribs were tender but combinations were found of adjoining ribs in about half of the patients. As to the actual sites of tenderness along the rib, this usually involved the whole rib – the costo-chondral junction, the shaft and the costo-vertebral joint. In just three instances were the costo-chondral junction and shaft only painful, whilst there were seven patients with tender 11th and/or 12th floating ribs and consequently tenderness of only the shaft and costo-vertebral joint.

In the 'vertebro-costal syndrome' the upper and lower portions of the dorsal spine were not affected. Single vertebrae were twice as often affected as several vertebrae. In this group tenderness was more usual in the ribs on both sides of the chest which were attached to the tender spine; this bilateral rib tenderness was not found in the simple 'costal syndrome'. Traction on the spine usually gave some relief.

INITIAL DIAGNOSIS (TABLE III)

In no instance was the diagnosis made outside hospital and patients could be divided into two groups. In the first group the presenting symptom for diagnosis was pain. In the second group the patients developed rib pain whilst in the ward or complained of it as an associated or secondary condition.

The initial diagnosis in the patients sent to hospital because of their pain show that the possibility of myocardial ischaemia was by far the most common cause for referral. The fact that 3 out of these 18 patients had had a previous episode of myocardial ischaemia confirmed by cardiograph was noted, but no evidence was found of recurrence. Pulmonary neoplasm, pleurisy, pneumonia and bronchitis were other presenting diagnoses when the upper and middle ribs were involved, whilst renal calculus, cholecystitis and peptic ulcer were suggested diagnoses with the lower rib syndromes.

TABLE III
Reasons for Referral to Hospital

Pain in chest presenting complaint = 30 *Cases*	
Myocardial Ischaemia	18
Pulmonary Neoplasm	4
Pleurisy	2
Peptic Ulcer	2
Cholecystitis	1
Renal Calculus	1
Virus Pneumonia	1
Bronchitis or Pulmonary Fibrosis	1
Pain in chest secondary complaint = 11 *cases*	

AGE AND SEX

No children were seen. Patients with ages ranging from 15 to 84 years presented, and of these 23 were in excess of 50 years. Sexes were almost equally affected – 22 males to 19 females.

PREDISPOSING FACTORS (TABLE IV)

No likely cause could be ascertained in 6 patients but in the remaining 35 cases there appeared to be factors of significance. In 14 patients there was evidence to suggest that a mechanical stress preceeded the symptoms, although in some instances this information was not immediately volunteered. Strains were produced by a sudden twist, usually in an attempt to save a fall, or in performing a sudden movement involving the trunk. There was evidence of osteoarthritis of the dorsal spine on radiological examination of 13 patients, and in 2 of these there were associated congenital anomalies. One had a congenital fusion of the lower three thoracic vertebrae with some degree of kyphosis and a lordosis in the upper dorsal region. In the other, there was a reduction in the vertical height of D.8. Cough appeared

TABLE IV
Predisposing Factors

	Costal	*Vertebro-Costal*
Falls or Twists	10	1
Osteoarthritis	4	4
Cough	6	–
Twist and Cough	2	–
Osteoarthritis and Cough	1	1
Osteoarthritis and Congenital Anomaly	1	1
Osteoarthritis and Twist	–	1
Operation	3	–
No Cause Found	4	2
	31 Cases	10 Cases

TABLE V

Suggested Nomenclature of Rib Pain

Costal Syndrome	Acute Costochondritis or Rib Syndrome Chronic Costochondritis or Tietze's Syndrome Ziphoidalgia Costal Margin Syndrome Precordial Catch Costo-Chondral Syndrome Chondro-Costal Precordial Syndrome Slipping Rib, Twelfth Rib Syndrome of Davies Colley Fibrositis of the Chest Pleurodynia
Vertebro-Costal Syndrome	Radicular or Root Syndrome Thoracic Disc Dorsal Osteoarthritis } Some cases Intercostal Neuritis

to precipitate the discomfort in 10 patients although associated with a twist or dorsal arthiritis in 4 instances; all of these persons had an acute or chronic respiratory infection. In three cases an operative procedure involving straining of the rib cage preceded the onset of symptoms. Osteoarthritis was more common in the vertebro-costal group, whilst cough, twists and operative strains were prominent in the simple costal syndrome.

ILLUSTRATIVE CASE HISTORIES

1. Housewife aged 45. A small frail woman who had been engaged in nursing her invalid father; work which involved shifting him around the bed. She complained of an 'agonizing' pain in the left side of the chest over three months and had been investigated elsewhere -- x-ray chest, cardiograph, blood count and sedimentation rate being described as normal, but the cervical spine x-ray showed degenerative changes C.4-5 disc. Referred to clinic as possible angina for further opinion.

She was unable to remember the exact commencement of her discomfort but on questioning localised the pain as being 'gripping' over the 3rd and 4th left costo-chondral cartilages going through to the back in the left scapular area and axilla. She had also pain down her arm at night and felt depressed and very worried about her heart.

On examination, radiology of the chest, thoracic spine and ribs was normal and the cardiograph again negative. Twisting her back was painful. She was tender over the 3rd-5th cartilages anteriorly, the shaft of the 3rd rib along its course to the axilla and the costo-vertebral joints of the 3rd, 4th and 5th ribs.

Diagnosis: Costal Syndrome involving several ribs probably due to mechanical strain.

2. Butcher aged 57. An eleven year history of 'angina' and 'high blood pressure' for which he had attended a cardiac clinic on previous occasions when affected. Four weeks before attending the clinic developed a 'more severe pain like a knife' which stabbed his chest on both sides, especially the left, and caught his breath mainly in the front of his chest. No history of injury was obtained but twisting and lifting his arms might produce a sudden exacerbation seizing him up. Referred as possible cardiac pain.

On examination, he had a hypertension 230/140 mmHg., his cardiogram showed a left ventricular ischaemic pattern, but enzyme tests were normal. X-ray chest showed some cardiac enlargement and the film of his thoracic spine osteroarthritis with osteophyte formation in the lower portion. In front he was tender over the 3rd-5th costo-chondral junctions on the left and the 3rd on the right, whilst posteriorly the same ribs were painful on compression over the costo-vertebral joints and the 3rd thoracic spine was tender. Rotation of the back produced pain whilst his discomfort was relieved by traction.

Diagnosis: Vertebro-costal syndrome involving mainly the 3rd dorsal vertebra and associated with osteoarthritis. Radicular type of pain. May have thoracic disc lesion.

Hypertension and previous angina were not the primary diagnosis.

Discussion

The fact that pain can arise in the structures of the thoracic cage has been recognised for many years and diagnoses of 'fibrositis' and 'muscular rheumatism' are made from time to time, usually when investigations of chest pain have proved negative. It is apparently not so well appreciated that pain originating in the ribs is of frequent occurrence in everyday practice. Reports of series of cases are relatively few, apart from those on Tietze's syndrome, yet the 'slipping rib' involving the lower two floating ribs and often named after its discoverer the 'syndrome of Davies Colley' has been known for over half a century (Bailey, H. 1960). Isolated case reports give the impression it is uncommon and usually confused with gall-bladder or renal pain.

In a previous paper by one of us (Grant 1966) a series of 38 persons were encountered with pain in the chest wall. These observations and the experience of 41 patients reported in the present paper confirm our views that many physicians may have met with these simple clinical conditions, yet lack of objective, pathological or technological confirmation, have kept them from a committed diagnosis.

To clarify the problem of rib pain is difficult, especially as X-ray films of the rib insertions do not seem helpful. The clinical criteria of always finding some part of the rib tender and sometimes an associated tenderness of the dorsal spines, have dictated our terminology. Pathological proof as to the basic causes is lacking and supposition takes its place. Our experience would be in keeping with the idea that many cases of pain in the chest wall are due to an anatomical misalignment of a rib. This need only be of slight degree to produce discomfort and disturb the equilibrum of the musclo-skeletal structures of the thorax. The pain may be localised by the patient anteriorly or posteriorly, depending on which insertion of the affected rib is more displaced, but in most instances some tenderness may be traced along the whole rib. On the mechanical principle that subluxation at even one insertion will affect the exact fitting of a rib, this finding is not unexpected. In the group which we call the 'costal syndrome' where the rib alone is tender, a simple sprain at either insertion would be sufficient explanation. However, in the 'vertebro-costal syndrome' our patients had, in addition, tenderness over one or more dorsal spines and bilateral involvement of the associated ribs was common especially at their posterior ends. It seems possible that here the problem originates in the dorsal vertebrae affecting the costo-vertebral joints on each side and the consequent fit of attached ribs. This could be produced by a torsion displacement hard to show on X-ray, and more likely to occur if osteoarthritis is present. Obvious misalignment and postural abnormalities may be present but not necessarily so, and in some

instances there may be even vertebral disc lesions. Root pain is more common in this type of patient and the symptoms more severe and intractable.

Most of the literature on chest wall pain has been focused on conditions with tenderness of the costo-chondral junctions, in particular the conditions described in 1921 and called after the author of the paper 'Tietze's syndrome'.

Histological study in this morbid condition sometimes called 'costo-chondritis' or 'costochondralgia' has been usually unrewarding (Giardina, Bencini and Gabrielli, 1965). Perhaps a clue may be found in Kayser's (1956) review on the subject and the statement that open operation has only revealed angulation at the costo-chondral junction. Indeed the validity of any inflammatory process being the cause is questionable. It seems likely that Tietze's syndrome may well be due to a chronic subluxation of the anterior end of a rib and related to all the other 'rib syndromes'. Indeed under this heading Rawlings (1962) considered 'xiphoidalgia', the 'costal margin syndrome', the 'twelfth rib syndrome', the 'precordial catch' (Miller and Texidor, 1959), the 'radicular syndrome', and 'costochondritis' all to be variants of sprained costochondral junctions. Series of cases with costochondral tenderness confused with angina have also been reported as the 'costo-chondral syndrome' (Benson and Zavalla, 1954) and the chondrocostal precordial syndrome' (Fiegel, Bargheer and Kukwa, 1965). Any misalignment of a rib we suggest may affect the costochondral junction and usually the costovertebral joint as well, and it seems more realistic to consider whether the rib alone is out of position 'costal syndrome' or whether the misalignment basically arises in the dorsal spine 'vertebro-costal syndrome'. The radicular syndrome (Gunther and Sampson 1929, Smith and Koutz 1942, Davis 1948) seems to be due to the latter cause and its description bears close resemblance to what Cyriax (1950) attributes to articular and nerve root types of 'thoracic disc' lesions. As proof of pathology is again often lacking we feel our classification on clinical grounds alone has some justification. Perhaps the terminology of rib pain may be simplified as in Table V. In doing this we recognise the exact diagnosis of pain in the chest wall may be difficult and it is not possible to correlate our findings with every author. For example, Allison (1950) divided his series of patients into three groups – muscle strain, fibrositis and kyphoscoliosis. We do, however, suggest that rib tenderness is a frequent finding even though it may not be present in every case of chest wall pain.

Summary

The clinical features in 41 patients with pain in the wall of the thorax are described and related to tenderness of one or more ribs. Cases fall into two groups: the 'costal syndrome' where only the ribs appear involved, and the 'vertebro-costal syndrome' where the problem is further complicated by tenderness of the associated dorsal spines. The possible aetiological factors are discussed and an attempt is made to clarify the somewhat confused nomenclature on chest wall pain. Results suggest that rib pain is relatively common but not well recognised and so may account for variously reported conditions. Reasons are given for considering the syndromes described as important in the differential diagnosis of obscure chest pain and of angina.

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BOOK REVIEW

HOSTELS IN HOSPITALS. By J. S. Meredith, M. A. Anderson, A. C. Price and J. Leithead. (Pp. 175; 21s.). London: Published for Nuffield Provincial Hospital Trust by Oxford University Press, 1968.

THIS publication is one of a long series of monographs published by the Nuffield Provincial Hospitals Trust. Coming from this stable it should command close attention for the Trust has had a long list of most important and telling publications to its credit. This monograph on hostels in hospitals is no exception and should be read by all those whether they take seriously or not the problems of making the best use of all the resources of the hospital service.

While its main theme is to highlight the place for hostels in the hospital service in the process of building up the case, a whole range of other techniques are argued and in many cases endorsed. All of these have as their common object the better utilisation of resources.

The case for hostel beds is not new and it is surprising, although the case for these beds has been acknowledged for many years and indeed the use of these beds has so long been demonstrated in Sweden, that official backing for them has been so long ignored. It could be thought that the term hostel beds is just another label for a group which already exist such as pre-convalescent, pre-discharge or convalescent beds. It may be thought too that some resistance from clinicians has been voiced for fear that their presence might interfere with the number of acute beds allocated to them.

Time spent in reading this monograph would be very well spent by all those who are involved in the development of the hospital service in Northern Ireland or indeed elsewhere. Many useful hints both in planning, running and staffing hostel beds have been well set out and a great deal of trouble has been taken to make the estimate of costs and the problems likely to be encountered as realistic as possible. Easy to read and assimilate, this publication should command wide reading. K.R.D.P.

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JUVENILE POLYPOSIS COLI.

By G. W. JOHNSTON, M.Ch., F.R.C.S., D. EAKINS, M.D., M.C.Path., A. D. GOUGH, M.B., F.F.R.
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A FEW decades ago intestinal polyposis was regarded as a single entity, but increasing knowledge has led to the identification of a number of different syndromes. The term polyposis coli is usually taken to mean familial adenomatosis coli, a premalignant condition occurring in adolescents and adults. Although there have been many reports of colonic polyposis in children, discussions on the subject have been confused because of the failure, until recently, to distinguish between the adenomatous polyp and the juvenile polyp. The commonest type of polyp in children is the juvenile or retention polyp which is present usually as a solitary lesion, but occasionally such polyps are multiple in the colonic mucosa and the term juvenile polyposis coli is used (Veale et al 1966). This is a rare condition: only six cases have been seen at St. Mark's Hospital, London, in contrast to 140 cases of familial adenomatosis coli (Lockhart-Mummery 1967). Nevertheless its recognition is important since it differs from adenomatosis coli in its aetiology, clinical presentation, pathology and prognosis.

We wish to present a patient with juvenile polyposis coli and an associated congenital cardiac lesion.

Case Report

S. McC., a 31 year old male with a known interventricular septal defect, was admitted to the Royal Victoria Hospital, Belfast, in May, 1967, for dental surgery. On admission he complained of passing large amounts of bright red blood in his motions for one week. On further questioning he admitted to occasional rectal bleeding from childhood. Three years previously, when the congenital cardiac lesion was first diagnosed, his haemoglobin was found to be only 2.8 g./100 ml. He required blood transfusion on that occasion and again 18 months later. On admission to hospital, in May, 1967, his haemoglobin was 7.2 g./100 ml.

At sigmoidoscopy, only the lower 15 cm. of the rectum were examined and no mucosal lesion was seen while a double contrast barium enema revealed two polyps in the caecal area and no other pathological lesion.

At laparotomy in June, 1967, the caecum, ascending colon and proximal half of the transverse colon were found to contain multiple polyps. Since no polyps were palpated beyond the mid transverse colon a right hemicolectomy was carried out. The specimen contained multiple polyps of varying sizes (Fig. 1). Many were haemorrhagic and could be plucked off the colonic wall with ease, leaving short stalks.

Histological examination revealed a variable picture. The polyps were composed of epithelial and connective tissue elements and there was both acute and chronic inflammatory cell infiltration of the stroma in almost all the polyps. The stroma varied in amount and did not contain smooth muscle fibres. It was abundant and oedematous in most areas. In some fields the glands were small while in other regions they were cystic (Fig. 2). Mucous secretion was retained. In a few glands the nuclei of the epithelial cells were larger than normal but there was no evidence to suggest malignant change.

During the post operative period repeat sigmoidoscopy was carried out and two rectal polyps at 15 and 18 cms. were discovered and removed. Repeat double contrast enema showed a few remaining polyps in the descending colon. The patient was discharged from hospital, but continued to have further minor episodes of rectal bleeding. He was readmitted

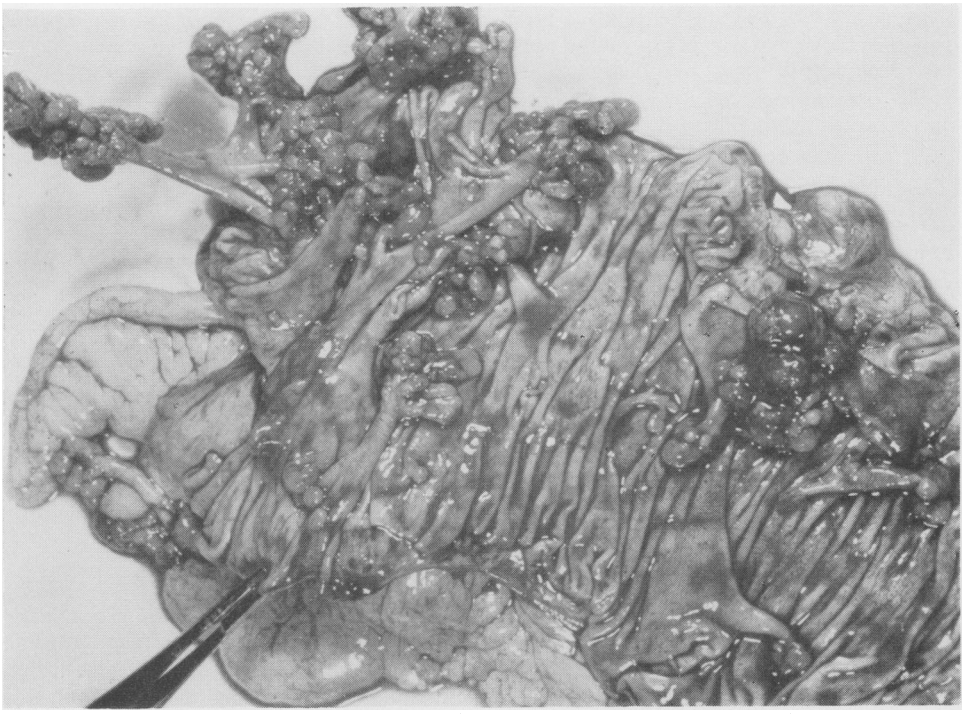

FIG. 1. *Surgical specimen showing pedunculated juvenile polyps in colonic mucosa*

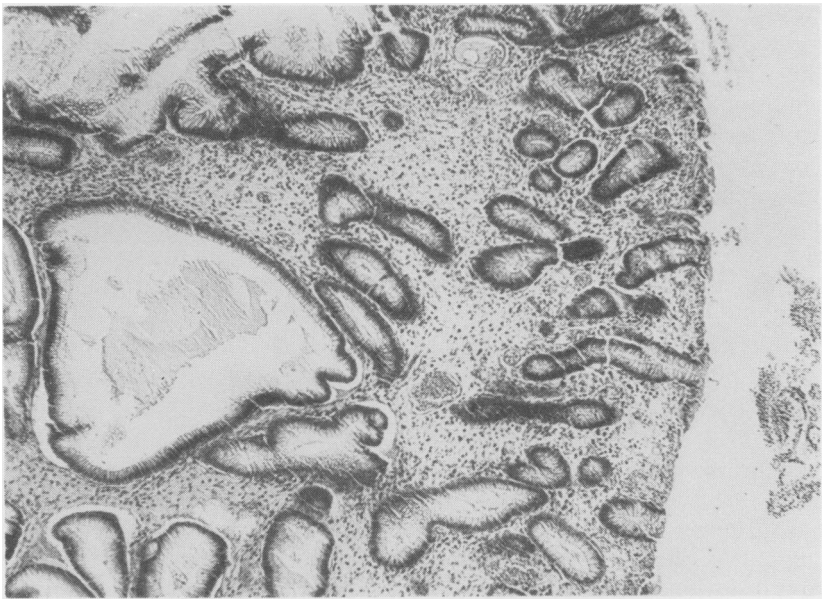

FIG. 2. *Juvenile polyp with abundant stroma in which there are many inflammatory cells. There is retention of mucous secretion by the epithelial cells lining the glands and some of the glands are cystic (Haematoxylin and Eosin X 90)*

in August, 1967, and the remainder of the colon removed. An ileo-rectal anastomosis was performed. At the second operation well formed bone and cartilage were present in the centre of the six weeks old abdominal fibrous scar.

The operation specimen contained only two further polyps and one stalk from which a polyp had sloughed. The post operative course was free of complications.

At review in September, 1967, he felt well and had gained 12 pounds in weight. He had two bowel movements per day but had again developed occasional spotting with blood. Six months later further sigmoidscopic examination was negative. He will continue to have six monthly reviews with sigmoidoscopy at each visit.

The father (aged 60 years), mother (aged 54 years), five brothers and one sister with ages ranging from 10-26 years were investigated by sigmoidoscopy and double contrast enemas but no polyps were found.

Discussion

Juvenile polypi are of uncertain aetiology and some authors (Kerr 1948, Gordon et al. 1959) have regarded them as essentially neoplastic. Another view (Horrilleno et al. 1957; Roth and Helwig 1963) proposes that they are formed by dilated glands whose orifices have been narrowed by ulceration and infection associated with mechanical faecal irritation, but in the present case the major lesion was in the ascending colon where faecal-induced trauma would be minimal. Juvenile polypi are now most widely accepted as hamartomatous (Lockhart-Mummery 1967).

Juvenile polyps differ from adenomas both in their gross and microscopic appearance. Their external surface is generally smooth, though some may be finely granular or even lobulated. They bleed readily on contact and often appear haemorrhagic due to infarction. They can be plucked off the rectal wall with ease; on sigmoidoscopy they are often detached with the slight trauma of the instrument, leaving short stalks.

On microscopical examination the surface of the polyp is often denuded of epithelium. There is abundant connective tissue between dilated epithelial tubules, much more than is seen in the adenomatous polyp and there is infiltration of this with acute and chronic inflammatory cells. There may also be scattered foci of old and recent haemorrhage within the stroma. There is no muscularis mucosa in the stalk of the juvenile polyp and this may explain why autoamputation is a common occurrence (Veale et al. 1966). The epithelial cells of the glands retain mucous secretion and while there may be some epithelial hyperplasia the increased epithelial activity and loss of differentiation of epithelial elements as seen in adenomas does not occur.

An investigation by histochemical reactions of colonic polyps and adenomas reveals that inflammatory and juvenile polyps have enzymatic activities similar to normal mucosa while those of adenomatous polyps, villous adenomas and hyperplastic polyps are all markedly different (Czernobilsky and Tsou 1968).

Unlike the adenomatous variety, the majority of polyps of this juvenile type occur within the first decade of life, but they can continue to form even into middle life (Roth and Helwig 1963; Lockhart-Mummery 1967). Rectal bleeding is the presenting symptom in the majority of patients, although this is rarely severe enough to require transfusion, as was the case in our patient. Prolapse of the polyps from the anus and even passage of polyps in the stool may occur ; this is not a feature of the adenomatous variety. Abdominal pain, probably due to minor intussusception

is common (Horrilleno et al. 1957). Associated congenital abnormalities are seen in a number of patients (Horrilleno et al. 1957; McColl et al. 1964).

Juvenile polyps are spongy and soft and therefore easy to miss on digital examination of the rectum. Sigmoidoscopy and histological examination of a polyp will establish the diagnosis. In a very small percentage of cases all the polyps may lie beyond the reach of the sigmoidoscope. Double contrast enemas should reveal these lesions, although the number of polyps present is likely to be underestimated by this technique.

Unlike familial adenomatous polyps juvenile polyps are thought not to have precancerous potential (Horrilleno et al. 1957; Knox et al. 1960; Roth and Helwig 1963; McColl et al. 1964). In a proportion of cases there is a family history of juvenile polyposis or large bowel cancer. Indeed juvenile polyposis has been reported in two patients with a family history of adenomatosis coli (Horrilleno et al. 1957; Veal et al. 1966). The number of reported cases of juvenile polyposis is too small to indicate with certainty whether or not it is an inherited disease, but evidence is accumulating that this may be the case (Annual Report St. Mark's Hospital 1966). In those patients with associated congenital defects there has been no family history of polyposis in the St. Mark's Hospital series (Morson 1967). In the case reported above the patient had a ventricular septal defect and the family was free of the disease.

Since juvenile polyposis is not thought to have any malignant potential radical surgery should not be necessary. However the number of cases reported so far is too small for any dogmatic statement to be made. Loss of blood and protein may be severe enough to warrant colectomy (Veale et al. 1966), as in the case reported here.

One interesting feature of this case was the formation of metaplastic bone in the scar within six weeks of the first operation. The most striking histological feature of the juvenile polyp is the greatly increased supporting connective tissue, and, indeed, formation of bone in the stroma has been reported (Todd 1963; Marks and Atkinson 1964). In familial adenomatosis coli and particularly in the Gardner's syndrome subgroup, there is a similar tendency to form excessive connective tissue elements including bone. It may be that this is the reason for the high incidence of adhesive obstruction in these patients – 20 per cent in one series (Lockhart-Mummery 1967).

Summary

1. The paper reports a patient with juvenile polyposis coli and a congenital cardiac lesion.
2. This is a rare condition which differs from familial adenomatosis coli in that:
   (a) the pathology is that of a hamartoma rather than an adenoma.
   (b) there is thought to be no malignant potential.
   (c) the clinical features of abdominal pain, bleeding, prolapse, and the spontaneous passage of polyps are unusual in adenomatosis coli.
   (d) associated congenital defects are present in a proportion of patients with juvenile polyposis.

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BOOK REVIEWS

FORM AND FUNCTION IN THE HUMAN LUNG. Edited by G. Cumming and L. B. Hunt. (Pp. xi+260; illustrated, 45s.). Edinburgh & London: E. & S. Livingstone, 1968.

THE Department of Medicine at Birmingham has always had a major research interest in pulmonary disease and lung function and a number of contemporary workers in this field were readily persuaded to visit Birmingham for this Symposium. They heard of the recent studies of the inhomogeneity of ventilation made by Dr. Gordon Cumming and his colleagues and of the work on the pulmonary vasculature by Donald Heath. And the visitors contributed a number of exciting and interesting communications. I myself thought that Giles Filley of Denver gave the most outstanding paper of the Symposium – a very thoughtful analysis of the use of models and concepts in the analysis of pulmonary function.

This small well produced rather expensive book is a 'must' for anyone whose major research interest is bronchitis, emphysema, pulmonary hypertension or pulmonary function tests. But I also commend it to all physiologists, clinicians and pathologists. They should browse through this. Even if their research interests are in different fields, the attitude of this group of workers in the field of respiratory disease and their readiness to approach their problem through many different scientific disciplines is an example that needs to be followed in many other fields of modern medicine. O.L.W.

PAIN. PSYCHOLOGICAL AND PSYCHIATRIC ASPECTS. By H. Merskey and D. G. Spear. (Pp. 232, 40s.). London: Baillière, Tindall & Cassell, 1967.

THE fact that it requires the combined efforts of the poet, the philosopher and the physician to provide a reasonably complete picture of the concept of pain, together with the need to rely heavily on what sufferers report, makes the study of this subject a particularly difficult one. Merskey formulates an operational definition and the authors subsequently grapple with the problem against this background. Pain is seen as 'an unpleasant experience which we primarily associate with tissue damage or describe in terms of tissue damage or both.' This delineates the medical usage of the term. Whether the patient's statement of experiencing pain should be accepted or not will depend on his qualifying statements, elicited in the same way as are those made by patients who claim that they are depressed or confused. The latter terms may be rejected as inappropriate by the clinician in the sense in which the patient uses them.

The authors quote Beloff's reference to what he calls the Russel-Feigl identity hypothesis. Briefly, this implies that the phenomena of 'physics' and psychology are the same, but are described in different languages. Whilst accepting this unity, the authors speak both languages with clarity and lucidity. They draw on a vast amount of clinical, psychological experimental and theoretical writings on the subject. According to their view, any attempt to distinguish between 'real' and 'imaginary' pain is futile. They lean to the views of Szasz that pain arises as a consequence of threatened loss of, or damage to, the body. Whether the symptom is considered to be of structural or non-structural origin depends on the observer's assessment of the reality of the threat to the body.

There are many interesting chapters in this book. That dealing with observations from clinical psychiatry includes a classification by Michaux of delusional, hallucinatory, intuitive and neurotic pain. There are chapters dealing with phantom limb phenomena and with the experimental approach including the measurement of reactions to noxious stimuli. The authors include a chapter on masochism which they classify into four types and analyse in a way that throws further light on the varieties of the phenomenon, its biological, social, and psychopathological significance.

This book will be of particular interest to neurologists and psychiatrists, but the general physician and the surgeon will also find much of relevance to their work in its penetrating analysis of the medical problem of pain. Those preparing for higher qualifications in medicine and psychiatry will also find it profitable to read. J.G.G.

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THIS book has 777 pages, including a wide, comprehensive bibliography. It requires detailed reading, but such a labour is very worthwhile.

Injuries are considered in great detail, and guest authors have contributed on subjects such as facial, eye, head and some other injuries. Injuries, including burns, are not only dealt with as hospital problems, but excellent and practical first-aid measures are described down to the instructions which should be given to the ambulance driver. Advice is given on the immediate treatment of burns, which means within seconds of the accident. The management of multiple and mass injuries is covered in an excellent manner, again with minute detail on some points which could have been overlooked by a less dedicated surgeon. There are chapters on anaesthesia, rehabilitation and the legal relationship between doctor and patient, containing sound advice and some clear-headed philosophy.

Some specialists will find argumentative points of detail in treatment, but there can be little argument about the principles behind the management and treatment.

This publication is a milestone in the treatment of the injured and may well be the book which will have the same effect as Watson-Jones 'Fractures and Joint Injuries' had when first published. It became the 'Bible' for such injuries for most orthopaedic surgeons, and London's book may well become the basic book of reference for traumatic surgery.

It is an outstanding publication, which must find a place in every department dealing with trauma. It will become dog-eared very quickly, because it will be used day and daily. Whole-hearted recommendation for this excellent book is made, and its production is up to Messrs. Livingstone's highest level.

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The earlier chapters of the book deal with the structure and function of the normal liver, and thus include some complicated biochemistry. The newer techniques available for diagnosis of liver diseases are then discussed by workers foremost in their development. These include electron microscopy, histochemistry, ultrasonic scanning, liver scintillography, selective coeliac axis catheterisation, etc.

The latter half of the book deals with advances in the field of portal hypertension. The difficult problems encountered in the treatment of hepatic coma are dealt with and the relative merits of extracorporeal perfusion using pig's liver, exchange transfusion using fresh donor blood, and the place of homotransplantation are discussed.

The final forty pages are concerned with the practical problems facing all clinicians who deal with portal hypertension, and should be read by every physician and surgeon. Many of the most helpful points come in the published discussion of the papers. Thus, for example, we learn from Dr. T. C. Chalmers that prophylactic portacaval shunt has been abandoned by the Boston Liver Group after a well controlled, randomised trial. The publication also captures some of the caustic comments of a conference room, e.g. 'Gastric cooling may be an expensive way of sucking ice' (Prof. Sheila Sherlock) or 'The dream of every internist is to find a better way of avoiding a good operation' (Dr. W. V. McDermott).

The book is a 'must' for every medical library and every serious student of liver disease. However, one feels that at seven pounds the volume has been priced outside the range of the reader whose interest in liver disease is secondary. The initial chapters are rather heavy for the clinician, but the rest of the book makes easy reading.

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The bibliography has considerably more than 1,000 references and after each chapter selected revelant books and review articles are given. This book by Sinclair will give the necessary stimulus and encouragement to anatomists and physiologists to engage in sensory research. One must agree with the view he expressed in the preface that a knowledge of cutaneous sensation can illuminate the diagnosis of neurological disorders. It is therefore compelling reading for the neurologist and psychiatrist and all clinicians. The preclinical student, the psychologist and the postgraduate medical examinee could consult this work with profit.

The style of writing is scientific and concise yet lucid, flowing yet not journalistic. In this book some of the quotes of other authors are apt, especially those of F. M. R. Walshe and the ethereal Sherlock Holmes. In the words of the latter "It is a capital mistake to theorize before one has data. Insensibly one begins to twist facts to suit theories instead of theories to suit facts". "Cutaneous Sensation" by Sinclair avoids this pitfall and will guide others similarly. L.J.H.

PORPHYRIA – A ROYAL MALADY. Published and Commissioned by the British Medical Journal 1968. (Pp. 68; Illustrated, 12s 6d). London: British Medical Association, 1968.

On the 8th January 1966 Dr. Ida Macalpine and Richard Hunter, who are well-known as psychiatrists and medical historians, published an article in the British Medical Journal entitled "The Insanity of King George III: A classic case of Porphyria". For the first time in a clinical study of the madness of George III, these authors consulted from that contemporaneous period, many volumes of Willis manuscripts, Queen's Council Papers, Sir Henry Halford's daily record over a 16 month period and the diary of Sir George Baker. Evidence was propounded that the King's illness was porphyria and not maniac-depressive psychosis as had hitherto been accepted. In essence the diagnosis of porphyria was based on the record of symptoms recurring during attacks, which included colic, painful limb paresis, marked tachycardia and sweating and "encephalopathy" with at times insomnia or excitement, raging delirium or stupor and fits. Also four references to discoloured urine being excreted during relapses were cited. A sister of George III, Caroline Matilda, was noted by the authors to have died of an acute ascending paralysis and if this were acceptable as a case of fulminating porphyria then the minimum requirements for a dominant inheritance of this trait would be fulfilled.

Two years later the authors and a distinguished scientist, Professor C. Rimington, jolted history in a startling way with an attempt to establish the diagnosis of porphyria beyond doubt. They surveyed the family history in the consanguineously related Royal Houses of Stuart, Hanover and Prussia for other cases of the disease and they sought biochemical evidence in living members of these families. In a scholarly, fascinating and exciting manner, evidence obtained from surviving medical records, is adduced that the disorder could be traced back to Mary, Queen of Scots and her son James VI of Scotland and I of England. Several members of the family, spanning 13 generations and more than 400 years, were con-

sense, that which can be initiated from the skin. The theories and the experimental evidence preferred by Von Frey and by Henry Head are critically described. The third and more modern major hypothesis, the pattern theory, finds its inspiration in animal electrophysiological findings. The second chapter gives a concise and worthy account of anatomical, physiological, psychophysical and mathematical methods available in the study of cutaneous sensation. The sensory apparatus i.e. the nerve endings, first sensory neurones and central pathways and their sensory correlates are described in detail. The author's expert grasp of a subject in which he himself has made notable contributions is everywhere apparent. The final section of the book is a general review of the subject and of future investigations and it gives some reasons for favouring the pattern theory. Correct emphasis is put on the necessity of agreement on precise definitions of technical terms, on the standardization of sensory testing methods and on presenting data in quantitative forms. This last prerequisite for a successful revival of interest in the clinical study of sensation could be achieved by the co-operation of clinician and workers in other disciplines.

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The style of writing is scientific and concise yet lucid, flowing yet not journalistic. In this book some of the quotes of other authors are apt, especially those of F. M. R. Walshe and the ethereal Sherlock Holmes. In the words of the latter "It is a capital mistake to theorize before one has data. Insensibly one begins to twist facts to suit theories instead of theories to suit facts". "Cutaneous Sensation" by Sinclair avoids this pitfall and will guide others similarly. L.J.H.

PORPHYRIA – A ROYAL MALADY. Published and Commissioned by the British Medical Journal 1968. (Pp. 68; Illustrated, 12s 6d). London: British Medical Association, 1968.

On the 8th January 1966 Dr. Ida Macalpine and Richard Hunter, who are well-known as psychiatrists and medical historians, published an article in the British Medical Journal entitled "The Insanity of King George III: A classic case of Porphyria". For the first time in a clinical study of the madness of George III, these authors consulted from that contemporaneous period, many volumes of Willis manuscripts, Queen's Council Papers, Sir Henry Halford's daily record over a 16 month period and the diary of Sir George Baker. Evidence was propounded that the King's illness was porphyria and not maniac-depressive psychosis as had hitherto been accepted. In essence the diagnosis of porphyria was based on the record of symptoms recurring during attacks, which included colic, painful limb paresis, marked tachycardia and sweating and "encephalopathy" with at times insomnia or excitement, raging delirium or stupor and fits. Also four references to discoloured urine being excreted during relapses were cited. A sister of George III, Caroline Matilda, was noted by the authors to have died of an acute ascending paralysis and if this were acceptable as a case of fulminating porphyria then the minimum requirements for a dominant inheritance of this trait would be fulfilled.

Two years later the authors and a distinguished scientist, Professor C. Rimington, jolted history in a startling way with an attempt to establish the diagnosis of porphyria beyond doubt. They surveyed the family history in the consanguineously related Royal Houses of Stuart, Hanover and Prussia for other cases of the disease and they sought biochemical evidence in living members of these families. In a scholarly, fascinating and exciting manner, evidence obtained from surviving medical records, is adduced that the disorder could be traced back to Mary, Queen of Scots and her son James VI of Scotland and I of England. Several members of the family, spanning 13 generations and more than 400 years, were con-

sidered to have had this Royal Malady. One living family member was found suffering from porphyria and in another biochemical abnormalities of variegate porphyria was found.

The above two articles form the main part of this handsome booklet produced by the British Medical Journal. Two shorter articles are also included, one on historical implications by John Brooke and the other a concise and easily understood medical account of the porphyrias by Professor A. Goldberg.

There can be no doubt that this has been a study of immense historical significance which must be taken very seriously because of the care exercised by the authors in consulting documents. The evidence which is so very well presented, will be discussed critically for many years to come. This, by itself, justifies the booklet which will intrigue all who read it. The interested student of medical history must also read the correspondence on the subject in the British Medical Journal subsequent to January 6th 1968 and in particular the letters of Dent (page 311 3rd Feb. 1968) and of Dean (page 443 17th Feb. 1968) and the replies by the authors. The repercussions of "Porphyria – A Royal Malady" may well be many so we should be prepared to read it with attention and be unbiased in its appraisal. Proven or not proven that will be the question. L.J.H.

EMERGENCIES IN MEDICAL PRACTICE. By R. G. Birch, M.D., F.R.C.P. Eighth Edition. (Pp. xvi+852; figs. 119. 60s). Edinburgh and London: E. & S. Livingstone, 1967.

A TEXTBOOK with this title could be written in two ways. Either it is one man's view of emergency work, emphasising his pet subjects and viewing the field from his particular viewpoint. This viewpoint is determined by whether the author works in an industrial town, down by the docks in a port, in the centre of a metropolis or in a small market town in a farming community. The pattern of emergencies which emerges in these places will be quite different and in all the pattern will change with time. New industrial processes, new materials, new psychotropic drugs and new agricultural chemicals bring with them new emergencies. Nevertheless one man's approach to emergencies, his philosophy of management, can be of great value to students of medicine and particularly to casualty physicians and surgeons. The care of emergencies requires skill and judgement which is born of years of experience coupled with an awareness of the latest hazards. For too long the hospital casualty department has been the domain of the inexperienced or of the doctor whose ambitions lie elsewhere. These departments require a special skill and those with it should be recognised in the same way as experts in the other branches of medicine and surgery.

The second way of writing a textbook on "Emergencies" is to endeavour to supply all the factual information a doctor may need to deal with any emergency. This is manifestly impossible, and even if, as has been done by Dr. Alan Birch, a team of doctors is employed to write such a text it is doomed to be incomplete by the time it is published.

Dr. Birch's book contains many excellent sections and in some, such as that dealing with mushroom poisoning, there is information which it would be hard to find elsewhere. But parts of the text are superficial and even misleading. While describing the respiratory symptoms which often occur when paraldehyde is given intravenously, there is no mention of the fact that fatal pulmonary oedema occurs and that therefore paraldehyde should not be given intravenously.

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THE first edition of this work was hailed as "the best book on the subject in the English language". Another reviewer stated "it should be in the library of every proctologist or abdominal surgeon". The second edition maintains the same high standard. It should not be confined to the personal library of the specialist, but should readily be available to all members of the staff of all units undertaking surgery of the colon, rectum and anus.

Although junior staff might, on account of the size of the book, feel that it is too detailed for them, they should be encouraged to read it. It describes fully minor procedures such as proctoscopy, sigmoidoscopy, injection of piles, haemorrhoidectomy, and operations for fissure and fistula-in-ano – work that is often delegated to senior house officer or registrar. The house surgeon will find the sections on general and specific pre-operative preparation and post-operative care invaluable, and be stimulated to take a more active role in the management of his patients.

The experienced surgeon will not have far to look for useful advice about diagnosis, management and operative technique in every chapter, and in particular those dealing with ulcerative colitis and Crohn's disease, which have been extensively revised.

The illustrations are a noteworthy integral part of the text. This applies not only to steps in operative procedure or to the portrayal of diagnostic features. The management of an ileostomy, regrettably often dealt with in a perfunctory manner in other works though of major importance to the patient, is illustrated lavishly and clearly in this volume.

The historical development of a particular form of management or operation is outlined and evaluated and should interest many, while the full reference lists at the end of each chapter facilitate further reading (if required!) and research.

No praise is too high for this work. W.A.H.

SOME RECENT ADVANCES IN INBORN ERRORS OF METABOLISM. Edited by K. S. Holt and V. P. Coffey. (Pp. 167; figs. 70. 30s). Edinburgh and London: E. & S. Livingstone Ltd., 1968.

THE Society for the Study of Inborn Errors of Metabolism has performed a valuable service to the medical profession in holding an annual meeting at which clinicians, biochemists, pathologists, pyschiatrists, geneticists and anyone with an interest in this subject can meet together to present and discuss their work. The present book represents the proceedings of the fourth symposium held at Dublin in 1966.

Jacobson gave an interesting account of the importance of pteridines in metabolic disorders particularly with regard to the action of tetrahydrobiopterin as a co-factor in the hydrocylation of phenylalanine to tyrosine. Allan and Brown reported on their apparently successful attempt to prevent foetal brain damage in the infant of a phenylketonuric mother. E.E.G. findings of phenylketonurics before and during treatment were presented by Poley and Dumermuth, and in phenylketonuria and other metabolic disorders by Pampiglione. Bickel gave an excellent review of the early detection of metabolic disorders and Holzel, his usual masterly account of disaccharide intolerances in which he has carried out so much of the pioneer work. The clinical and biochemical aspects of the mucopolysaccharidoses were presented by the Dublin workers Coffey and Baker.

This is an excellent little book which will be of interest to all workers in this field.

The proceedings of the first three symposia were published in paper back form and in view of the ephemeral nature of many of these reports, this would seem an excellent idea. It therefore, seems a retrograde step to publish this symposium between hard covers at twice the price of the previous ones. C.M.B.F.

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The opening chapters cover the History of Medical Hypnotism, legal aspects, a discussion of the nature of the hypnotic state and a description of some of the techniques of induction. These are clearly written.

The remaining nine chapters cover hypnosis in various branches of medicine: General Medicine, Psychiatry, Anaesthesia, Paediatrics, Obstetrics and Gynaecology (3 chapters) and Dermatology. These are much more disappointing. The authors give superficial accounts of psychosomatic theories of causation of many diseases, with no discussion of the real uncertainty of these theories. When treatment is described, illustrated by case histories, the importance of *the hypnosis*, rather than the general psychotherapeutic approach, is not made clear. Some sweeping claims are made—for instance in the field of preventive psychiatry—which this reviewer feels could not be substantiated.

This is a book by committed protagonists, not a critical review. The opening chapters can be recommended to those interested in finding out about the approach and techniques. The claims in the later chapters would need to be substantiated. W.O.McC.

STUDIES IN PSYCHIATRY. Edited by Michael Shepherd, D.M., M.R.C.P., D.P.M., and D. L. Davies, D.M., M.R.C.P., D.P.M. (Pp. xi+345. 65s). London: Oxford University Press, 1968.

THE members of the junior medical staff of the Bethlem Royal and the Maudsley Hospital have paid their tribute to Professor Sir Aubrey Lewis on his retirement from the Chair of Psychiatry at the University of London by publishing in two volumes a selection from his writings. The present volume represents part of the harvest that has been reaped as the result of his inspiration and foresight in recognising those aspects of Psychiatry that could be more sharply defined and coaxed to yield valuable information by the application of the scientific method. It is the clinician whose knowledge is enriched by many of the studies described in this book. Little by little facts emerge that help to make psychiatric formulations more precise and treatment more rational.

The work described in this volume is the output of only one of the several departments of the Institute of Psychiatry between 1945 and 1966. The reader will quickly appreciate how frequently the clinician turned to the laboratory and back again to his patients in his quest for explanations of some of the phenomena of Psychiatry. The research worker emerges not as one working in isolation but as a clinician who turns aside from time to time to try to answer some of the questions posed by his patients' illnesses. How closely this approach is in line with Sir Aubrey's views is exemplified by Dr. Davies' quotation in his chapter on Psychiatric Education and Training: '. . . formulating the problem, relating it to what may be learnt elsewhere than in the company of the patient—this is the body of psychiatric opportunity'.

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The need for medical students to be more conversant with the diagnosis and treatment of sexual disorders has been emphasised in recent years. A knowledge of the psychology of young people should help students to understand sexual disturbances in their proper perspective, indicating as they so often do, much more widespread problems of adjustment. Sexual behaviour is not an isolated phenomenon, bearing little or no relationship to the total personality, but an integral part of it. Disorders in the one may be reflected in disturbances in the other, and vice versa.

It is against this total background that the material discussed in this book should be considered. The first chapter deals with physical disorders, including congenital adrenal hyperplasia, eunuchoidism and primary amenorrhoea. The second chapter is devoted largely to a detailed consideration of intersexuality. This is a very useful summary of the differential diagnostic problems that can arise and of associated chromosomal anomalies. The third chapter dealing with sexual problems of adolescence is straightforward and succinct. It will be of much value to general practitioners for its clarity and direct approach. The psychological aspects of sexual problems in other age groups are dealt with too. In addition there are chapters on homosexuality and perversions. Other topics include impotence and frigidity, infertility and artificial insemination.

This book can be commended especially to medical students and general practitioners. In the reviewer's opinion its value would have been enhanced by a chapter dealing with the range of normal sexual behaviour in different age groups. Such information would be useful to the doctor in dealing with some of the less complicated problems he may see in his work. J.G.G.

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Your reviewer is sorry to say that the book is so insightful that it could hardly have been written by a man. It recalls the work of Agnes White and Kathleen Fitzpatrick. The work of the Ulster kailyard school (e.g. Archibald M'Ilroy's—The Auld Meetin' Hoose Green) is valuable as a record, and dear to those who know the North, but this work goes deeper. The Ulster Medical Journal congratulates Mrs. McDowell on the life of observation which has come to harvest in this book. J.S.L.

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Your reviewer is sorry to say that the book is so insightful that it could hardly have been written by a man. It recalls the work of Agnes White and Kathleen Fitzpatrick. The work of the Ulster kailyard school (e.g. Archibald M'Ilroy's—The Auld Meetin' Hoose Green) is valuable as a record, and dear to those who know the North, but this work goes deeper. The Ulster Medical Journal congratulates Mrs. McDowell on the life of observation which has come to harvest in this book. J.S.L.

application of a wide variety of apposite research techniques, adapted for specific purposes.

The work reported can be seen not only in historical perspective but an overall picture emerges of the inter-relatedness of diverse aspects of clinical and academic work. The candidate for higher examinations should read this book. Its extensive canvas and the references provided will enrich and deepen his knowledge. Not only do the essays present the reader with much factual information but they provoke constructive thought. The book is indeed a fitting tribute to the man in whose honour it was written. J.G.G.

SEX AND ITS PROBLEMS. Edited by W. A. R. Thompson. (Pp. 90. 15s). Edinburgh and London: E. & S. Livingstone, 1968.

THIS book comprises a series of articles published in 'The Practitioner' throughout 1967. They were written with the family doctor particularly in mind, but they could well be of interest to a wider readership.

The need for medical students to be more conversant with the diagnosis and treatment of sexual disorders has been emphasised in recent years. A knowledge of the psychology of young people should help students to understand sexual disturbances in their proper perspective, indicating as they so often do, much more widespread problems of adjustment. Sexual behaviour is not an isolated phenomenon, bearing little or no relationship to the total personality, but an integral part of it. Disorders in the one may be reflected in disturbances in the other, and vice versa.

It is against this total background that the material discussed in this book should be considered. The first chapter deals with physical disorders, including congenital adrenal hyperplasia, eunuchoidism and primary amenorrhoea. The second chapter is devoted largely to a detailed consideration of intersexuality. This is a very useful summary of the differential diagnostic problems that can arise and of associated chromosomal anomalies. The third chapter dealing with sexual problems of adolescence is straightforward and succinct. It will be of much value to general practitioners for its clarity and direct approach. The psychological aspects of sexual problems in other age groups are dealt with too. In addition there are chapters on homosexuality and perversions. Other topics include impotence and frigidity, infertility and artificial insemination.

This book can be commended especially to medical students and general practitioners. In the reviewer's opinion its value would have been enhanced by a chapter dealing with the range of normal sexual behaviour in different age groups. Such information would be useful to the doctor in dealing with some of the less complicated problems he may see in his work. J.G.G.

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PHYSICS APPLIED TO ANAESTHESIA. By D. W. Hill, M.Sc., Ph.D., F.Inst.P., F.I.E.E. (Pp. xii+226; illustrated; 70s.). London: Butterworth, 1968.

THIS book, by Doctor D. W. Hill, has a preface by Professor J. P. Payne, the British Oxygen Professor of Anaesthetics. The book originated from a series of lectures presented by Doctor Hill to the postgraduate students in the Royal College of Surgeons, and these lectures have been enlarged into this comprehensive coverage of Physics as applied to Anaesthetic Apparatus and Anaesthetics. Professor Payne states that because of the changes in the primary F.F.A.R.C.S. examination, the appearance of this book is opportune and should be valuable for those interested in this subject.

The first two chapters are concerned with some fundamental concepts of mathematics and mechanics. Although they are useful for orientation in these disciplines, many primary fellowship candidates will be alarmed at the prospect of being required to know these subjects in the details given here, and many practising anaesthetists will sympathise with them. It is interesting to learn how the computer works, but the detailed integrations and calculations on pages 23 and 24 are difficult to follow and compared with how cursorily some problems of more immediate practical application are dealt with later in the book – as for example the solubility of volatile anaesthetics in water and blood page 94 – these details seem scarcely justifiable. It is also irritating to find the definition of the Torr on page 37, when it has already been used freely on pages 28 and 29.

The chapter on Mechanics contains much useful and essential information on pressure gauges, regulators, cylinders and concepts of work, power and energy.

The chapters on automatic lung ventilators and anaesthetic vaporisers are of wider interest than to those with immediate examination committments. Further chapters on the Properties of Liquids, Gases and Vapours, the Gas Laws, Heat, Operating Room Hazards, Optical Problems and Ionizing Radiations give an idea of the extensive range which the book covers. Anaesthetists who may have felt unhappy in some disgnostic X-ray theatres will be interested to read the chapter on Ionizing Radiation.

The way extensive mathematical calculations and arguments are given so little space, as for example on page 199, makes them difficult to follow and they really require to be re-written by the reader for clarity and understanding. A little more space given to these aspects, would have been justified by easier reading for the purchaser.

Dr. Hill has made use both of his own very large experience and research work and also uses extensively material from other workers. Each chapter ends with a full bibliography and this is a very valuable aspect of the book. There are many illustrations and diagrams which effectively compliment the text.

This is a book which many anaesthetists will like to have as a reference book and it will provide the answer to many problems of the anaesthetist's everyday work. M.L.

PROGRESS IN MEDICAL LABORATORY TECHNOLOGY. Edited by F. J. Baker, F.I.M.L.T., F.I.S.T., F.R.M.S. (Pp. vii+209; Illustrated; 58s.). London: Butterworth, 1968.

THIS is the fourth volume in this series and each has dealt with a wide range of subjects. The progress of this series is evidence that it meets a need in modern laboratory technology. This and the other volumes have each covered recent progress in bacteriology, immunology, haematology and histopathology. The articles are practical and reflect advanced medical technology and with two exceptions are contributed by technologists working in hospital laboratories. We note with pleasure an article on modern histological techniques, discussing paraffin mould techniques and automatic staining by Mr. Orchin of the Belfast City Hospital. The field covered is so wide and most of the articles are so specialised that no one person should be concerned with it all. but this book, like the earlier members of the series, should be available for reference in all larger hospital laboratories.

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CANCER EPIDEMIOLOGY: METHODS OF STUDY. By A. M. Lilienfeld, E. Pedersen and J. E. Dowd. (Pp. xiii+165; 62s.). London: Oxford University Press, 1968.

THE purpose of this book is stated by the authors to be to present epidemiological methods to those interested in cancer who may not be epidemiologists. The book would also be of value to those whose interests are in other chronic diseases and who wish to investigate them epidemiologically.

Some basic concepts of epidemiology are first described such as the variation in the incidence of disease in population groups with different characteristics, e.g. age, sex, occupation, habits and other characteristics. The measurement of the incidence and prevalence of cancer in such groups by the use of mortality and morbidity rates is described and the precautions which have to be taken to standardise these measurements for other relevant variables and the need to minimise observer variation, bias or error. The methods and relative merits of retrospective and prospective surveys are set out and there is a useful discussion on the measurement of risks of developing cancer and the ways in which first, association, and later causation, can be established. The development of our knowledge of the causal relationship between cigarette smoking and lung cancer is used to illustrate the advance in knowledge of this relationship through retrospective and prospective population studies and through the demonstration of biological and pathological mechanisms. The need for biological plausibility before accepting a causal hypothesis is emphasised and evidence of a definite dose risk relationship helps to establish the existence of a carcinogenic cause.

There are two useful appendices, the first describing some elementary statistical procedures, and the second consisting of an excerpt on the classification of neoplasms from the latest W.H.O. International Classification of Diseases. J.P.

ANTIBIOTICS AND CHEMOTHERAPY. By Lawrence P. Garrod, M.D.(Camb.), Hon. LLD.(Glasg.), F.R.C.P., and Francis O'Grady, M.D.(Lond.), M.Sc.(Lond.), M.C.Path. Second Edition. (Pp. viii +475; figs. 34; 50s.). Edinburgh and London: E. & S. Livingstone, 1968.

THE second edition of this book commemorates the late Professor Mary Barber, who shared the authorship of the notable first edition, and the second edition continues to compel the reader's admiration for its use of carefully selected practical information and its common sense. Anyone in any way concerned with the choice and use of antibiotic and chemotheraputic drugs is bound to find information and advice of great value in it: it will appeal alike to under-graduate and post-graduate, practitioner and consultant.

This work is clearly the fruit of great experience and critical thought and the main theme which runs through the whole is the effective employment of the drugs discussed. The text is clear, direct and positive; it is notably firm where others might hedge—e.g. the comment about the use of antitoxin in the treatment of gas gangrene on page 298. Apart from the value of the text in general there is a particularly useful final chapter on "Laboratory Control" which is of great interest to anyone concerned with laboratory medicine.

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