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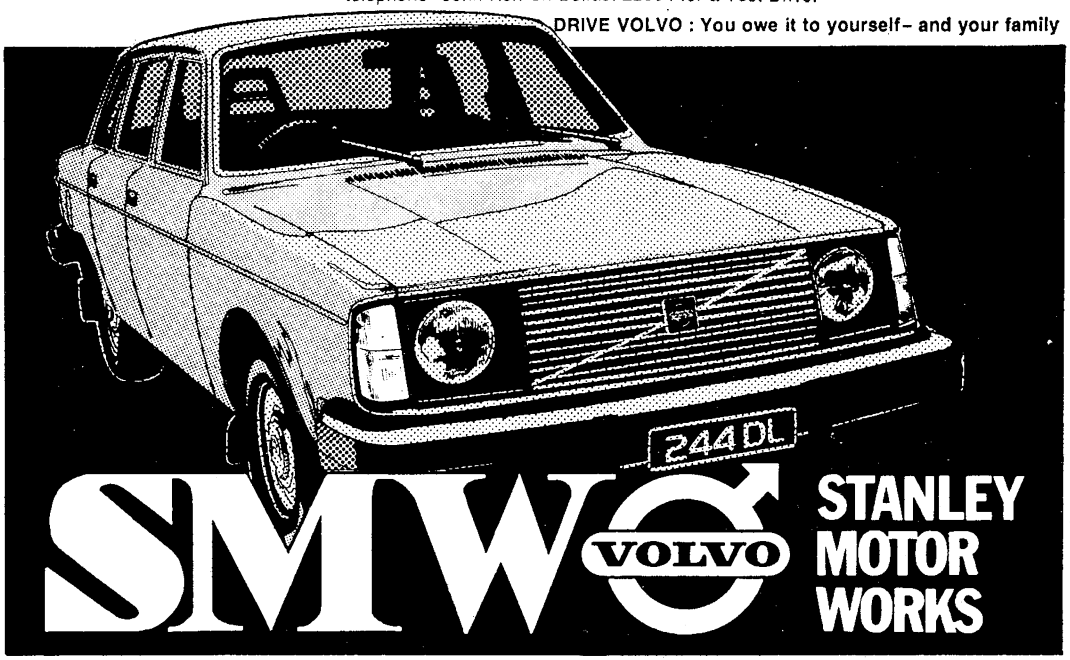

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The Ulster Medical Journal

VOLUME 46

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THE ULSTER MEDICAL SOCIETY

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THE
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VOLUME 46 1977 No. 2

A SHORT REVIEW OF INFECTIOUS MONONUCLEOSIS, WITH HAEMATOLOGICAL AND SEROLOGICAL FINDINGS IN 465 CASES

by

C. COTTON KENNEDY, D.M. (Oxon.), F.R.C.Path.
S. I. DEMPSEY, M.B., B.Ch., B.A.O., M.R.C.P. (U.K.)
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GLANDULAR FEVER, now known as infectious mononucleosis (I.M.), was described in children by Pfeiffer of Wiesbaden in 1889. Byers (1904) wrote of 33 cases in Northern Ireland, which occurred in the age group thirteen months to twenty-five years. An epidemic in a children's ward in Baltimore was reported by Burns (1909). The condition was well reviewed by Tidy and Morley (1921); and in 1923 Tidy and Daniel came to the conclusion that glandular fever was a clinical entity, an absolute lymphocytosis was usual and that it was the same condition described as 'infective mononucleosis'.

A notable advance in diagnosis was made by Paul and Bunnell (1932), who found high concentrations of heterophil antibodies, in the form of sheep cell agglutinins, in the active stages of I.M. Since then important modifications by Davidsohn and Walker (1935) and Davidsohn (1937) have led to the development of the more accurate differential absorption test where the antibodies in I.M. are not removed by titration with guinea-pig kidney. In recent years a rapid slide test, using a suspension of horse erythrocytes as the antigen, has been shown to have a high degree of specificity (Hoff and Bauer, 1965, and Davidson, 1967).

CLINICAL PICTURE

Seventy-one per cent of cases of I.M. occur between the ages of fifteen and thirty years (Newell, 1957). The incubation period is uncertain and Pullen (1973) surmised 7 to 49 days. A variety of non-specific symptoms such as malaise, headache and anorexia may appear as initial features, but the most characteristic complaint is of sore throat accounted for by a mild to moderate pharyngitis.

Virtually all patients develop a variable fever. Cervical lymphadenopathy, often accompanied by axillary and inguinal lymphadenopathy, is usually present by the end of the first week and slight splenomegaly may be detected in fifty per cent of patients during the second week. Although most show some derangement of liver function only a few develop overt jaundice or hepatomegaly.

The disease follows a benign course as a rule and two-thirds appear to be fully recovered by the third week. Few, in this country, are admitted to hospital. A small number develop complications during the course of the illness and it is in this group that occasional fatalities are noted. In a critical review of fatal cases Penman (1970) pointed out the lack of proof of I.M. in some reports: he came to the conclusion that the mortality rate is "probably less than 1 per 3,000 cases". He grouped the reported causes of death as splenic rupture, neurological complications (excluding cerebral haemorrhage), respiratory obstruction, secondary infection, liver failure and miscellaneous. Other published fatal cases include those of Ainley (1949), Shinton and Hawkins (1956), Dawson and Dowling (1962), Harries and Ferguson (1968), and Jain and Sherlock (1975).

In the present series no fatalities have come to our notice.

NOTIFICATION

I.M. is statutorily notifiable in Eire, but not in England or Scotland. It was previously notifiable in Northern Ireland, from 1949 to mid-1968, but this is no longer required.

AETIOLOGY

Evidence points to a virus as the cause, probably the herpes-like virus found in cultures of cells derived from Burkitt's lymphoma (Epstein et al., 1964), but this remains unproven. The virus (now known as the Epstein-Barr virus or EBV) may be a latent "passenger" virus activated by I.M. rather than the true aetiological agent (Lancet, 1968). Investigations have continued and Henle and Henle (1973) consider that there is now no doubt that the EB virus is the cause of I.M., although one of Koch's postulates remains unfulfilled.

MODE OF INFECTION

Despite records of "epidemics" since the turn of the century clearly many cases were not patients with I.M. Not until the advent of the Paul-Bunnell test and its later modifications could an accurate diagnosis be made. However, although apparently not highly infectious, outbreaks within families are not rare. Although not all cases were proved, Klaber and Lacey (1968) reported an epidemic involving 75 patients in a rural practice. Thirteen families had "two or more cases" and in six families three or four members were involved.

In Dameshek's view (1969) I.M. appears to be an individual infection and it has been suggested by several authors that intimate oral contact, with consequent salivary exchange, is the likely mode of infection (Hoagland, 1955, Odegaard, 1967). Indeed, it is often referred to as "the kissing disease".

Solem and Jörgensen (1969) reported a rare mode of infection—the third case of transmission of the disease by blood transfusion. The donor developed proved I.M. two days after giving the blood and the recipient three weeks after receiving it.

CRITERIA FOR DIAGNOSIS

Ideally the triad of a clinical picture of I.M., a diagnostic heterophil antibody (Paul-Bunnell) titre and typical blood count findings should be present. For the purpose of the present survey an absorbed Paul-Bunnell titre of 1 in 56 at some time during the course of the illness was required, plus blood count findings of an absolute or relative lymphocytosis, with atypical mononuclear cells in the blood film. Because few of the patients were seen by us and because we have frequently had to rely on the clinical summary provided with the specimens the importance of the clinical picture has not been stressed in the selection of cases.

In this paper the heterophil antibody procedure is referred to as the "Paul-Bunnell" test or titre.

SEROLOGICAL TECHNIQUES

Since about 1967 all sera for Paul-Bunnell tests have been screened with the 'Denco'-I.M. slide test[1]. Negative results are reported as "Paul-Bunnell negative": sera giving a positive result have been further tested by the full three-row differential agglutination technique described by Davidsohn (1937) using Wellcome Reagents[2] guinea-pig kidney and ox red cell suspensions for the absorption procedures. Titres of 1 in 56 or greater after guinea-pig kidney absorption have been regarded as diagnostic of I.M.: lower titres are reported as "suggestive" and repeat specimens requested.

Recently Wellcome Reagents have ceased to produce their guinea-pig kidney and ox red cell reagents. Therefore since late 1975 the absorption tests have been omitted; the 'Denco'-I.M. slide test is done instead and, if positive, is followed by a single row titration against sheep cells.

SOURCE OF SPECIMENS

The material analysed was collected over seven years (Sept. 1969 to Aug. 1976) from specimens submitted to The Laboratories, Belfast City Hospital. Eighty-six per cent were referred initially by general practitioners and fourteen per cent from hospital doctors. The 465 cases came from a cross-section of the general public and not as in some surveys from selected groups such as army personnel or university students.

[1] Denver Chemical Manufacturing Co., Stamford, Conn., U.S.A.

[2] Wellcome Reagents Ltd., 299-303 Hither Green Lane, Hither Green, London SE13 6TJ.

ANALYSIS OF RESULTS

No accurate incidence of I.M. in the population can be assessed because it is not nationally notifiable, some patients are never diagnosed and some do not consult their doctors. Where strict diagnostic standards have been applied Penman (1966) found the overall incidence in the Portsmouth area in 1962-63 to be 38 per 100,000 population "... an average of one case annually in a medium-sized general practice". Despite what was considered a conservative estimate this is about five times the 1962 figure in Northern Ireland of only 7.7 per 100,000—and at a time there when I.M. was statutorily notifiable.

AGE AND SEX INCIDENCE

Results in the current series in Northern Ireland are shown in Table 1.

TABLE I

Age and Sex Incidence

Ages last Birthday	Males	Females	Total	Approx. %
Below 11	29	23	52	11
11—15	38	58	96	21
16—20	65	109	174	37
21—25	46	33	79	17
26—30	24	7	31	7
31—35	1	6	7	2
36—40	4	2	6	1
41—45	3	3	6	1
46—50	0	0	0	0
51—60	3	1	4	1
Age unknown	5	5	10	2
Total	218 males (47%)	247 females (53%)		

It is of interest that Hoagland (1955) and Penman (1966) found that I.M. was uncommon in children, which contrasts with results in the present series where it will be seen that nearly a third were under the age of sixteen, with about 23 per cent less than fourteen years. The youngest was aged four years. The highest incidence (37 per cent) was in the sixteen to twenty age group, while between sixteen and thirty years 61 per cent developed the condition. There was one in his sixtieth year: "very few" over sixty have been described. Finch (1969) and Corr (1967) could only report eight substantiated cases in the literature. It was perhaps surprising that no patients in the 46 - 50 age group were affected.

MONTHLY INCIDENCE

The Public Health Laboratory Service (1972) received reports of 7,479 cases of I.M. in 1971 in the British Isles: of these over 3,000 were recorded in the

three-and-a-half months between mid-February and the beginning of June. This source also points out that the continuing increase in the number of serologically proved cases may, in part, be due to the growing popularity of the simple slide agglutination test. Dunnet (1963), in an analysis of eighty cases, noted a peak incidence in February. However, in the present series we were unable to detect any significant seasonal variation (Table II).

TABLE II

Incidence in the Four Seasons

Seasons	Cases	Per Cent
Winter (Dec. - Feb.)	113	24.3
Spring (Mar. - May)	120	25.8
Summer (June - Aug.)	109	23.4
Autumn (Sept. - Nov.)	123	26.5
TOTAL = 465		

In numerical order the four leading months were June, November, March and May, with fifty-four, forty-nine, forty-eight and forty cases respectively.

BLOOD PICTURE

Except for the first fifteen months of the survey blood counts were done on the Coulter[3] automatic blood cell counter, Model S.

Normal ranges for haemoglobin and leucocytes were taken as follows: Haemoglobin (g/dl): male adults 13.5 - 18.0; female adults 11.5 - 16.5; children (under 15) 12.5. Leucocytes (10^9/l 4.0 - 11.0 (adults).

Haemoglobin Levels

Anaemia is reported to be not uncommon in I.M. and is usually slight: where it is marked it results either from acute haemolysis or bleeding secondary to thrombocytopenia. Samples were available from 465 patients comprising 155 adult males, 179 adult females, and 121 children under the age of fifteen: 27 adult males and 13 adult females were anaemic and 43 children. This represented, respectively, anaemia in 17, 7 and 36 per cent—figures which are probably less than the true incidence. The lowest haemoglobin levels (g/dl) were: adult male 11.1, adult female 10.6; and child 10.6.

Total Leucocyte Count

White cell counts were carried out on all patients. Because there is uncertainty about the upper normal limit of the total white cell count in children those under the age of fourteen years have been excluded from 'a'.

[3] Coulter Electronics Ltd., Cold Harbour Lane, Harpenden, Herts. AL5 4UN.

(a) *Above* 11.0 x 10^9/1. 70 males (45%) and 59 females (33%) fell into this category. The highest figure was 28.1 x 10^9/1. None showed a polymorphonuclear leucocytosis, which is thought occasionally to occur in the early stages (Tidy, 1952, Emond, 1968, de Gruchy, 1970, Smith, 1972).

(b) *Below* 4.0 x 10^9/1. Only 3 patients out of 465 had a leucopenia, the lowest count being 2.6 x 10^9/1. Their ages were 13, 15 and 16 years. This is in contrast to Dunnet (1963) who found leucopenia in the first few days of illness more usual than a leucocytosis.

Differential Leucocyte Count

As previously mentioned an absolute or relative lymphocytosis, with atypical mononuclear cells, was essential to the diagnostic triad. The percentage of atypical mononuclear cells was not routinely calculated.

Platelet Count

Too few were carried out for an assessment. Marked thrombocytopenia is rare, but about 50 per cent of cases show some degree of thrombocytopenia during the first four weeks of illness (Carter, 1965).

Eosinophil Count

Nine patients (2%) had an eosinophilia (more than 0.44 x 10^9/1) in the first blood count. Smith (1972) stated that eosinophilia is more common during convalescence.

HETEROPHIL ANTIBODY TITRES AFTER ABSORPTION WITH GUINEA-PIG KIDNEY (G.P.K.) SUSPENSION

These positive Paul-Bunnell results were obtained from the first positive sample of clotted blood received. (Table III).

TABLE III

Paul-Bunnell Titres after G.P.K. Absorption

Titre	Number of patients	Percentage
1:56	87	18.7
1:112	131	28.2
1:224	83	17.8
1:448	78	16.8
1:896	39	8.4
1:1792	24	5.2
1:3784	14	3.0
1:7168	6	1.3
1:14336	2	0.4
1:14336	1	0.2
TOTAL=465		

It is almost certainly true that the Paul-Bunnell titre does not reflect the stage or severity of the disease (Librach, 1961). In the current series of 465 patients full follow-up was not always achieved and must at times have failed to demonstrate the diagnostic value of a rising titre in some cases. In fact 27 originally non-diagnostic titres became diagnostically positive within three weeks when the test was repeated.

It is of interest that the longest period an absorbed Paul-Bunnell titre was held at the diagnostic level of 1 in 56 or higher was twenty weeks. Titres of this order tended to disappear after about four weeks.

HAEMOLYTIC ANAEMIA: ANTI-i SPECIFICITY: ANTI GLOBULIN (COOMBS') TEST

When haemolytic anaemia occurs it is frequently associated with cold agglutinins of anti-i specificity. However, Jenkins et al. (1965) tested sera from 85 patients with uncomplicated I.M. and found weak anti-i agglutinins in about 8 per cent of cases. Hossaini (1970), on the other hand, reported the incidence of anti-i agglutinins to be 69.2 per cent in 52 patients in uncomplicated I.M. It is evidently only in those who develop antibody of sufficient titre or thermal amplitude that overt haemolysis appears. The direct Coombs' test may be positive in association with the presence of anti-i, but anti-i tests were rarely performed in the current survey.

Following a probable case of I.M. complicated by haemolytic anaemia screening of all proved I.M. cases was started in September 1970. Coombs' tests were carried out on 624 first and follow-up samples. In seventeen patients (3.7 per cent) the direct Coombs' test was found to be positive. To our knowledge in none was there clinical evidence of haemolytic anaemia, although it must be conceded that there was no opportunity to screen patients routinely for occult haemolysis.

The haemoglobin levels in the seventeen Coombs'-positive cases ranged from 11.1 g/dl to 17.8 g/dl. Therefore, judged by these initial tests and clinical evidence, no frank haemolytic anaemia developed. Where Coombs' tests were repeated the evidence was that positive results became negative in a matter of days although the Paul-Bunnell test remained positive.

RELAPSES OR FRESH INFECTIONS

Kaufman (1950) and Tidy (1952) considered that relapses or recurrences were by no means rare. Bender (1962) reported a recurrence in a student four-and-a-half years after the initial attack. On the other hand, Rose (1972), with extensive experience of I.M. in a university population, stated that he had never seen a bona fide recurrence. Similarly Edmunds (1972), usually with two to three years follow-up study, never encountered a recurrence. Smith (1972) thought that there were unquestionable recurrences, but that they were "extremely rare".

Bearing in mind that "false positive" seriological reactions are reported in association with conditions other than I.M. the question of a genuine relapse or

fresh infection was carefully considered. However, in the current survey neither of these diagnoses could be substantiated despite suspicion on clinical grounds on some occasions.

FAMILY INFECTIONS

Epidemics and outbreaks of I.M. in families have already been mentioned. No outbreaks of epidemic proportions were encountered in the present series, but four families are known to have had more than one member infected within a short period. One family had three members affected from mid-March to the 1st June. Two from each of the three other families were affected and the period between infections varied from one to eleven weeks. Two other families had two members almost certainly affected, but insufficient tests were carried out to enable them to be included in the series.

A SEPARATE "DOUBTFUL" CATEGORY

Not included in the present series are 160 additional cases (116 with diagnostically positive Paul-Bunnell titres) where I.M. was probable but the diagnostic criteria could not be met. Sometimes the clinical picture was suggestive, but either the haematological findings or negative or low titre serological results were not in agreement; or occasionally diagnostically positive Paul-Bunnell results were inconsistent with other findings.

Anyone dealing with I.M. is well aware that this category of "false positive" serological reactions exists, while, on the other hand, in some true cases the Paul-Bunnell test remains negative throughout. Indeed, one stimulus to starting this seven year survey was the unusual case in general practice some years before of a young girl with I.M. who almost certainly transmitted it to her grandfather. He acknowledged kissing her on the mouth on many occasions during the incubation period. He developed the clinical picture of I.M., but unfortunately the only specimen sent to the laboratory was for a Paul-Bunnell test, which was diagnostically positive.

The following three cases, not of I.M., are examples of false positive Paul-Bunnell reactions.

1. Girl (10 years), in the care of Dr. C. M. B. Field, who presented with idiopathic thrombocytopenic purpura, twice had an absorbed Paul-Bunnell titre of 1 in 56 and once a titre of 1 in 28. Blood films on five different occasions and bone marrow aspirate were not suggestive of I.M.
2. Another patient (20 years), in early pregnancy, recorded an absorbed Paul-Bunnell titre which varied from 1 in 56 to 1 in 448 over a six week period, with normal blood films. At fifteen weeks gestation she was shown to have a rubella infection.
3. A female (24 years), thirty-two weeks pregnant, presented with a marked megaloblastic anaemia, sore throat, epistaxis and urinary infection. The absorbed Paul-Bunnell titre was 1 in 112, but blood and bone marrow films were not suggestive of I.M.; nor had the husband been affected.

An example of a "false negative" serological test was the case of a 19-year-old male student, with clinical and haematological findings consistent with I.M., who developed an auto-immune haemolytic anaemia with anti-i specificity. The I.M. slide test was weakly positive on two occasions but the Paul-Bunnell remained negative.

Hobson et al. (1958) also gave figures in their survey for a separate group of 100 patients whose diagnosis was in doubt. They were suspected clinically of having "glandular fever", and although haematologically typical they remained Paul-Bunnell negative.

SUMMARY

A total of 465 cases of infectious mononucleosis in Northern Ireland with characteristic haematological and serological findings and presenting over a seven-year period (1969-1976) are reviewed. The history, clinical findings, aetiology and epidemiology of the condition are discussed.

Nearly a third of 465 patients were under sixteen years with sixty-one per cent presenting between the ages of sixteen and thirty. Despite occasional reports to the contrary no significant variation in seasonal incidence was recorded. Seventeen patients had a positive direct Coombs' test though in none of these was there evidence of frank haemolysis; repeat testing showed that the positive results became negative in a matter days. Four families were noted to have more than one infected member within a short period. No report of a fatal outcome in any of the 465 cases was noted.

We are grateful to the many doctors who submitted specimens and to Dr. T. S. Wilson and Mr. L. Crothers for the serological studies.

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INVESTIGATION INTO THE HAZARDOUS USE OF ASBESTOS. NORTHERN IRELAND 1960 - 76

by

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INTRODUCTION

THE opportunity for medical research arises from the fortuitous coincidence of the right patients, the right investigators, time and nowadays money. The last often seems the main barrier to successful research. But perhaps because the financial demands of the work I am going to describe were not great at first, money did not hold it up.

During the 1950's Dr. Elliott McCaughey† collected in Belfast some 15 cases of what appeared to be primary pleural tumours and described them as a pathological entity "Primary Diffuse Mesothelioma of the Pleura". His findings in the form of a thesis and subsequently published (McCaughey, 1958) were not universally accepted. Primary localised pleural tumours had been described in the past (Stout, A. P., 1952) but both clinically and pathologically these were not the same as those described by McCaughey. Isolated cases had been described elsewhere, but the Belfast cases had been collected over a number of years and derived from a population of only 1¼ million. It was considered a rare tumour, but not so rare in Belfast as elsewhere.

The curious discovery of 16 cases within one year in a Kimberley sanatorium forced Wagner and his colleagues (Wagner, Sleggs and Marchand, 1960), to look for an environmental cause. Asbestos bodies were seen in the lungs and further investigation revealed that these patients had been exposed to blue asbestos from the mines, tips and dirt roads along the crocidolite bearing hills of the N.W. Cape Province.

When he came to the British Isles, Wagner visited the only person who had reported a large series of diffuse mesotheliomas to discuss the histological features and to look for asbestos bodies in the underlying lung. The findings with respect to the peculiar cellular pattern of the tumour and the presence of asbestos bodies in the lung proved to be the same in the Belfast patients as in the South Africans.

By this time Professor Wade†† and the author had had admitted to their care as acute medical emergencies two patients with diffuse pleural malignancy. One was diagnosed as mesothelioma after three surgical biopsies and the second was diagnosed only at autopsy. They were impressed by two things, the peculiar

†Now Director, Canadian Tumour Reference Centre, Department of Pathology, University of Ottawa, Ontario, Canada.

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clinical pattern of the illness and the fact that two cases of so 'rare' a disease should present to the same medical unit within a year.

Professor Pemberton, the Professor of Social and Preventive Medicine, was at the time carrying out a study of byssinosis in the linen mills. But Professor Wade and the author had had experience of research into environmental disease and were therefore able to undertake the work which was obviously needed. They carried this out with the active help and encouragement of Professor Pemberton and the Medical Inspector of Factories (Dr. Swain) and in collaboration with Dr. Elliot McCaughey.

PRELIMINARY STUDIES

There were three questions to be answered:

(1) Were the Belfast tumors related to asbestos exposure?

(2) Where was the asbestos exposure occurring?

(3) What was the extent of the hazard created by this exposure?

Question 1: *Relation of tumours to asbestos exposure*

Before embarking on an expensive long-term study we needed an answer to the first question. By December 1965 occupational histories had been obtained from 42 patients identified with mesothelioma of the pleura either from them or their relatives. Occupational histories were also obtained from age and sex matched controls (Elmes and Wade, 1965). These histories were obtained by trained social workers (Mrs. Dudgeon and Mrs. Simpson) and the results showed a statistically significant association between occupational exposure to asbestos and mesothelioma. Three-quarters of the mesothelioma patients had been so exposed, whereas only one-quarter of the controls had been exposed (Table 1).

TABLE 1

Industrial Exposure, Asbestos Bodies and Mesothelioma of the Pleura

	Exposure			
Patients with	Heavy	Light	None	Total
Mesothelioma	8	24	10	42
Matched controls	2	7	33	42
Asbestos bodies	2	12	6	20
No asbestos bodies	1	4	15	20

Combining the light and heavy groups the differences are significant: Between mesothelioma and controls $P > 0.001$; between asbestos bodies and none $0.02 > P > 0.01$.

In a series of related studies certain other facts emerged. Firstly the presence of asbestos bodies in the lungs were usually but not always attributable to a history of occupational exposure (see Table 1). Secondly 21 (88%) our of 24 patients with mesothelioma had asbestos bodies in the lung whereas they were present in

only 6 (25%) of matched controls (Table 2). Thirdly that asbestos bodies were present in the lungs of about a quarter of the elderly males dying in Belfast at that time. There was no relationship between the finding of asbestos bodies and

TABLE 2

Asbestos Bodies at Autopsy and Malignancy of Pleura and Lung

Patients	Number examined	Per cent with bodies	Significance of difference
With mesothelioma	24	88	$X^2 = 19.05$
Matched controls	24	25	$P < 0.005$
With carcinoma of bronchus ...	100	20	
Most recent 50 of these ...	50	18	X^2 0.94
Matched controls	50	26	$0.4 > P > 0.3$
Without cancer of lung			
Aged 50 to 59	100	14	$X^2 = 5.18$
Aged 60 to 69	100	27	$0.05 > P > 0.02$

the presence of lung cancer. The work indicated that there was no special risk of lung cancer but perhaps a quarter of the male population were at risk of developing mesotheliomas. With development of more precise methods of measuring the asbestos content of the lung, it now seems that both these initial conclusions were misleading. But these initial studies justified further work on question (1) as well as the need to answer questions (2) and (3).

Question 2: Where was the asbestos exposure occurring?

When the mesothelioma cases were plotted on a map there was no indication that they lived in any particular area as there had been in the South African cases. This supported the concept that the exposure was occupational. When 62 cases were available, analysis showed that 45 had worked in the shipyard and 17 had never worked in the shipyard (see Tables 3 and 4). Ten of the shipyard workers and two of the others worked with insulating material. The relatively large number of plumbers and boilermakers was thought to be due to the exposure to asbestos which they described vividly. The general impression was that for many years all workers inside a ship were exposed from time to time to the dust produced during the application or removal of insulation. The men responsible for the insulation work were employed by one or other of a group of contractors, most of whom were financially dependent upon the asbestos industry in England. Because these employers acknowledged the hazards of asbestos in England they realised the importance of establishing safer working conditions in Northern Ireland, where (unlike England, Wales and Scotland) asbestos regulations had not existed. So that it was with the active help of the employers, the Medical Inspectors of Factories (Drs: Swain, Paisley and Hood), the insulation

TABLE 3

Mesotheliomas in Shipyard Workers

45 of a group of 62 cases

INSULATORS :—		
Full-time	5)	
		10
Transient	5)	
OTHER OCCUPATIONS		
(Helpers and Labourers included) :—		
Plumbers, Pipefitters and Boiler Makers ...		17
Engine Fitters		4
Platers, Riveters and Welders		4
Electricians		8
Other		2

TABLE 4

Mesotheliomas in Non-Shipyard Workers

17 of a group of 62 cases

INSULATORS :—	
Heating Engineers and Boilermen	2
Builders' Labourers and Joiners	6
Dockers	1
NO KNOWN EXPOSURE :—	
Linen Workers (Women)	2
Sawyers and Timber Workers	2
Baker	1
Postman	1

contractors and the trades unions that we were able to track down the sources of asbestos exposure and identify the most exposed population.

There was a small factory filling asbestos cloth quilts with fibrous asbestos employing up to 20 women at a time which had opened during the war to supply the shipyard. No other long-term factory exposure was important at that time. The follow-up of these women has not been completed. The factory has since been closed and reopened but no longer handles asbestos material.

The only other groups continuously exposed to asbestos dust were the insulation workers and the men responsible for cutting and fitting marinite partitioning in the ships. These latter were shipyard employees and it has not been possible to study them in detail. The insulation workers all belonged to one branch of the Transport and General Workers Union. Although this working group had belonged to this union branch for many years none had survived to the retiring age to draw on their own pensions fund. Mrs. Simpson, who became responsible

for contacting all these men and bringing them for follow-up, found that they were aware of the risks of their trade and had modified their way of life accordingly. Up until the hazards of asbestos received wide publicity it was not uncommon for several generations within one family to follow this trade, and as we subsequently discovered it was not uncommon for several of the men within one family to die prematurely leaving the women dependent on the remaining men. As a group they earned relatively high wages and spent the money on enjoying their shortened lives.

Question 3: The extent of the hazard created by exposure

Helped by the Pneumoconiosis Unit of the Medical Research Council (Dr. J. C. Gilson, Dr. J. C. Wagner and Dr. P. D. Oldham) and the London School of Hygiene (Dr. M. Newhouse and Dr. Thomson) formal research studies were set up to determine the health hazards for the insulation workers.

(i) *Living Workers.* Dr. J. Langlands and Dr. W. Wallace, both then working in the Department of Therapeutics, carried out two studies. One (Wallace and Langlands, 1971) was a comparison of the clinical, physiological and radiological findings in 50 randomly selected insulation workers, with 50 employees of the Belfast Corporation matched for age, height and smoking habits. The elaborate measurements and tests carried out on this group were part of an international attempt to discover the best method of detecting and measuring the extent of asbestos induced disease. Although this comparison revealed that the insulation workers showed some physiological evidence of asbestosis, these tests were no more sensitive than good chest x-rays. Nine out of the 50 men showed definite radiological evidence of asbestosis and 11 others showed changes probably due to asbestos. These workers were more likely to have a productive cough, basal rales and clubbing of the fingers and on physiological testing they were more likely to show a restrictive lung lesion with some impairment of gas transfer .They showed no more evidence of airways obstruction than the controls.

The second study (Langlands, Wallace and Simpson, 1971) was the application of these tests to all the men then working as insulators (laggers) and achieved 93 per cent co-operation which indicates the high level of effort put into the work and the good co-operation from the employers and men. Evidence of asbestosis and pleural lesions increased with the age and duration of exposure. Radiological evidence of parenchymal lung damage, basal rales, finger clubbing, a restrictive lung lesion and impairment of gas transfer appeared to be the signs of serious lung disease. Evidence of this type of damage increased from 13 per cent of men with only 10 years exposure to 85 per cent of those with more than 30 years. Pleural changes alone on x-rays were not usually associated with evidence of serious lung damage, but did not appear until many years after first exposure. High levels of cigarette smoking were associated with increased physiological evidence of airways and parenchymal lung disease in workers with normal and abnormal radiographs but there was no evidence that cigarette smoking increased the incidence or severity of radiological change.

Although these studies revealed ample evidence of occupational lung disease they did not reveal why the men were not surviving to the retiring age. The 80 per cent of the men over 60 who had radiological evidence of asbestosis did not often have a life threatening degree of impairment of lung function.

(ii) *Dead Workers.* The reason became apparent when the third study was analysed (Elmes and Simpson, 1971). In order to get the full picture of the hazard it was necessary to find out how many men had had to give up work and why. 168 men who were working in 1940 were identified and as far as is known this represented the entire population of insulation workers in Northern Ireland. By 1966 five were untraced, but 98 had died when age adjusted predictions based on mortality amongst Northern Ireland males predicted 37 deaths. Most of the unpredicted deaths were due to cancer of the respiratory tract, especially primary lung cancer. The two diseases then thought to be caused by asbestos exposure were less important. Mesothelioma caused only a third as many deaths as lung cancer. Asbestosis appeared to contribute to between 9 and 21 of the 61 unpredicted deaths. This study of mortality has been extended for another 9 years and one must suppose that the full extent of the hazard to this group of men has now been revealed (Elmes and Simpson, 1977). Unlike most prospective morbidity and mortality studies this group of men showed no initial advantage compared with the general population but the excessive mortality did not become statistically significant until the third five year follow-up period (1950-55, Figure 1). This

Fig. 1. SURVIVAL OF INSULATION WORKERS

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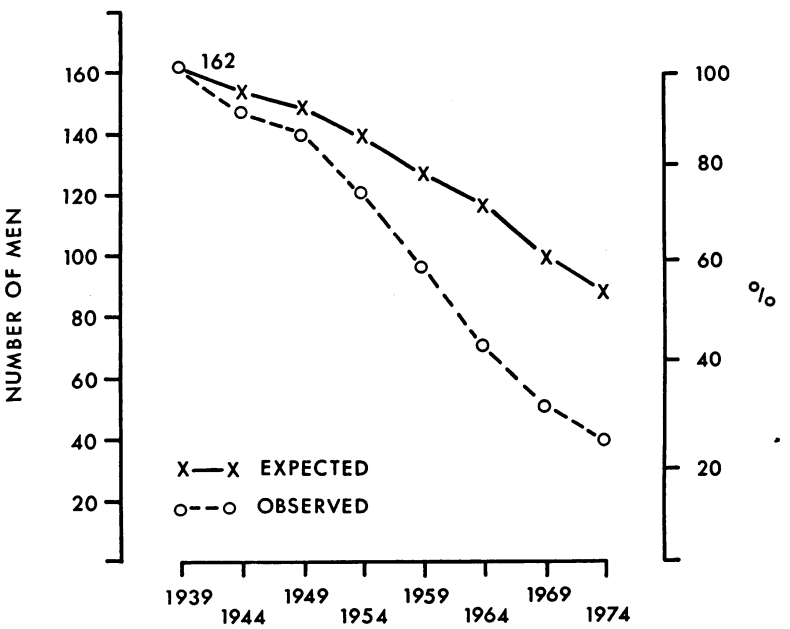

excess of deaths continued until 1965. Those still surviving (who were youngest amongst the original workers in 1940), now have nearly the same annual mor-

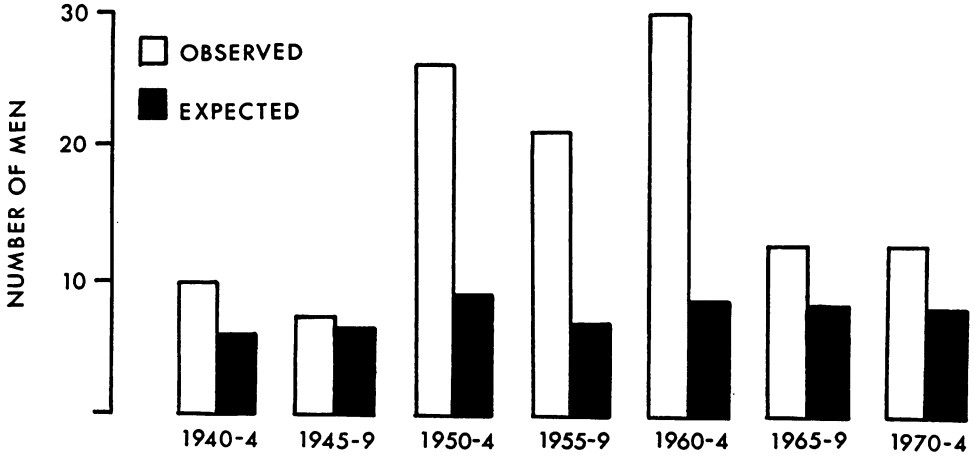

Fig. 2. DEATHS FROM ALL CAUSES
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tality rate as predicted (Figure 2). Nevertheless these hardy survivors still show a relative excess of deaths due to cancer (Figure 3). During the last 10 years there

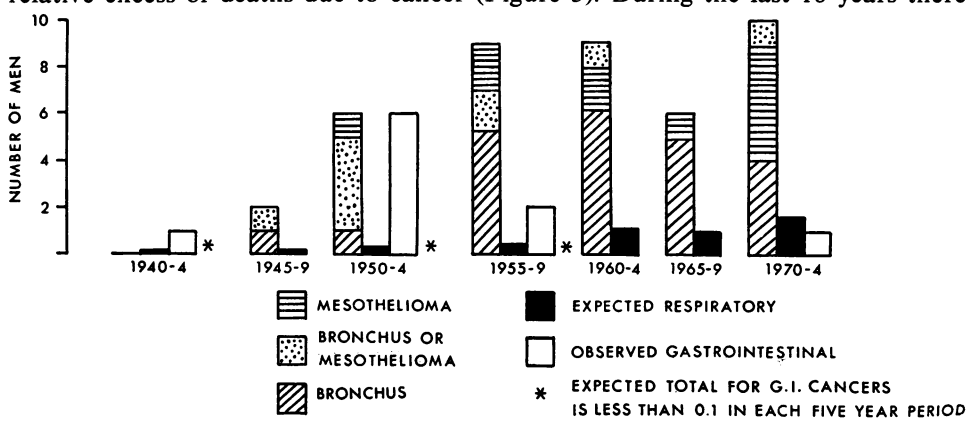

Fig. 3. CANCER IN ASBESTOS WORKERS
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have been no deaths due to asbestosis nor have there been any excess due to gastro-intestinal cancer. There were eight deaths due to gastro-intestinal cancer between 1950 and 1959 when only 0.2 were expected. Mesotheliomas have accounted for about one-third of the unexpected deaths due to cancer since 1950 and bronchial cancer the rest. Even before 1965 the amount of asbestos dust to which these men were exposed had started to fall because of the replacement of dry powder material by preformed slabs. Since 1965 there has been a substitution of glass and

rock wool material for asbestos and limpet spraying has almost completely disappeared. Although there have been changes in the pattern of deaths amongst insulation workers there is no evidence from this series that changes in work environmemnt have had any effect on the total death rate yet.

MESOTHELIOMAS

The spur which has led to these epidemiological studies was the high incidence of pleural mesothelioma. Although this tumour was not the main cause of unpredicted deaths in insulation workers, its frequency in other workers with less occupational exposure to asbestos is alarming because apparently trivial exposure may lead to a tumour 40 years later. With the help of the physicians, surgeons and pathologists in Northern Ireland it has been possible to investigate large numbers of patients with this disease during the last 15 years. The Northern Ireland cases were used as the test group for a much larger study of proven cases dying in the United Kingdom between 1960 and 1970 (Elmes and Simpson, 1976). The clinical picture which emerged is of a tumour which most frequently arises in the parietal pleura but can arise in the peritoneum. It occurs at a wide age range from about 30 to over 80 years and in this country the majority (perhaps 95 per cent) have had some occupational exposure. The remainder may constitute the natural incidence of this disease which would occur if no asbestos was used. In Northern Ireland one such case appears to occur every 3-5 years. Most of the 12 to 15 cases we see here every year have had exposure to asbestos in the shipyard.

Mesotheliomas usually produce rather vague symptoms at first, a dull ache or heaviness in one side of the chest, breathlessness of gradual onset or a dry cough. These symptoms are common enough in the elderly and few patients are referred to the hospital until they have had the symptoms for 4-5 months. At this stage the clinical picture may be typical but it is difficult to prove the diagnosis. Although other signs of asbestos disease (basal rales, pleural calcification, clubbing of the fingers and radiological or physiological evidence of asbestosis) are uncommon, a history of exposure is very important. In about half the cases there is a serous effusion, 30 per cent have a bloody effusion and the remainder have a solid lesion. Only in the serous effusions is it possible to make a diagnosis by cytology. Even open biopsy may be unsuccessful in all three types unless a pleurectomy is attempted. The prognosis from the time of referral to death averages about a year but ranges from a few weeks to five or more years. In retrospect it is possible to say that the tumours with a predominantly epithelial cell pattern tend to survive for nearly 18 months, whereas those with a mainly spindle celled sarcoma pattern survive for only 8 months.

During the latter part of the illness pain due to infiltration of the chest wall and spinal column and breathlessness due to the accumulation of fluid and the immobilisation of one lung dominate the clinical picture. The pain responds poorly to radiotherapy, root section and cytotoxic drugs. It is better relieved

by aspirin than by powerful analgesics, whose addictive properties lead to problems in patients with a relatively long survival.

Death is usually associated with compression of vital structures in the mediastinum, the oesophagus or major blood vessels. It may also result from spread of tumour to the opposite pleura or peritoneum. Pulmonary embolus is often a terminal event. Distant metastases are found at autopsy in nearly half the patients but seldom contribute to the clinical illness.

This detailed clinical picture which has been built up is the result of careful observations by many observers. Dr. C. F. Stanford has for instance been investigating the contribution of damage to the sympathetic chain by tumour to the subjective and objective changes observed in the skin of these patients.

CONTINUING RESEARCH

There are several important unanswered questions. The simple solution to the problem would seem to be the prohibition of the use of asbestos in any form. However, it is an essential component in certain fire preventing situations where it probably saves more lives than it kills. It is also a very cheap and efficient reinforcement for sheet cement materials and for brake linings. Although substitutes have been devised they are very much more expensive and we have no guarantee that they will be appreciably safer than asbestos. A large programme of research is going on elsewhere to settle these points.

Meanwhile we must make the continued use of asbestos as safe as possible. Continuous monitoring of exposed workers will determine whether the new measures have been effective. This applies to asbestos factory workers and insulators and especially to maintenance and demolition workers where old insulation has to be removed. Dr. Jean Langlands is doing this work in Northern Ireland and she has the unenviable job, with Mrs. Simpson's help, of determining whether the abnormalities she is detecting in workers are due to old exposure (before the regulations) or to new.

This sort of surveillance is effective as far as asbestosis is concerned. In so far as the elimination of asbestosis nearly eliminates the carcinoma risk, it will also prevent the second fatal illness produced by asbestos. The mean interval between first exposure and death in this province is 42 years and exposure need only last a few months. From the introduction of the current regulations until the incidence of mesothelioma falls to half its peak level (which has not yet been reached), will be about 40 years or the year 2010. This is dependent on crocidolite being the main cause of occupational mesothelioma. More work is needed and will depend in part on the sophisiticated electron probe analysis of the lungs of patients dying of mesothelioma. Considerable amounts of material have been collected here for this purpose with the painstaking help of many pathologists and my assistants (Dr. D. P. Bell, Miss Wheeler, Miss Stevenson and Marie Gordon).

CONCLUSION

At a critical time for the prevention of increasing illness and death from asbsetos exposure this province provided the material and the people for important research. The work carried out here was done synchronously with work in other parts of the British Isles, in the USA and South Africa and also on the continent of Europe. This work was co-ordinated at a series of international meetings and helped by funds from the World Health Organisation and various funds for research in cancer. The work in Northern Ireland was a significant contribution to the whole in spite of the relatively small scale on which it could be carried out. Its main contribution was to stimulate others to carry out large scale studies to confirm our findings. The main drawback of the Northern Ireland work was that there was no information on either total dose levels or the contributions of the different types of asbestos. The main advantage of the work here was the willingness of people to pool their information and to collaborate. I am sorry I cannot make out a list of all their names because there were many hundreds and they came from many different walks of life.

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ONE HUNDRED KIDNEY TRANSPLANTS IN THE BELFAST CITY HOSPITAL *

by Mary G. McGeown, M.D., Ph.D., F.R.C.P.E. (consultant nephrologist, Belfast City Hospital, and honorary reader in nephrology, Queen's University of Belfast); S. D. Nelson, M.B., M.R.C.P. (consultant clinical pathologist, Craigavon Hospital); and J. A. Kennedy, M.Ch., F.R.C.S. (consultant urologist, Belfast City Hospital)

IN 1959 an artificial kidney service for Northern Ireland was commenced in the Belfast City Hospital. The original intention was to treat only temporary renal failure, but inevitably patients were referred with other types of kidney disease, and it became necessary to attempt to provide treatment for end-stage renal failure. During the seven year period 1962-1968 seventeen patients were treated by short periods of maintenance haemodialysis, then sent for kidney transplant to the few centres in Great Britain then engaged in kidney transplantation. In 1968 financial provision was made for the treatment of chronic renal failure by hospital haemodialysis and kidney transplantation, two beds being provided for regular dialysis. A ten bed unit for regular dialysis was brought into operation in 1971. The first kidney transplant was carried out in November 1968 and the hundredth transplant in November 1976.

PATIENTS AND METHODS

During the early years when regular dialysis treatment was greatly restricted, patients could be accepted only when a space occurred as the result of a transplant or death, even if they were suitable in all respects. Later when the ten bed unit was ready for use, patients without medical contra-indication were accepted between ages 15 and 50. Patients with a history of myocardial infarction, cerebro-vascular accident, multi-system disease such as diabetes mellitus or systemic lupus, severe disease

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The following also made valuable contributions during the eight years covered by this paper: W. G. G. Loughridge, M.A., M.D., F.R.C.S. (consultant urologist, Belfast City Hospital); J. Douglas, M.Ch., M.R.C.P. (consultant nephrologist, Belfast City Hospital); J. A. Alexander, F.F.A.R.C.S. (consultant anaesthetist, Belfast City Hospital); Claire Hill, M.D., M.R.C.P.I. (senior registrar, Department of Pathology, Queen's University); K. V. Rajkumar, B.Sc., M.B., S.S. (locum registrar in renal medicine, Belfast City Hospital); S. N. Mehta, M.B., B.S., M.S. (surgical registrar, Belfast City Hospital); R. A. Donaldson, M.B., F.R.C.S. (consultant in renal transplant surgery, Belfast City Hospital); D. Middleton, B.Sc. (senior scientific officer in immunology, Belfast City Hospital); S. D. Clarke, M.Ch., F.R.C.S. now Kuwait Oil Company, Kuwait), J. McEvoy, M.D., M.R.C.P. (consultant nephrologist, now The Christ Hospital, Cincinnati, Ohio); J. C. Hewitt (consultant anaesthetist, now Hull); Kay Maguire, S.R.N. (nursing officer, Belfast City Hospital); J. Lyness (chief technician, Renal Unit).

* These results have been briefly reported by McGeown, Mary G., *et al* (1977), Lancet, *2*, 648.

unrelated to the renal disease or known mental instability were excluded. Hypertension, left ventricular failure and pericarditis were considered acceptable complications. Often perfectly suitable young patients could not be accepted because no places were available. Similarly at other times patients somewhat older than 50 were accepted because a space existed at the time they needed it. The age range of patients receiving transplants was 13 to 53; 34 were between the ages of 15 and 34, 24 between the ages of 35 and 40, 25 between the ages of 41 and 49, and 7 aged 50 or over, at the time of the first graft.

Ninety-one patients received the 100 kidney transplants, there being seven second transplants and two third transplants. The commonest primary renal diseases leading to terminal renal failure were glomerulonephritis (48 per cent), chronic pyelonephritis (18 per cent), polycystic disease (16 per cent) and hypoplastic kidneys (5 per cent).

PREPARATION FOR TRANSPLANTATION

Once accepted for the programme, the patients were informed as fully as possible of the details of the treatment planned for them. Whenever possible an arterio-venous fistula was prepared in advance of need, usually when serious restriction of dietary protein was commenced. Patients referred when already in terminal failure were maintained by regular peritoneal dialysis until a fistula could be prepared and developed ready for use. Peritoneal dialysis was also used as a temporary measure for patients already accepted who reached the terminal stage when the programme was full. Patients were transplanted either after hospital haemodialysis or occasionally after hospital peritoneal haemodialysis; only one patient was transplanted following home haemodialysis. One patient, the youngest, aged 13, received a transplant from his mother just in advance of actual terminal renal failure.

The general aim was to restore the patients to a reasonable state of health and nutrition before considering transplantation. A few patients had a kidney transplant while still very unfit and still being treated by peritoneal dialysis, either because the haemodialysis programme was full or because a satisfactory arteriovenous fistula could not be made. Ten patients received peritoneal dialysis only. The median time on dialysis was nine months, 47 patients receiving a kidney graft in nine or more months, and 44 in less than nine months. Nine patients waited longer than two years on dialysis.

The patients received 14 hour haemodialysis twice a week on Kiil kidneys or capillary kidneys, using a single pass system either from a batch tank or a Dylade. For a six month period during an outbreak of HBs Ag hepatitis in 1971, all haemodialysis was on disposable flat plate or capillary kidneys. Dialysers were not reused in hospital dialysis. Patients treated with peritoneal dialysis received 30 one litre exchanges twice weekly.

Dietary restriction of protein and sodium was used until the patients were established on dialysis but after this the diet contained 60 g protein, the sodium intake being prescribed according to the difficulty experienced in the control of hypertension, and the potassium intake, according to pre-dialysis level of plasma potassium varied from 50 to 70 mmol/day.

Orovite tablets were prescribed for all patients. A few patients required methyldopa and/or clonidine for hypertension not controlled by dialysis. Even after bilateral nephrectomy a few continued to require these hypotensive drugs, although in smaller dosage. Since 1973 patients with low plasma iron receive oral iron, and prior to that some received intravenous iron total dose infusion. Considerable quantities of diazepam (Valium) were prescribed during the earlier years, but the consumption of this became less after the conclusion of a psychiatric study of the patients. Nitrazepam (Mogadon) was taken for night sedation by many of the patients, although flurazepam (Dalmane) displaced it for a short time. Later the patients were advised to avoid flurazepam because of a cerebral syndrome possibly related to its use. Patients with hypocalcaemia were treated with calciferol or dihydrotachysterol, some also received aluminium hydroxide—none developed any evidence of dialysis dementia. Persistent hypercalcaemia unrelated to these drugs was treated by subtotal parathyroidectomy in a few patients.

All the patients had a micturating cystogram to determine adequacy of bladder capacity and bladder emptying and the presence or absence of reflux. All patients had a barium meal but more recently bleeding occurring during dialysis from duodenal ulcers not shown on the barium meal has led us to do a more detailed study of gastric function (Doherty, O'Connor, Buchanan, Douglas, McGeown, 1977). One patient required vagotomy and later a subtotal gastrectomy for bleeding from recurrent ulceration.

Bilateral nephrectomy was carried out almost routinely until the end of 1975, 65 out of 76 patients undergoing removal of their kidneys prior to transplantation. In another patient the kidneys were removed after the transplant because of severe hypertension. In 1976, because of severe hypertension not satisfactorily controlled by dialysis, or because of polycystic disease, seven of 16 patients underwent bilateral nephrectomy.

The bilateral nephrectomy was carried out as a one stage operation through a single incision except in patients with bilateral polycystic kidneys. In one patient with polycystic disease, a very large kidney was removed on one side, the other being left. The thymus was not removed in any patient, and the spleen in only one, when it had been damaged inadvertently during the bilateral nephrectomy.

As the patients were to have a major operation at short notice when a kidney became available, it was thought unwise to allow the packed cell volume to fall below 15 per cent, and a liberal policy as regards blood transfusion was followed compared with most units. Only six patients

did not receive transfusion. The fact that the majority of patients had undergone bilateral nephrectomy no doubt increased the need for blood transfusion.

Tissue typing was carried out, using a standard lymphocyte toxicity method. Seven transplants were carried out before the tissue typing service was established and these grafts were given on the basis of ABC match only. The donor tissue type was known and was used to select the best matched recipient for the other 93 transplants. The direct cross-match was negative in all except one patient where the cross-match was not carried out because the kidney was received without a lymph node. The result of the cross-match was not known until the operation was under way, for the 58 patients who received an imported kidney.

DONORS

Ninety-six cadaver and four live donor grafts were carried out. One patient received a kidney from his identical twin (Nevin and McEvoy, 1973) and three patients received a kidney from a parent. Thirty-eight of the cadaver kidneys were from local donors, the initial warm ischaemia time varying from 15 to 80 minutes, two patients receiving kidneys with a warm ischaemia time of 70 minutes and one of 80 minutes. The warm ischaemia time was generally shorter for kidneys received from other centres but, in all, 18 kidneys with warm ischaemia of 50 minutes or more were used.

The total ischaemia time varied from 159 to 855 minutes. The longest total ischaemia time (805 and 855 minutes) were associated with long-term good function. Drugs were not given to local donors as preparation for transplantation but nine had already received Decadron, one mannitol and seven antibiotics. Some of the donor kidneys from other centres had received pre-treatment with various drugs including heparin, phenoxybenzamine, dibenyline, rheomacrodex and frusemide.

TECHNIQUE OF REMOVAL OF DONOR KIDNEYS

Ante-mortem assessment of the donor's physiological status was carried out by a senior member of the team in all of our kidney retrieval procedures. Very critical attention was paid to the general vital signs such as peripheral capillary circulation, urinary output, blood urea and creatinine levels and blood pressure in the period before demise. Whilst beating heart donor retrieval was not practised, the timing for retrieval was carefully judged to provide as "vital" tissue as possible.

Depending on the anatomical chest/abdominal configuration, either a total midline exposure or curved upper abdominal incision was used. Meticulous dissection to find polar vessels was performed but no on-block renal removals were carried out. Care was taken to prevent traction on the renal pedicle to avoid circular intimal tears which had been noted in two imported kidneys.

Immediate perfusion gave the first and most reliable sign of having obtained a good organ for transplantation—a five star perfusion being noted as being a solid flow in the drip chamber. The local kidneys were perfused manually and the solutions used were fructose/bicarbonate, Gelin's solution or Perfudex. The majority of kidneys received from other centres were perfused with Perfudex.

TRANSPLANT OPERATION

The transplant operation was a standard iliac fossa extra-peritoneal insertion. After wide and thorough surgical toilet, a urethral catheter was passed and bladder irrigation carried out with 2 per cent Neomycin solution, usually about 150 ml of this solution being left in the bladder to facilitate lateral wall vesical dissection. Peri-vascular lymphatic dissection was carried out with 90 linen ligature of the tissues to avoid lymphoceles.

In the majority of cases the renal vein was anastomosed to the external iliac as end to side, using 5/0 ethiflex. Particular attention was paid in the siting of the venotomy in the recipient vessel to produce a "coned out" open anastomosis at the venostomy. Arterial reconstitution is now practised as end to side anastomosis, using 6/0 ethiflex after a sharp linear arteriotomy is done on the recipient vessel. On two occasions, arterial bench surgery was required to join a large polar vessel to the main renal artery.

At all times very careful attention was paid to haemostasis to avoid post-operative haematomata and infection. Ureteroneocystostomy has been carried out by two techniques. Cystotomy and a Leadbetter-Politano mucosal tunnel was initially used, using 4/0 chromic gut without a splint. Subsequently, vesical myotomy and on-lay direct anastomosis of ureter to vesical mucosa, using 4/0 chromic gut, was found easier and simpler. The anastomosis should be placed well down on the side wall of the bladder. Whilst requiring a meticulous technique, this has the advantage of placing the asanastomosis in the relatively non-mobile part of the bladder and at the same time renders future uretogram studies easier if required.

The wound was always drained by two corrugataed drains. Post-operatively, six hourly vesical irrigation was continued until the effluent was pink and the risk of clot retention ceased. Urethral catheters were usually removed between the fourth and fifth day.

IMMUNOSUPPRESSION AND POST-TRANSPLANT CARE

The patients given living donor grafts, with the exception of the identical twin, received their first immunosuppression 24 hours before the transplant. The other 87 patients receiving cadaver kidneys were given the first immunosuppression as soon as the intravenous infusion was

commenced in theatre, well before the actual transplant. They were then given azathioprine 5 mg/kg body weight and hydrocortisone 200 mg intravenously. The dose of hydrocortisone 200 mg was repeated at six hour intervals intravenously over the first 24 hours (800 mg in total). During the second 24 hours azathioprine 1.5 mg/kg body weight and prednisolone 20 mg were given orally. This treatment was repeated daily until the creatinine clearance exceeded 20, later 30 ml/min, when the azathioprine was increased to 3 mg/kg body weight and continued at this level unless leucopenia occurred. Maintenance treatment was azathioprine 3 mg/kg body weight and prednisolone 20 mg daily. After six months the dose of prednisolone was reduced gradually to 10 mg daily, this dose being reached some time during the second year. Patients developing a Cushingoid appearance were changed to a double dose of prednisolone given on alternate days.

Rejection episodes were treated by increasing the dose of prednisolone to 200 mg daily in divided doses reducing in two to five day steps through 150, 100, 75, 50 to 20 mg daily. At first the dose of azathioprine was doubled for five days and actinomycin C 400 ug was given once intravenously, but this was discontinued after two patients died of sepsis following treatment of late rejection episodes. Increase in the dose of prednisolone alone appears to be satisfactory for treatment of rejection, without an increase in cytotoxic drugs. In a few patients rejection was treated with an intravenous bolus of methylprednisolone 1 g repeated at 24-48 hour intervals up to a maximum of four doses, but this method did not appear to be superior to the previous method.

Considerable care was taken to exclude other causes of a decline in graft function before making a diagnosis of rejection, especially after finding that a rising plasma urea and creatinine in two patients were associated with severe hyperglycaemia rather than rejection (Hill, Douglas, Rajkumar, McEvoy and McGeown, 1974). Renography has been found valuable in the early post-transplant period to show that the graft blood supply is intact, and later to exclude ureteric obstruction, although care and experience is needed in interpretation (Doherty, Douglas and McGeown, 1977).

Other tests used at times included urinary osmolality, estimation of fibrin degradation products (Lameire, Baele, Hilderson and Rengoir, 1973; Hoq, Anderton, Cunningham and Cash, 1974) in urine, excretion of N-acetyl-beta-D-glucosaminidase (N.A.G.) (Wellwood, Ellis, Hall, Robinson and Thompson, 1973), the rosette inhibition test (Bach, Dormont, Dardenne and Balner, 1969; Bewick, Ogg, Parsons, Snowden and Manuel, 1972), the accumulation of radioactive fibrinogen in the graft (Salaman, 1972; Howard, Sutherland and Najarian, 1973), and evidence of increase in graft size by radiographic measurement of metal clips inserted in the capsule of the graft at both poles. At present rejection is diagnosed by a combination of clinical features and laboratory tests. The

laboratory tests most helpful are the plasma urea, serum creatinine, creatinine clearance, amount of proteinuria, blood sugar level, urinary excretion of N.A.G. and exclusion of virus infection, in particular cytomegalic virus infection.

Other aspects of post-transplant care may be of importance. The transplants were carried out in a theatre within the Renal Unit and the patient was treated throughout the immediate post-operative period in an area receiving filtered air under controlled pressure, the patient's room being situated between "clean" and "dirty" corridors. All used and waste materials and specimens were disposed of via the "dirty" corridor.

Until the bladder catheter and drains were removed and the wound was completely healed, the patient was isolated as much as possible. Visits by doctors were reduced to the minimum really necessary and visitors were not allowed in the patient's room although they could visit freely in the "dirty" corridor and chat through a polythene panel in the door. Nursing duties were planned so that the nurses who looked after the patient had as little contact as possible with other patients within the unit—which also includes facilities for treatment of patients with acute renal failure. Daily wound swabs, urine cultures, throat swabs and blood cultures were taken during the period of strict isolation. Prophylactic antibiotics and antifungal agents were not used. The use of antibiotics was sparing, if possible being withheld during episodes of fever until a positive diagnosis was made by culture.

Daily urea, electrolytes and full blood count with film were taken and once urine was produced daily serum creatinine and creatinine clearance were also carried out. Serum alkaline phosphatase was estimated twice weekly. Elevation of plasma potassium within the first 36 hours of operation was treated by intravenous infusion of sodium lactate, glucose and insulin, and later by calcium resonium followed by haemodialysis when necessary. During the diuretic phase, sodium and potassium supplements were given as required.

Frusemide was not given during operation or early in the post-operative period and few patients were given it at any time. Heparin, rheomacrodex and antilymphocyte serum were never used and local irradiation of the graft was used once.

After discharge from hospital, usually about three weeks after operation, the patients were reviewed twice weekly for the first three months, after which the frequency of attendance was reduced according to whether problems had been encountered, and during this time the dose of steroid was reduced as described above. At the beginning of the second year most patients were seen once every four weeks and at the end of that year once every eight weeks. Even the "oldest " transplants are reviewed at 12 week intervals. At each review the patient is weighed, urine is tested for sugar, etc., a mid-stream urine specimen, serum creatinine and creatinine clearance, urinary protein, urea and electrolytes and full blood

count are done. If sugar is detected on routine urine testing, the blood sugar is estimated. At longer intervals the serum calcium and alkaline phosphatase are estimated. HBs Ag testing is carried out at frequent intervals over the first six months. All patients were HBs Ag negative at the time of the transplant and remain negative.

METHOD OF ANALYSIS

The data on patient and graft survival were analysed by the life-table method (Cutler and Ederer, 1958) and the cumulative survival rate and its standard error expressed as percentages. The analysis was completed for survival of grafts and patients at 31st December 1976.

RESULTS

Table I shows the source of all the grafts. The four kidneys taken from live donors functioned immediately and three of them continue to func-

TABLE I

Kidney Transplants in Belfast, 1968-1976

Source	*Number of grafts*	*Number of patients*
Identical twin	1	1
Parent to child	3	3
First cadaver graft	87	87
Second cadaver graft	7	7
Third cadaver graft	2	2
Total	100	91

tion well, two for nine months, one (identical twin) for five years. The remaining patient died, with excellent graft function, 22 months after the transplant from a catastrophic haematemesis at home. He had been treated for rejection three weeks previously, the rejection having been thought to have been precipitated by failure to take his immunosuppressive drugs during a New Year holiday in Scotland.

Seventy-six patients survive, one of whom has returned to haemodialysis to await a second graft. Two patients died three months after return to regular haemodialysis. The cumulative patient survival is shown in Table II and 80.7 per cent survive two years or longer, no deaths

TABLE II

	Months			Years						
	0-3	3-6	6-12	1-2	2-3	3-4	4-5	5-6	6-7	7-8
Patients at risk	91	81	72	64	51	33	21	10	9	3
Deaths	8	3	1	1	2	0	0	0	0	0
Lost to follow-up*	0	0	0	0	0	0	0	0	0	0
Withdrawn alive ↓	2	6	7	12	16	12	11	1	6	3
Cumulative survival	91.1	87.6	86.2	84.7	80.7	80.7	80.7	80.7	80.7	80.7
(± S.E.) (%)	3.0	3.5	3.6	3.9	4.6	4.6	4.6	4.6	4.6	4.6
Grafts at risk	100	81	72	63	50	32	22	10	9	3
Failures	13	3	1	0	0	0	0	0	0	0
Lost to follow-up*	4	0	1	1	2	0	0	0	0	0
Withdrawn alive ↓	2	6	7	12	16	10	12	1	6	3
Cumulative survival	86.6	83.3	82.1	82.1	82.1	82.1	82.1	82.1	82.1	82.1
(± S.E.) (%)	3.5	3.8	3.9	3.9	3.9	3.9	3.9	3.9	3.9	3.9
First grafts at risk	91	74	66	57	45	30	21	10	9	3
Failures	11	3	1	0	0	0	0	0	0	0
Lost to follow-up*	4	0	1	1	2	0	0	0	0	0
Withdrawn alive	2	5	7	11	13	9	11	1	6	3
Cumulative survival	87.5	83.8	82.5	82.5	82.5	82.5	82.5	82.5	82.5	82.5
(± S.E.) (%)	3.5	3.9	4.1	4.1	4.1	4.1	4.1	4.1	4.1	4.1

* Died with functioning graft

↓ Not yet completed time interval

occurring between three and seven years. Eight of the 15 patients who died had excellent graft function up to the time of death (Table III)

TABLE III

Causes of death related to kidney transplant

With functioning graft:	*Number of patients*
Myocardial infarction	3
Cerebrovascular accident	1
Cerebral syndrome	1
Late infection	2*
Haematemesis	1
Without functioning graft:	
Death on dialysis, graft rejected	1
Cerebral syndrome	2
Stenosis ureter, chest infection	1†
Cerebrovascular accident	1
Total	13

* one at three months, one at nine months

† one at one year

and postmortem examination of the transplant showed no evidence of rejection or other abnormality. The causes of death in these eight patients were myocardial infarction (3), cerebrovascular accident (1), cerebral syndrome (1), late chest infection (2), haematemesis (1). Four died with non-functioning grafts and another patient died soon after removal of an early rejected graft. This patient and two of the others died from a peculiar cerebral syndrome, cause unknown; an association with ingestion of flurazepam, or a combination of flurazepam and diazepam, was suspected but could not be proved (Taclob and Needle, 1976). One died from a cerebrovascular accident at 10 days post-transplant and the other patient from unrecognised ureteric obstruction and chest infection at one year. Infection caused no deaths within the first 60 days after transplantation although chest infection led to two of the later deaths, which followed leucopenia due to antirejection therapy including high dosage (6 mg/kg body weight) of azathioprine and also actinomycin C. There have been no further deaths from infection since it was decided to treat rejection episodes with increase in prednisolone without increase in azathioprine, and actinomycin C was omitted.

TABLE IV

Fate of all cadaver kidney grafts 1968-1976

	Number of grafts	*Number of grafts functioning*
First	87	64
Second	7	5
Third	2	2
Total	96	71 (73.9%)

The fate of all the cadaver grafts in shown in Table IV and overall 73.9 per cent of the grafts survive. Two of the 71 surviving grafts have poor function after 3½ years (serum creatinine 515 and 770 umol/1), one from recurrence of chronic pyelonephritis in the graft (Hill, Loughridge, Bharucha and McGeown, 1977), one probably from chronic rejection although the precise cause is not known. The other 69 grafts have adequate to excellent function. The survival of the small number of second and third grafts is gratifying, both third grafts surviving. One patient who received three grafts thrombosed the first two grafts on the third day, but the third graft continues to operate after more than two years. A second patient received three grafts; the first was removed at the primary operation because the middle two-thirds did not become vascularised, the second was rejected at three weeks, and the third continues to function at over nine months.

The cumulative survival of all grafts is shown in Table II and is 82.1 per cent (S.E. ±3.9) from one to seven years.

The cumulative survival of all 91 first transplants (including the four live donor grafts whose survival does not differ from the cadaver donor grafts) is shown in Table II. The life table method of calculation makes an allowance for the eight patients who died with excellent graft function (Table III). The cumulative survival of first transplants is 82.5 per cent (S.E. ±4.1) from one to seven years.

TABLE V

Cause of loss of graft

	Number of grafts
Rejection	5
Arterial problems	5*
Venous thrombosis	2
Primary non-function	2
Haemorrhage	1
Stenosis of ureter	1
Early death of patient	1
Death with functioning graft	8
Total	25

* Rejection could be excluded in 1 only, although pathological appearances not typical of rejection in others.

The cause of the loss of graft is shown in Table V. It can be seen that rejection clearly was responsible for five of the graft failures and may have contributed to four of the five arterial thromboses although the pathological appearances were not typically those of rejection. Rejection was not implicated in the loss of the remaining 16 grafts.

There were 19 first transplants without a mismatch on the B locus and the cumulative graft survival of the group was 94.6 per cent (S.E. ±5.3) from three months to seven years. There were 48 first transplants with one mismatch on the B locus and the cumulative graft survival of this group was 77.1 per cent (S.E. ±4.3 at three months, 70.7 per cent (S.E. ±5.4) at one to seven years. Seventeen first transplants had two mismatches on the B locus and the cumulative graft survival was 75 per cent (S.E. ±10.8) at three months to seven years. These differences were not statistically significant ($p>0.05$).

There were 48 patients of group 0 receiving a first transplant and their cumulative graft survival was 93.6 per cent (S.E. ±3.6) at three months, 88.6 per cent (S.E. ±4.8) at one to seven years. Twenty-eight patients of

group A received a first transplant from a donor of group A and their cumulative graft survival was 77.4 per cent (S.E. ±8.1) at three months, 69.3 per cent (S.E. ±9.1) at one to seven years. These differences were not statistically significant ($p>0.05$).

TABLE VI

Transfusions before first transplant

*Number of units of blood**	*Number of patients*		*Number with functioning grafts*	
0	6		3	
1 - 9	32		29	
1 - 4		16		14
10+	31		28	
Total	69		60	

* Packed cells or whole blood

The number of units of blood given before the first transplant was known accurately for 69 patients and this is shown together with the fate of the grafts in Table VI. The small number of patients who did not receive blood precludes statistical analysis although it appears that first grafts did less well in these patients than in those who received blood, but the quantity given does not seem to have affected the outcome.

In patients treated by dialysis for less than nine months the cumulative function of first transplant was 71.2 per cent (S.E. ±5.2) at three months and 69.0 per cent (S.E. ±5.5) at one year. In patients dialysed for longer than nine months it was 93.3 per cent (S.E. ±3.7) at three months and 85.9 per cent (S.E. ±5.3) at one year. These differences were significant at three months ($p<.01$) but not at one year ($p>0.05$).

The 10 patients treated by peritoneal dialysis did not differ significantly from those treated by haemodialysis as the grafts of eight functioned well for long periods. Seven of the eight grafts still function while one was lost on the death of the patient from myocardial infarction at 26 months. The remaining two grafts were rapidly rejected—it may be of significance that these two recipients were not transfused.

REHABILITATION

Seventy-four of the 76 remaining patients have been well rehabilitated. One patient who has returned to haemodialysis to await a second graft is not fully rehabilitated, and one who was disabled by peripheral neuropathy before haemodialysis remains disabled although living at home and

capable of caring for personal needs. Two further patients who were working full-time have ceased to work because of severe angina. One received his graft at the age of 53, developed venous thrombosis of the graft after a few weeks, the thrombus was successfully removed (Clarke, Kennedy, Hewitt, McEvoy, McGeown and Nelson, 1970), underwent transurethral prostatectomy at the age of 59 and still has a serum creatinine of 85 umol/l at the age of 61. The second was 46 at the time of the graft and three years later had a myocardial infarct followed by persistent angina but his serum creatinine remains unchanged at 280 umol/l after four-and-a-half years. The remaining 72 patients are all capable of full-time work although not all have been able to find a job because of the high level of unemployment here.

DISCUSSION

It is generally accepted that the patient with a successful kidney transplant becomes more fit and has a better quality of life than the patient treated by regular dialysis. The mortality following transplantation is thought to be considerably higher than that associated with regular dialysis. Sixty-six of our 91 patients who received a kidney graft survive, and moreover, eight died with functioning grafts. In four of these the cause of death (myocardial infarction in three, cardiovascular accident in one) could not be attributed to the transplant operation, although attributable to the hypertension and chronic renal failure prior to it. Two deaths occurred more than three months after removal of the rejected transplanted kidney. Including all these deaths, the over-all survival of patients was 83 per cent. The cumulative survival of our patients after transplantation was 86.2 per cent at one year, 84.7 per cent at two years, and 80.7 per cent at five years. The most comparable figures are those reported for Europe by EDTA for patient survival after the first cadaver graft (Gurland, Brunner, Chantler, Jacobs, Schärer, Selwood, Spies and Wing, 1976) of 72.8 per cent at one year, 65.8 per cent at two years and 60.7 per cent at three years. They can also be compared with the survival figures on home dialysis, which is generally considered to give the best survival rates, reported by EDTA (Gurland *et al.*, 1976), of 93.1 per cent at one year, 86.7 per cent at two years and 80.8 per cent at three years, and with those reported by Henari *et al* (1977) of 91.2 per cent at one year, 82.6 per cent at two years and 71.5 per cent at five years.

Seventy-four per cent of all the grafts survive. The cumulative survival of the first graft was 82.1 per cent at one to seven years. The cumulative survival of first cadaver grafts reported by EDTA was 50.1 per cent at one year, 43.9 per cent at two years and 39.4 per cent at three years (Gurland *et al.*, 1976). There were only four living donor grafts in our series and as their fate was similar to the cadaver grafts, and as their number was small, it seems reasonable to combine the results.

Infection is the commonest cause of death following transplantation (Henari *et al.*, 1977) and accounted for 37.5 per cent of all deaths during the first 60 days after transplantation in the EDTA series (Gurland *et al.*, 1976). The low incidence of serious sepsis in our patients after transplantation and the fact that no patient died from sepsis during their hospital admission for the transplant can mainly be attributed to the reverse barrier nursing in our specially ventilated unit and the care taken to follow the strict discipline involved. However, the sparing use of steroid and the fact that anti-lymphocyte serum was not used may also have been important. Falling renal function is investigated as a matter of emergency as it is our policy to prescribe anti-rejection therapy only after careful exclusion of other causes of falling graft function, and when a kidney fails to remove it rather than persist too long with high dosage of steroid. Episodes of fever due to cytomegalic virus infection were the commonest reason for readmission during the first three months. During the high fever associated with cytomegalic virus infection the serum urea and creatinine became elevated in some patients, but this was not a manifestation of rejection and we feel it should not be treated by increased dosage of steroid.

Immediate function of the graft was exceptional in the 96 cadaver kidney grafts, presumably because of the relatively long warm and total graft ischaemia times. Only one patient received a kidney with zero warm ischaemia (from a continental donor). The majority of the patients required one or more haemodialysis (or peritoneal dialyses in patients previously treated in this way) in the post-operative period. However, the early period of acute renal failure, even when the initial warm ischaemia was prolonged, did not adversely affect the future function of the graft. The three patients who received the kidneys with the longest warm ischaemia (two of 70, and one of 80 minutes) have excellent function seven to eight years after the graft was carried out. Eight of the kidneys which function well had a total ischaemia time of over 720 minutes, and the kidney with the longest total ischaemia of 855 minutes continues to function well over three years later. White, Evans and Calne (1968) have also noted that acute renal failure does not prejudice the future of the graft.

In grafts which functioned during the first 24 hours a fall in urine volume, associated with swelling of the graft and fever, often occurred on the third to fourth day. This was probably due to acute tubular necrosis rather than to rejection, but if it was due to rejection it usually recovered gradually and spontaneously without anti-rejection therapy.

At first we thought that the degree of fitness of the recipient at the time of transplant was very important but surprisingly the ten patients transplanted from peritoneal dialysis, who were in general the least fit, did not differ from the patients transplanted from haemodialysis as 80 per cent had functioning grafts at one year.

The frequent use of bilateral nephrectomy may have affected the results in several ways. There is no doubt that the patients required more blood transfusions after the nephrectomy and there have been many recent suggestions that blood transfusion improves graft survival in patients (Festenstein, Sachs, Paris, Pegrum and Moorehead, 1976; Opelz and Terasaki, 1976; van Hooff, Kalff and van Poelgeaste, 1976) and in animals (van Es, Marquet, van Rood, Kalff and Balner, 1977). We have noted that the incidence of urinary tract infection is lower amongst our nephrectomised patients (Douglas, Clarke, Kennedy, McEvoy and McGeown, 1974) than in other series (Hamshere, Chisholm and Shackman, 1974; Steen, Pedersen and Vejlsgaard, 1975). The bilateral nephrectomy did not lead to the death of any patient although several developed troublesome wound infections and two were left with wound hernias.

The excellent survival of the grafts is not easily explained. Thirty-five patients received a first transplant with none or one HLA mismatch, and 48 with two or more mismatches, so that in more than half the patients the match grade was not particularly good. The 19 first transplants without a mismatch on the B locus had a cumulative survival of 94 per cent S.E. ± 5.3) compared with a survival of 75 per cent (S.E. ± 10.5) in those with two mismatches on this locus, but the difference was not statistically significant.

Most of the patients received kidneys of the identical rather than the compatible ABO group, and the NOMS data for 1976 suggest that group A recipients receiving kidneys from group A donors do better than those receiving kidneys from group O donors. However, the 28 group A patients, despite receiving group A kidneys as their first transplant, did less well than the 58 group O patients (group A 69.2 per cent, group O 88.6 per cent at one year). The numbers are small and the differences may well have occurred by chance, but they are in the same direction as other reports that group O recipients have superior graft survival (Joysey, Roger, Evans and Herbertson, 1973; Opelz and Terasaki, 1977). Opelz and Terasaki suggested that this might be due to the fact that in general group O patients wait longer on dialysis before receiving their transplant. This is true of our patients and we have found that patients dialysed for longer than nine months had better cumulative survival of their first grafts than those dialysed for less than nine months (93.3 per cent and 71.2 per cent at three months, $P>0.01$; 85.9 per cent and 69 per cent at one year, $P>0.05$). This is in keeping with Opelz and Terasaki's suggestions. The patients who waited longer on dialysis usually received more blood.

We have satisfactory data on the transfusions received by 69 patients before the first transplant. Only six did not receive blood but three of those lost their graft within a few weeks while 57 of the 63 patients receiving blood have functioning grafts. However, the quantity of blood did not appear to be important, provided blood was given (Table VI).

Unfortunately, statistical analysis of these small numbers is not meaningful.

Rejection clearly accounted for five of the 17 grafts which were lost. There were five lost from arterial thrombosis, but one of these was certainly mechanical. Arterial thrombosis is often associated with rejection (although these four were not typical examples of rejection by any other criteria) but even if they are considered due to rejection, at most nine out of the 17 lost grafts were from this cause.

It is clearly important to establish the cause of a rise in plasma urea or a decline in graft function as these are by no means always due to rejection. Vascular and ureteric lesions must be considered and we have found ureteric obstruction an important and frequent cause of late fall in graft function (Doherty, Douglas and McGeown). It should be remembered that the plasma urea and creatinine rise during acute febrile episodes and this is not an indication for increasing steroid. There were only two kidneys with primary non-function although NOHMS data suggest that about 17 per cent of transplanted kidneys never function.

Meticulous follow-up seems essential so that complications can be detected and treated promptly.

The survival of our patients treated by cadaveric kidney transplantation is nearly as good as that claimed for home dialysis and the survival of grants is well above the European average. The costs of regular dialysis therapy continue to escalate and we believe that the only hope of providing treatment for a substantial proportion of those who could benefit lies in transplantation (McGeown, 1977). The scarcity of kidney donors continues and we must convince our colleagues that kidney transplantation is a worthwhile method of treatment capable of returning many to full health and fitness.

Summary

One hundred kidney transplants have been carried out on 91 patients, there being seven second transplants and two third transplants. Four transplants were from living related donors, 96 from cadavers. Seventy-six patients survive, all but one with functioning kidneys. The cumulative survival of patients was 82 per cent at two years and 80.7 per cent at five years. Eight patients died with functioning grafts, and two of the other deaths occurred more than three months after removal of a rejected kidney and return to haemodialysis. There were no deaths from sepsis in the first 60 days after transplantation. The cumulative survival of all grafts was 82.1 per cent at two and five years. The cumulative survival of first grafts was 82.5 per cent at two and five years.

ACKNOWLEDGMENTS

We wish to thank the many present and former members of the Renal Unit medical, nursing and technical staff who took part in the care of these patients; Dr. G. Welshman and the staff of the Clinical Chemistry Laboratory; Drs. T. Wilson, P. Ferguson and W. Shepherd and the staff of the Bacteriological Department; Dr. C. C. Kennedy and the staff of the Haematology Laboratory; Dr. J. Connolly for HBsAg and virological tests; Northern Ireland Blood Transfusion Service; Dr. W. Brown and the staff of the X-ray Department; Sisters Young and Cox and staff of wards 6 and 9; Miss Feely and the staff of Outpatients' Department; Professor D. Gardner, Dr. H. Bharucha and Professor K. A. Porter for their opinion on histology; staff of Intensive Care Units of the Royal Victoria Hospital, Craigavon Hospital, Ulster Hospital, Mater Hospital and Altnagelvin Hospital for providing kidney donors; National Organ Matching and Distribution Service staff; Ambulance Service and Royal Ulster Constabulary for loyal help with transport of patients, sometimes under difficult circumstances; Miss Mary Martin for patient typewriting help.

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PHENSIC ADDICTION

by

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Phensic tablets have not contained phenacetin since 1966 (1976). Phenacetin was first introduced in 1887 but it was not until 1953 that suspicion was aroused that it might cause renal damage (Lawrence, 1973). There is only circumstantial evidence for this, but it has become so strong that in the United States of America it is compulsory for a warning label to be displayed on all preparations sold to the public. In Sweden it has to be sold on prescription only, and in Great Britain "The Medicines (Phenacetin Prohibition) Order 1974" prohibited the sale of phenacetin-containing compounds except on prescription, because, if used regularly, it could cause renal damage (Prescribers Journal, 1974). Currently, the tablet of Phensic contains aspirin 380 mgm, salicylamide 30 mgm, caffeine 16 mgm (Martindale, 1972).

A CASE REPORT

A 37-year-old married woman, who worked in a bakery, presented with a history of severe headaches and inexhaustible energy. She was happily married with one daughter, aged 5 years. After careful questioning she reluctantly admitted that she had been taking an average of 14 tablets of Phensic per day for 6 years. She looked healthy, appeared happy but agitated. The heart was normal, pulse 82 and regular, and the blood pressure was 110/70mm/Hg. All other systems including optic discs were normal. She was taking Ovulan 50.

Investigations

Blood count, thyroid function, sedimentation rate, plasma protein levels and urine analyses were normal. Serum bilirubin 54.4. umol/1 (normal range 1-17) and liver enzymes including alkaline phosphatase 886 IU/1 (normal range 115-320), asparate transaminase 307 IU/1 (normal range 5-40), alamine transaminase 605 IU/1 (normal range 5-50), gamma glutmyl transpepitase 140 IU/1 (normal range 5-50)10-45), cholinesterase 2220 IU/1 (normal range 2000-500) were greatly elevated. The blood urea was 12 mmol/1 (normal range 2.3-6.6).

(Dr. J. N. Brown) "There is no intra-renal calcification. The kidneys are normal in size and outline. There is no opacification of the renal papillae throughout, due to contrast in the distal tubule. This (pyelotubular reflux) can be seen in normal people, but it is unusual to be seen to this extent and particularly in the film without compression. It is felt that the appearances described are likely to be a result of her phenacetin intake, and probably reflects some change in the renal papillae prior to the necrosis of a fully developed case."

Progress

The patient was warned of the damage done to kidneys and liver, and of the dangers if the addiction was allowed to continue. She was given diazepam 5 mgm three times a day for the expected withdrawal symptoms and fluazepam 30 mgm for the insomnia. She was seen regularly so that the withdrawal period was closely scrutinised, and she was extremely co-operative. She made excellent progress and one month later the liver function tests had returned to normal and the blood urea was 4.6 mmol/1. On the advice of the consultant radiologist an intravenous pyelogram was carried out after six months and he reported that there was no change in the appearance of the renal papillae. The patient is still being reviewed after nine months and remains well and free from addiction.

COMMENT

Phenacetin was introduced in 1887 and until 1953 it was not thought to have any serious effects. Since then many observers have tended to incriminate it as causing renal papillary necrosis as well as certain blood dyscrasias. All the evidence so far tends to be circumstantial because in animal studies phenacetin has not produced the renal changes that have supposedly been found in man (Strimer and Morin, 1975. This difficulty in proving that phenacetin was toxic was due to the fact that some phenacetin was contained in a large number of analgesic preparations but now that it has been taken out of Phensic since 1966 the reason for this patient's liver and renal damage must be sought elsewhere. D'Arcy and Griffin (1972) state that it is clear that there is an association between papillary necrosis and heavy consumption of preparations containing not only phenacetin but also salicylates. Salicylates cause renal irritations and cells, casts and albumin can appear in the urine. Prescott (1968) has reviewed salicylate toxicity and has stated that impaired renal function, obliguria and anuria with renal tubular necrosis may occur with overdosage of salicylates. Nanra and Kincaid-Smith (1970) reported that nearly half the rats fed with aspirins and aspirin-containing compounds developed papillary necrosis in 20 weeks.

There is strong circumstantial evidence to suggest that this patient suffered renal damage by prolonged ingestion of aspirin, and when this was discontinued the blood urea reverted to normal although the radiological picture has not yet returned. Her withhdrawal symptoms could be assumed to be due to the cessation of the caffeine intake. It is difficult to know whether the liver damage was due to salicylate or caffeine, but it returned to normal very quickly after stopping the Phensic. The further precautions to be taken in this case would be to ensure that this patient should not take any analgesic compound as further serious and indeed fatal results could ensue.

This case is reported to draw attention to the dangers of prolonged ingestion of a simple compound "Phensic", containing salicylates and caffeine.

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THE SIR THOMAS AND LADY EDITH DIXON LECTURE

by

IAN FRASER

Shortly after the death of Sir Thomas Dixon, Bt., I was contacted by his widow, Lady Edith Dixon. She was anxious that, as she and her husband had been so closely associated with the medical profession for so many years, something should be arranged to perpetuate this happy relationship. She proposed donating a certain amount of money, and at that time one felt that the best way to use this was to invest it and from the proceeds to finance an annual lecture, and with the honorarium there would also be a medal which we later arranged would carry on one side the Dixon coat-of-arms and on the other side the crest of the Royal Victoria Hospital.

As Sir Thomas and Lady Dixon had been so closely associated, and in fact inseparable, in their lives doing good, I insisted that the lecture should be called the Sir Thomas and Lady Edith Dixon Lecture. This perhaps explains the reason for this rather cumbersome name.

In the early stages, and for the first few years, Lady Dixon herself, although unable to go to the lecture, was always anxious to meet the lecturer, and on each occasion she gave a very elegant lunch party at Wilmot, where she entertained doctors interested in the particular subject as well as a few of her own personal friends.

The first lecture was, in fact, given by Sir Lionel Whitby, an expert in blood diseases, and it was a happy coincidence that he was able on this visit to elucidate the cause of a vague type of anaemia from which Lady Dixon was then suffering.

As years went on, Lady Dixon became increasingly blind, and so the lunch parties could no longer be continued. She decided that the best thing was to give to the fund some further money, with the wish that before each meeting the visiting speaker might be suitably entertained at a small dinner party.

There were no restrictions at all on the type of lecture, but it was felt that, since the Royal Victoria Hospital had its own eponymous lectures, and since the Queen's University was similarly well equipped, the Dixon Lecture might be given a loose attachment to the Ulster Medical Society.

The lecture has attracted very important speakers from all over the world. As far as possible, no single speciality has been allowed to monopolise it. It is a nice thought that this link between the medical profession in Ulster and these two very generous people will go on now, we hope, for ever.

Sir Thomas Dixon was the second Baronet. He was the eldest son of the late Sir Daniel Dixon, D.L., M.P. Sir Thomas was born in Groomsport in 1868—his mother sadly died in the same year. He was educated in England before returning to Belfast to enter the timber firm of Dixon—now Denny, Mott & Dixon.

In his early life Sir Thomas confined himself to business, taking no part in public affairs until in 1907, when his father died and he succeeded to the title. Now, at the age of 40, he came prominently before the public. He became in time chairman of the Belfast Harbour Board and a director of several Ulster steamship companies. He was an excellent businessman, having inherited great business acumen from his father. He made a great success of his commercial life and became a very rich man. Among his many public positions he was one of His Majesty's Privy Councillors, he was His Majesty's Lieutenant for the City of Belfast, he was a senator of the Northern Ireland Parliament, as well as a member of the Senate of Queen's University—just to mention a few.

On the other side of his life it was said there was hardly a single "good" cause, whether it was social, philanthropic or athletic, that he did not help generously with his financial support. He was particularlly generous to the hospitals of this city, to the Church of Ireland, as well as to the State. He left his lovely home at Cairndhu, on the coast road near Larne, to the Northern Ireland Hospitals Authority. It was his intention that this should be a convalescent home to allow the hospital patient a full recovery period before going back to the hurly-burly of a busy life.

In all his public and private life he was supported by Lady Dixon, a daughter of a Clark of Paisley and a Smiley of Larne. As they had no family, Lady Dixon was able to throw her entire energy into philanthropic work.

Sir Thomas is always known as The First Mayor of Larne, and the large Dixon Park in Larne commemorates that event. Lady Dixon was a Freeman of the borough also. After Lady Dixon's death, their lovely house at Dunmurry was given over to the Corporation to be a home for old people, and the surrounding grounds are now a much enjoyed park and in the spring each year are resplendent with roses.

Sir Thomas was a wonderful man: a good businessman, a good administrator, a farmer, a good judge of cattle and horseflesh, but his greatest quality was his love for his fellow man and his charity. He remained a simple man all through, with a homeliness of speech and thought. He has given more than most to help this province of which he was so proud.

ARE WE AS DEPRESSED AS WE THINK WE ARE?

by

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from

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* (The contents of this paper were first presented at a meeting of The Pharmaceutical Society of Northern Ireland on 23rd February, 1977.)

MEDICAL attitudes to psychotropic drugs in general and antidepressants in particular tend to be casual, and their effects seen as innocuous. Indeed if used as recommended by their manufacturers tricyclic antidepressants are not very effective drugs, although some of their side effects and interactions can be very serious. It has been stated that tricyclics generally have a margin of superiority over placebos of 20 - 30 per cent, and given an average placebo response of 40 per cent in most psychiatric patients, they thus fail in 30 - 40 per cent of cases (Lehman, 1966). There are a number of factors contributing to this including a wide individual variation in pharmacokinetics (Alexanderson *et al,* 1969; Asberg *et al,* 1971) and poor patient compliance (Willcox *et al,* 1965), but perhaps the most important, although controversial, is the failure to distinguish depression as an illness from depression as a symptom.

THE ENDOGENOUS-NEUROTIC DISTINCTION

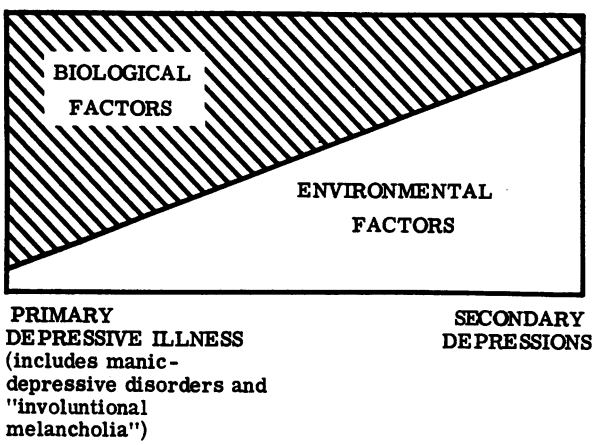
Opposition to an endogenous-neurotic distinction in depressive conditions has come, for different reasons, from two quarters, viz. academic psychiatry and drug companies. The Maudsley group from the time of the late Sir Aubrey Lewis argued that (a) environmental factors could almost invariably be found in every type of depression if one looked hard enough (Lewis, 1934), and (b) statistical analyses of case history material (Kendell, 1968) or of data based on standardised interviews of depressed patients (Kendell and Gourlay, 1970) had failed to show a clustering of two separate syndromes. The drug companies, on the other hand, have opposed the distinction presumably because it would limit the market, particularly if say only 10 - 20 per cent of depressed patients were deemed to suffer from "endogenous" depression. Consequently their products are often advertised as being effective in both depression (of any type) and anxiety.

Nevertheless many psychiatrists, particularly those working in mental hospitals, daily make a judgment between those depressions which represent an abnormal personality change and are likely to respond to E.C.T. or tricyclic drugs, and those which do not, and will not. This distinction has always been upheld by the Newcastle School who developed a rating scale for doing so (Carney, Roth and Garside, 1965). The North Americans have only recently joined in this argument and it is interesting that a series of papers based on a collaborative study involving nine hospitals, supports the endogenous-neurotic distinction as a predictor of response to antidepressant drugs (Raskin and Crook,

1976). A recent British statistical review of thirty controlled trials of imipramine and placebo in the treatment of depressive illness found that only in those trials where an endogenous-neurotic distinction was made, was imipramine consistently found to be significantly better than placebo (Rogers and Clay, 1975).

A working compromise is frequently adopted whereby every depression is seen as having both constitutional and environmental components which are mutually complementary with regard to aetiological specificity (see Figure 1). This continuum is based on the ideas of Angst (1974). Kendell, who had also adopted a similar continuum, has recently made a very helpful and fair review of the numerous ways of classifying depressions now in use (Kendell, 1976). The degree to which biological factors appear to be present, and thus the extent

Fig. 1. CONTINUUM OF DEPRESSIONS



to which a favourable response to drugs or E.C.T. can be expected, is judged from the descriptive phenomenology of the presenting symptoms rather than from the recent history. Thus, on the one hand, diurnal variation in mood, early morning wakening, loss of appetite, weight, energy and libido are marked and the environmental factors are seen as non-specific "triggers"; whereas, on the other, the depression is an understandable reaction, given the previous personality and the specific prevailing circumstances, and "biological symptoms" are minimal. In addition to biological symptoms, guilt, remorse, hopelessness, psychomotor retardation and impaired insight are important aspects of the mental state in primary depressive illness. Severity probably varies independantly in both types of depression and is not of itself indicative of a good response to drugs, and the terms "deep depression" or "severe depression" are therefore confusing. Confusion can also arise if too much weight is placed on trying to assess the specificity of environmental factors, particularly in older age groups, for such patients are often only too willing to offer "reasons" for feeling miserable. The failure to see agitated elderly patients as "depressed", and miserable

youngsters as primarily "anxious" (or angry), leads to further confusion and confusing support for the drug companies' claim that antidepressant drugs are equally effective in anxiety and depression.

DANGERS OF ANTIDEPRESSANT DRUGS

The indiscriminant use of tricyclic antidepressant drugs is not only wasteful but dangerous. They are among the most toxic of commonly used psychotropic drugs. In 1973 9 per cent of 2,914 deaths from suicidal, accidental and "undetermined" poisoning, were attributable to tricyclic drugs (Brewer, 1975). Death from tricyclic overdose may vary from 5 to 10 per cent of adult cases to nearly 50 per cent in children (Crane, 1970). A correlation between availability and the frequency of adult self-poisoning has been shown from the poison enquiries recorded at this department (Elmes, 1977). There is also an unnecessary risk of cardiac conduction defects, sudden death, anticholinergic effects, and drug interactions. Jääskeläinen and Viukari (1976) go even further and have argued that since E.C.T. has been giving way to tricyclic antidepressants in the management of depressive illness, there has been an increased length of hispital stay, decreased degree of recovry, more psychomotor impairment and drug toxicity, and a greater number of accidents and suicides.

AVAILABILITY OF ANTIDEPRESSANT DRUGS

In the following calculations all tricyclic, bicyclic and tetracyclic antidepressants and monoamine oxidase inhibitors have been included as "antidepressant drugs", but not L-tryptophan or lithium. Table 1 shows the increasing number of antidepressant drugs available to general practitioners from 1966-1975. Table 2 shows the increase in the number of drug companies involved. In 1966 7 drug companies were marketing 14 antidepressant preparations containing 7

TABLE 1

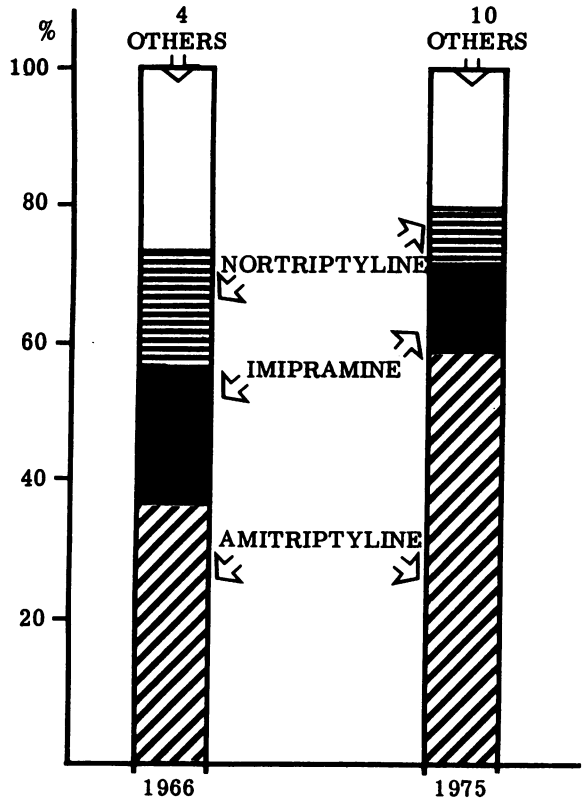
	1966	1970	1975
Number of Antidepressant Drugs	14	18	21
Number of Antidepressant Drugs (all strengths)	21	32	38

TABLE 2

	1966	1975
Number of companies producing Antidepressant Drugs	7	11
Number having more than 10% share of market	4	3

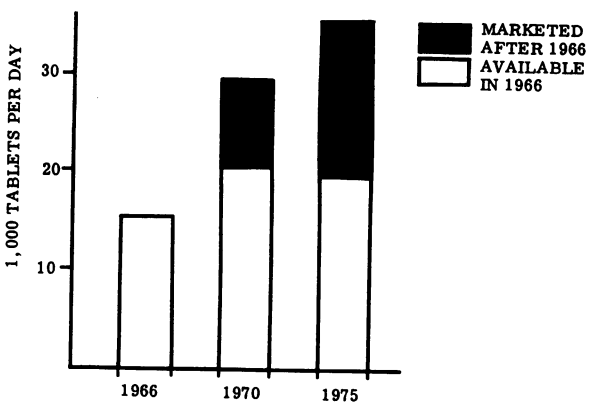
different drugs; in 1975 this had risen to 11 companies marketing 21 preparations containing 13 drugs. Figure 2 shows the distribution of these drugs expressed as percentages of the total prescribed. In 1966 5 preparations covered three quarters of the market, and 90 per cent of the total market was covered by 4 drug companies; by 1975 10 preparations were competing for the same three

Fig. 2. CHANGES IN PRESCRIBING OF ANTIDEPRESSANTS 1966–75



quarters of the market, and the top 3 companies shared little more than 50 per cent of the total market between them. Thus an almost 100 per cent increase in the number of antidepressant drugs available in the last 10 years,

Fig. 3. CHANGES IN THE PRESCRIBING OF ANTIDEPRESSANTS

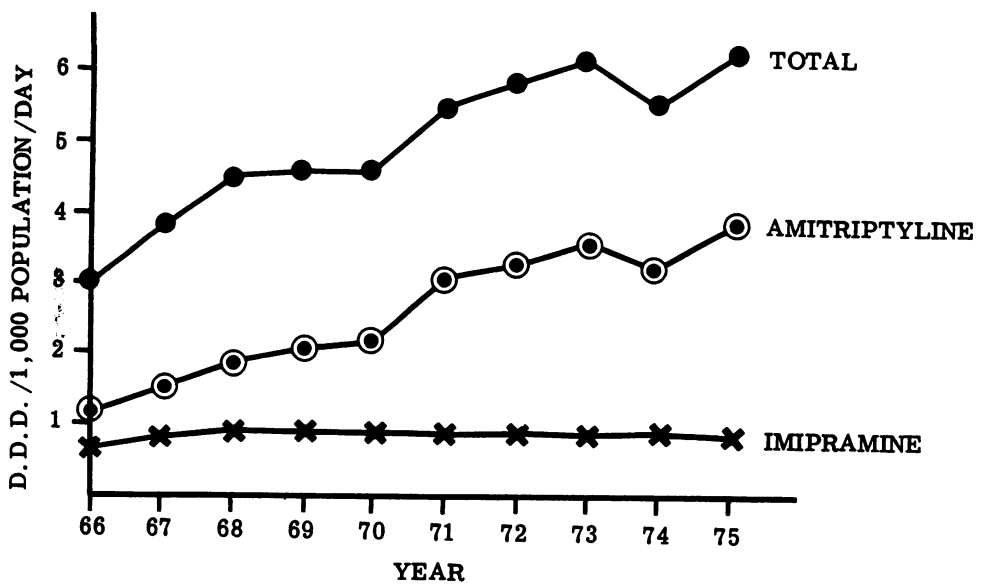


from an increasing number of drug companies, means increased competition for smaller percentages of the total market. Not surprisingly the net result would appear to be an expansion in the market. This is illustrated in Figure 3, where it can be seen that there has been a 100 per cent increase in the number of tablets for depression issued per day in the same 1966 - 1975 period. Most of this increase has been due to the introduction of new preparations; the prescribing of preparations available in 1966 being quite similar to their use in 1975.

PRESCRIBING OF ANTIDEPRESSANT DRUGS IN NORTHERN IRELAND

Figure 4 shows the steady increase in the prescribing of antidepressants in Northern Ireland between 1966 and 1975, expressed as defined daily doses per 1,000 of population (Elmes, *et al*, 1976). Amitriptyline is still the single most

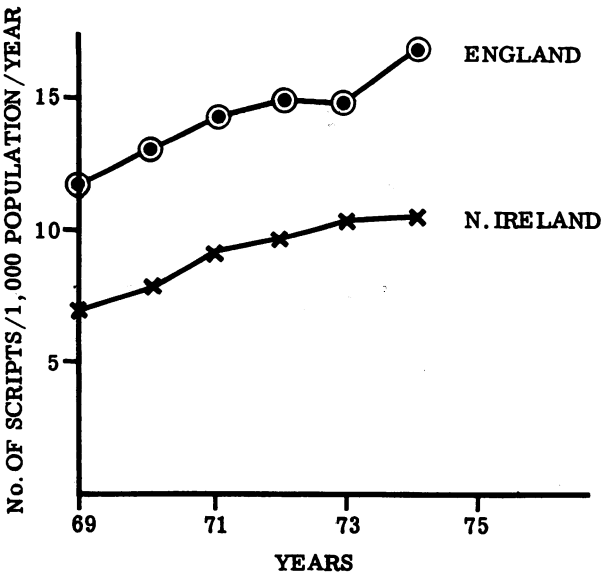
Fig. 4. PRESCRIBING OF ANTIDEPRESSANTS IN GENERAL PRACTICE 1966–75



frequently prescribed antidepressant. These figures take no account of the fact that, apart from their occasional use in eneuretic children, the drugs are presumably only prescribed for adults (over 15 years). If the figures are adjusted accordingly it is found that whereas in 1966 4½ adults per thousand were taking a daily dose of an antidepressant drug, this had more than doubled to 9½ adults per thousand in 1975.

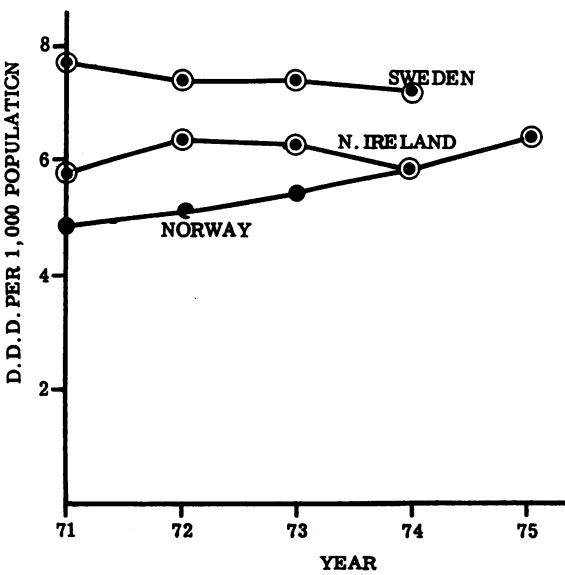
No publication has been found in the psychiatric literature which suggests there has been a real increase in primary depressive illness in the past 10 years. Nor can the increase in the use of antidepressants be attributed to increasing secondary depression due to our political troubles, unless the English are more

Fig. 5. COMPARING NUMBERS OF SCRIPTS ISSUED IN ENGLAND AND NORTHERN IRELAND 1966-75



depressed by them than we are ourselves (see Figure 5). In fact it has been shown that there was a reduction in both types of depression in Belfast in the

Fig. 6. SALES OF ANTIDEPRESSANTS IN NORWAY, SWEDEN AND NORTHERN IRELAND 1971-75



12 months following the outbreak of trouble here (Lyons, 1972). The trend of increasing antidepressant prescribing is widespread in the western world and Figure 6 shows that our prescribing of antidepressants is intermediate between that in Norway and Sweden. The problem of increasing use of phychotropic drugs in general seems to be world-wide and is no greater in the West than in the East, nor related to availability of psychotherapy as an alternative (Lall and Parish, 1975).

DISCUSSION AND CONCLUSIONS

The figures on antidepressant prescribing reflect a complex situation. There is likely to be an interaction between at least three variables, viz. (a) patients' increasing demands for and expectations from medical remedies, (b) doctors' increasing sophistication and awareness of psychological medicine, and (c) the interest of drug companies in a market of almost unlimited potential. It has been suggested in this paper that this latter factor can by itself change our use of these drugs. This is a particularly great liability in an area where there is so little objectivity in diagnosis or assessment of severity. Clearly the recent increase in antidepressant drug prescribing is not likely to be associated with any increase in depression as an illness, but rather with the use of these drugs for depression as a symptom. It is a modern aspect of an old endeavour, that of trying to treat or ameliorate personal problems with drugs. It is therefore indiscriminate, unnecessary, unlikely to be effective and potentially dangerous. On the other hand more careful attention to the proper clinical diagnosis of depressive illness, adequate dosage and patient compliance is likely to improve the efficacy and predictability of response to antidepressant medications (Knesevich and Biggs, 1976; Asberg, *et al*, 1971).

SUMMARY

An analysis of the prescribing of antidepressants in Northern Ireland in the last decade shows that there has been a 100 per cent increase in the number of people taking these drugs, to an estimated 9½ adults per thousand each day. This is less likely to be associated with a corresponding increase in either primary or secondary depression, than with an increasing number of drug companies manufacturing a greater number of antidepressant preparations.

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TEN YEARS OF PORTAL SYSTEMIC SHUNTS

by

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WITH the experience of over a quarter of a century of portacaval anastomosis, it has been established that the operation prevents bleeding from oesophageal varices, but there is still some doubt as to the therapeutic value of the procedure. A number of individual randomized controlled trials have failed to demonstrate that either prophylactic or therapeutic portacaval shunt significantly prolong life. However, if one combines the results of these trials, then the superior survival of the shunted patient becomes significant (Conn, 1974). Although the quantity of life may be greater, it is possible that the quality may not. Certainly, the risk of recurrent haemorrhage is almost eliminated, but the incidence and severity of portal systemic encephalopathy is undoubtedly increased. The mode of dying is changed from one of terrifying torrential haemorrhage to one of drowsy drifting into delirium. In a small community like Northern Ireland, with relatively few patients with bleeding varices, a prospective controlled trial is impractical, but some useful information can be obtained from a retrospective study. This paper presents the results of a small personal series of shunt operations over the ten year period ending December 1976.

PATIENT SURVEY

During the ten years reviewed, 58 shunts were carried out in 55 patients, of whom 28 were male and 27 female. All patients have been followed up to the time of death, or until the completion of this study, and of the survivors, only three patients have been shunted for less than one year. Forty-six patients with intra-hepatic block due to cirrhosis, had a total of 48 shunts, and the other nine patients with extra-hepatic aetiology had 10 shunts (Table 1). It is proposed to look at these two very different groups of patients separately.

TABLE I

All Shunts 1967-1976

Block	Patients	End-to-Side Porta-Caval	Conventional Spleno-Renal	Distal Spleno-Renal	Mesenterico-Caval
Intrahepatic	46	38	5	4	1
Extrahepatic	9	1	9	—	—
	55			58	

CIRRHOTIC GROUP

All 46 patients had needle or wedge biopsy of the liver, demonstrating macronodular cirrhosis in 23, micro-nodular cirrhosis in 19, secondary biliary cirrhosis

in 3, and Wilson's Disease in 1. In 14 patients, alcohol was considered the aetiological factor; chronic active hepatitis was proven in 6 others, but was probably the primary aetiology in many more. Three patients had associated sarcoidosis of the liver, and in one, it appeared to be the main aetiological factor in the production of the portal hypertension.

The mean age at the time of shunt was 48, with a range of 13-69 years. All patients had bled from their varices on one to six occasions prior to shunt (mean 2.3). In almost half the patients, the acute haemorrhage had been controlled by injection therapy initially, the shunt being carried out at a later date. Of the 48 shunts, only four were carried out as urgent procedures, that is, within 48 hours of the onset of bleeding; 21 were performed within four weeks of the last haemorrhage, and the remainder at varying intervals up to one year. End-to-side portacaval shunt, considered the procedure of choice, was used on 38 occasions. Conventional spleno-renal shunt was used in five, distal spleno-renal shunt in four, and H-graft mesenterico-caval shunt in one. Using Child's classification, 17 patients were Grade A, 15 patients Grade B, and 14 Grade C. There was only one operative death in the series, and this occurred in a 31 year-old Child's Grade C diabetic with jaundice and previous hepatic coma. Pre-operatively, he required over 400 units of insulin daily, and following surgery, went into irreversible ketosis.

At the time of review, only 24 of the 46 patients were still surviving, but a more meaningful figure is the five year survival of 50 per cent. The major cause of death was liver failure (Table 2). Post-shunt bleeding occurred in five patients,

TABLE 2
All Deaths 1967-1976

Liver Failure	11	
Haemorrhage	3	Bleeding Duodenal Ulcer Blocked Conventional S/R Shunt Blocked Distal S/R Shunt
Unrelated Causes	6	
Unknown	1	Home Death
Post-Operative	1	Uncontrolled Ketosis
Total	22	

but in only one did it result from a blocked portacaval shunt. This patient had had organised thrombus removed from one wall of the portal vein at the time of shunt, and following rebleeding nine weeks later, a successful conventional splena-renal shunt was carried out. Two patients with conventional spleno-renal shunts rebled; one due to a proven block, subsequently successfully treated by mesenterico-caval H-graft. The other was a terminal haemorrhage in a patient with presumed block and subsequent liver failure. One patient with a distal spleno-renal shunt died from recurrent variceal haemorrhage three years after

the primary operation, but shunt patency was not investigated. In the fifth patient, fatal post-shunt bleeding was proven to be due to duodenal ulceration.

A more major morbidity was that of portal systemic encephalopathy. Of the 45 patients who survived surgery, 18 (40 per cent) had some symptoms of encephalopathy, and 10 (22 per cent) required hospital admission on this account on one or more occasions. About half of the patients who developed encephalopathy did so within six months of the shunt, and it is of interest that some of these patients appeared to develop tolerance to the state, improve clinically, and subsequently continue with their occupation. About one-quarter to one-third of Child's A and B cases developed encephalopathy, but almost two-thirds of Grade C patients were affected. Incidence of encephalopathy in the under 50 age group was low, but surprisingly, there was no difference in the incidence in the 50 - 60 or 60 - 70 age groups (Table 3). Diabetics had a particularly high incidence of encephalopathy — 5 of the 6 diabetics in the series survived surgery, and 4 developed encephalopathy.

TABLE 3

Encephalopathy 1967-1976

CHILD'S CLASSIFICATION	
A	24% (4/17)
B	33% (5/15)
C	64% (9/14)
AGE GROUP	
under 50	16% (3/18)
50 - 60	53% (9/17)
60 - 70	54% (6/11)

Of the 14 patients with alcoholic cirrhosis, 7 returned to excess alcohol consumption — a major factor in their deterioration or death.

NON-CIRRHOTIC GROUP

There were nine patients in the non-cirrhotic group. Eight had portal vein thrombosis of varying degree, and one had a splenic arterio-venous fistula. There were 6 males and 3 females in the group, with a mean age of 29 years (range 10 - 53). One patient with intra-hepatic portal vein thrombosis had a portacaval shunt, but at 14 months, rebleeding due to shunt thrombosis necessitated conversion to conventional spleno-renal shunt. The others had splenectomy and conventional end-to-side spleno-renal shunt. Only one patient with conventional spleno-renal shunt had further bleeding, and this occurred soon after the shunt — the patient has subsequently remained free from haemorrhage for five and a half years to the time of review. There has been no post-shunt encephalopathy, and no operative or delayed deaths in this group, now followed up for from two months to ten years.

DISCUSSION

One-half to one-third of patients with proven varices never bleed, but once the first haemorrhage occurs, approximately two-thirds will rebleed within a year, each episode carrying a high mortality. This high mortality is related not only to the effects of hypovolaemia on an already sick liver, but also to the associated circulatory, metabolic, renal and coagulation problems. Our approach has been to try and control bleeding initially by conservative or relatively minor surgical procedures, and then make every effort to improve the general clinical status of these very ill patients over the next few weeks or months prior to undertaking definitive surgery. Using oesophageal tamponade and injection therapy, one can expect to save over 80 per cent of all patients with acute variceal bleeding, and thus eliminate the need for emergency shunt. Orloff and colleagues (1974) have been strong advocates of the emergency portocaval shunt, but report a 52 per cent operative mortality, which we consider prohibitive. Unfortunately, only one-quarter to one-third of the survivors of conservative management are ever considered fit for shunt, but the shunt rejects can be satisfactorily managed by oesophageal transection using the SPTU stapling gun (Van Kemmel, 1976; Johnston, 1977). Encouraging results with this trans-abdominal method of transection have made us more selective in the patients chosen for shunt, with the result that in the last year of the review, only three patients were subjected to shunt. During the ten years reviewed, our criteria for shunting have been less strict than in many centres, in that 11 of the 46 cirrhotics (24 per cent) were aged 60 or over at the time of operation, and 14 (30 per cent) were Child's Grade C patients. In spite of this, the operative mortality in the cirrhotic group was only 2 per cent, and the five year survival 50 per cent. It looks as though no specific perimeters can be used consistently and accurately to predict those patients who will do well with a conventional shunt (Schwartz, 1975). Hepatic function tests may indicate the chance of early survival, but do not predict the long-term outcome (Moody, 1975). In the past, I have felt that "the patient who looked well and felt well, did well". Since Mikkelsen's trial (1962), end-to-side portacaval shunt became the standard procedure in most centres, conventional spleno-renal shunt or mesenterico-caval shunt being reserved for the patient with portal vein block or previous surgery in the right hypochondrium. The relatively new distal spleno-renal shunt, with its selective decompression of the varices, is now challenging all other shunts because of low incidence of post-shunt encephalopathy reported (Warren et al, 1967). However, it is technically more difficult and carries a higher mortality than the other forms of shunt, and we await with interest the results of an on-going controlled trial (Salam et al, 1975). In this series, the occurrence of some degree of encephalopathy in 40 per cent of the shunted patients, with severe symptoms in 22 per cent, proved to be the main obstacle to return to full productive life. Its occurrence in four out of five diabetics, two-thirds of the Grade C patients, and over one-half of the over 50's would encourage one to exclude these three categories in any future selection of candidates for shunt.

Other complications attributed to portacaval shunt have included duodenal ulcer, diabetes, and shunt thrombosis. Only four of the cirrhotics developed

post-shunt duodenal ulcer, and this is no more than might be expected from a sample of the general population of the same age and sex. Certainly, haemorrhage from an ulcer is poorly tolerated in these patients, and was the cause of death in one patient. The severity of symptoms in one other patient with duodenal ulcer necessitated vagotomy and drainage three years after distal spleno-renal shunt.

Diabetes is known to occur more commonly in cirrhotics than in non-cirrhotic patients, but there is no conclusive evidence that portacaval anastomosis increases the incidence (Conn, 1973). There were six diabetics in this series, but none developed diabetes subsequent to the shunt.

Thrombosis of a portacaval shunt is unusual unless there is pre-existing thrombus in the portal vein, as occurred in both our patients with post-shunt thrombosis. In the Bristol series, 8 of 10 cirrhotics who had mural thrombus removed at the time of shunt, subsequently developed thrombosis (Windle and Peacock, 1975). In retrospect, one would not advise portacaval shunt in this situation. The thrombosis rate in conventional spleno-renal shunt is generally much higher, due to the reversal of normal blood flow and the smaller vessel calibre. There were two definite and one possible shunt thrombosis in the 14 conventional spleno-renal shunts. Patients with portal vein thrombosis are said to be particularly liable to blockage of their shunts, but in this group, there was only the one possible failure just mentioned. Anyhow, where the liver function is normal and the portal hypertension extra-hepatic in origin, the prognosis is good — there were no deaths or portal systemic encephalopathy in the group during the ten year period.

SUMMARY

In the ten years reviewed, 58 portal systemic shunts were performed in 55 patients with bleeding oesophageal varices, with only one operative death. In the patients without cirrhosis, there was no encephalopathy or death. In the cirrhotic group, the incidence of post-shunt encephalopathy was high (40 per cent), and the five year survival low (50 per cent). End-to-side portacaval shunt had a five per cent thrombosis rate compared to over 20 per cent for spleno-renal shunt. Stricter criteria for shunt selection and more extensive use of transabdominal oesophageal transection for the shunt rejects is advocated.

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I wish to thank my medical and surgical colleagues throughout the province for referring most of the patients included in this series.

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WHAT IS A GENERAL PHYSICIAN? HIS ROLE IN THE TEACHING HOSPITAL

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OVER the last few years the nature of the work of the general physician in the teaching hospital has changed considerably. His exact functions are no longer clear and it is not certain whether the general physician has a future in the large general hospital. The reasons for this include—

1. The growth of sub-specialities in medicine. These tend to attract direct referrals from general practitioners. This affects the work of the general physician. He finds that many of the patients whose disorders he has been trained to manage, and which he is competent to manage, no longer come to him. The work-load of the general physician thus becomes unbalanced and a large proportion of his patients are those who have chronic illnesses, whose problems are social rather than strictly medical, and who have diseases which are not fashionable for specialists to manage.
2. The increasing age of the population and the high preponderance of diseases of old age which require hospital treatment often for social rather than strictly medical reasons is reflected in the work of the general physician. Because it is traditional for general medical wards to admit patients with all disorders, whereas the more specialist units carry out a selective admission policy, the general medical wards are becoming increasingly filled with patients who no longer have acute medical illnesses but who for various reasons cannot be discharged home. While there is no upper age limit for patients managed by the general physician, the increasing occupation of medical beds by long-stay geriatric patients seriously distorts his work-load.

The results of this trend is that more and more young physicians in training are finding general medicine an unattractive career and are tending to train in the sub-specialities of medicine. In many hospitals sub-specialist physicians now outnumber general physicians. The question then arises — does the general physician have a function and a future in the large teaching hospital, or should future appointments to such hospitals be entirely of sub-specialists? If the general physician has a future, what should his functions be?

The general physician remains important although his role may have to change to meet changes in medical practice. It is essential in any hospital that there should be broadly based doctors who have wide experience and training and who are able to look at the patient as a whole. The dangers of general medicine performed by a committee of specialists are obvious. There are several particularly important functions for the general physician—

(a) He is important in dealing with emergency medical cases. In the emergency situation the nature of the patient's illness may not be clear and over the ensuing days as the patient is managed and investigated, the nature of the illness and the emphasis of his treatment may well change and become quite different from the initial impressions. The same points apply to patients referred to the out-patient department for diagnosis. It is at this stage that the patient should be seen by a physician who takes a broad view and does not have pre-conceived ideas of the patient's condition. In this way a correct diagnosis is made as quickly as possible and the patient is not put to the inconvenience, pain and perhaps danger of unnecessary and inappropriate investigations.

(b) There remain patients who have multi-system diseases which do not fall into any particular specialist's domain and in these the general physician remains supreme. Indeed the increasing recognition of diverse manifestations of disease, for example, the non-metastic manifestations of tumours, make general physicians even more relevant. The patient's initial symptoms and signs may not indicate disease of a particular system, and once again a broadly based physician skilled in diagnosis will be best at managing this type of patient.

(c) Medicine is a rapidly developing subject and new topics of importance can rapidly arise. It is important therefore that there should be broadly based physicians who are able to appreciate the new advances in medicine, to assess how they can be applied to the clinical situation and who can develop their clinical applications. In due course, some of these physicians may become specialists or have special interests in these new topics. If hospitals are entirely staffed by physicians who are already fully committed to existing specialities, then there will be no scope for new specialities to arise.

(d) The fourth and not least important function of the general physician is his teaching role. It is essential that medical students should be taught by physicians who have a global picture of the patient and his illness, who are not restricted to narrow specialities, and who are able to teach students the diagnostic process in dealing with patients who present with symptoms and signs of any or many systems. In postgraduate education, the general physician also has an important role. The present recommendations for the training of physicians include a period of three years in which the trainee is expected to gain a broad experience in a wide field of medicine. Experience with general physicians in general medical wards is a valuable part of this training. Training which consists only of rotation through specialised units will leave large gaps in the trainee's experience.

How then can the general physician's functions be best organised for the future in the general hospital in such a way that his pre-eminent role is recognised and that he and his specialist colleagues can most efficiently give their respective

services to the hospital and its patients? It is sometimes suggested that medical care can be divided into three strata — primary medical care or the general practitioner service, secondary medical care or the specialist general physician, and tertiary or sub-specialist care. The inter-relationship of these three parts of the medical team is the key to the future of the general physician. There are a number of possibilities.

1. The first and second strata could be merged, with the general practitioner assuming the role of the general physician and tertiary care becoming the only solely hospital based medical service. This has considerable disadvantages. The general physician and the general practitioner do not have the same roles. The general practitioner has to deal with many illnesses other than those falling strictly in the medical field. He has to be able rapidly to differentiate trivial illness from serious disease and deal appropriately with each. The physician is trained to be thorough and to go into each patient's problems in depth. He is not well trained to assume the role of the general practitioner any more than the general practitioner can assume the role of the general physician.
2. A hierarchial system could be devised where the general practitioner is only allowed to refer patients to the general physician, who would then, if he felt it appropriate, refer the patient to the sub-specialist. The general practitioner would not be entitled to refer directly to the sub-specialist. While this would certainly broaden the general physician's field of work in many areas, it would lead to unnecessary duplication of work and place unreasonable restrictions on the freedom of the general practitioner.
3. The secondary and tertiary strata could be merged so that all general physicians will have a special interest and experience, and conversely all sub-specialists will undertake general medicine. With the increasing complexity of medicine it is impossible for any physician to remain expert in all fields of medicine. The general physician should keep generally up-to-date in most aspects of medicine, and become specially interested in one field. It would also be advantageous to sub-specialists if they undertook some general medicine and thus kept abreast of a wider field than their own speciality. There will, of course, still have to be sub-specialists who spend the whole of their time working in their speciality. In this way they will contribute to advancing knowledge in their field.

It is likely that the last proposal would be best for general medicine. The development of exclusive specialisation divorced from general medicine should be discouraged and all sub-specialists should be encouraged to take some part in the general medical load of the hospital. Clearly those with busy specialities will be able to undertake less general medicine than general physicians. In the same way general physicians should be encouraged to develop special interests, particularly in areas which are not adequately served by the existing sub-specialities. The sub-specialist should encourage general physicians to participate in appropriate areas of their specialities.

It is interesting that the role of the general physician is also being questioned in the United States (Petersdorf, 1976). However, the problems there are quite different from those in the United Kingdom, being chiefly the cost of technological advance in medicine and the role of the general physician in family practice. Differences in the organization and financing of medical practice in the two countries largely account for the different problems faced by general physicians.

In conclusion, therefore, the general physician should have an assured future in the large teaching hospitals. His position has been eroded in recent years, but the greater combination of general medicine with specialist medicine would probably improve the situation. It would be a sad day, both for patients and for future generations of doctors if the general physician disappeared from the teaching hospital and his place was taken entirely by a team of highly specialised physicians.

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HYPEROSMOLAR NON-KETOTIC HYPERGLYCAEMIA DURING ORAL DIAZOXIDE THERAPY OF PROLONGED HYPERGLYCAEMIA IN INFANCY

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SEVERE prolonged hypoglycaemia in infancy due to hyperinsulinism does not always respond to treatment with glucocorticoids or glucagon. Baker et al in 1967 suggested that diazoxide might be used as an alternative method of treatment.

Diazoxide is a benzothiadiazine derivative, chemically closely related to thiazide diuretics but lacking diuretic activity. Fajans et al (1968) have recorded this agent's ability of supress insulin release from normal and abnormal islet cell tissue. This property was exploited in the treatment of our patient, a 16 week-old infant with severe, prolonged symtomatic hypoglycaemia. Unfortunate adverse effects of the treatment included hyperosmolar non-ketotic hyperglycaemia and marked hirsutism.

CASE REPORT

A 16 week-old male infant was referred from a peripheral hospital for investigation following a convulsion during which his plasma glucose was unrecordable. He had been delivered normally at term after an uneventful pregnancy and weighed 3.5 kgs. There were no problems in the neonatal period. He was the second child of healthy unrelated parents with no family history of diabetes, epilepsy or unexplained infant deaths.

At the age of 4 weeks he had a brief hospital admission with an upper respiratory tract infection and at that time appeared developmentally normal. During the following months he was brought to his family doctor on several occasions with episodes which his mother called "colic". During these attacks he screamed, became rigid and later appeared drowsy. She also reported that he was an exceptionally hungry baby demanding frequent large feeds of cow's milk and cereal.

On admission he was at the 97th centile for height and weight (Tanner and Whitehouse, 1966) and his head circumference was on the 90th centile (Westrup and Barber, 1956). He was an obese hypotonic infant. There were no demonstrable tendon reflexes or response to stimuli other than pain. Complete head lag and palmar thumbing were noted but there were no localising neurological signs. The fundi were normal and there were no cataracts. The liver was palpable one finger breadth below the costal margin and there was no clinical evidence of visceromegaly and this was later confirmed by barium meal and intravenous pyelogram.

He continued to have focal left-sided convulsions after admission when his plasma glucose was found to be 0.5 mmol/l. Initial treatment was with a continuous intraveous infusion of 20 per cent dextrose with a total of 125 mls of 50 per cent dextrose given intermittently. This regimen maintained the plasma glucose between 1.0-1.5 mmol/l, reaching a peak of 2.0 mmol/l on one occasion.

Full investigations were performed during the first few days following admission but failed to establish evidence of hepatic disease or enzyme deficiency including galactosaemia and glycogen storage disease. Inborn errors of amino acid metabolism were excluded. EEG and all other neurological investigations revealed no abnormality. Endocrine studies other than insulin levels were normal. There was no response to a low leucine diet.

Intravenous dextrose was discontinued for 8 hours before measurement of plasma insulin. Inappropriate levels of 42 and 44 IU/ml (normal range 10-15 IU/ml) were found on 2 occasions when the plasma glucose levels were less than 1.0 mmol/l.

Satisfactory control of the hypoglycaemia was not achieved until diazoxide 50 mg. 3 times daily was introduced as therapy. Using this dose, his plasma glucose was initially maintained at a satisfactory level, but on the 10th day, this rose over a period of 24 hours to 24 mmol/l. Serum sodium was 154 mmol/l, urea 25 mmol/l and plasma osmolality was estimated as 352 milliosmols. Diazoxide was discontinued for 36 hours and osmolar correction was achieved using intravenous 0.45 per cent saline solution and a single dose of 4 units soluble insulin subcutaneously. Subsequently the diazoxide was recommenced at 90 mgs, (equivalent to 9 mg/kg per day) in 3 divided doses. The plasma glucose on this regimen was maintained at a satisfactory level and no further episodes of hyperglycaemia occurred.

A repeat EEG one month after admission showed a generalised slow wave abnormality in all regions. Salaam epilepsy developed and was controlled with clonazepam 0.5 mg twice daily. Unfortunately, despite adequate control of plasma glucose there was no neurological improvement prior to death. He remained hypotonic and unresponsive although he sucked well from a bottle. The head circumference diminished by 1 cm and was only 42 cm at 7 weeks.

Hirsuitism was first noticed after 2 weeks treatment with diazoxide and was severe after 4 weeks.

Death occurred from an intercurrent chest infection at the age of 7 months. Permission for a post mortem could not be obtained.

DISCUSSION

Hyperinsulinism was the cause of hypoglycaemia in this case. A comprehensive review of the causes of hypoglycaemia was published by Pagliara et al in 1973. Histological and histochemical studies were suggested, when one wishes to distinguish between pancreatic B-cell tumours, islet cell hyperplasia, nesidioblastosis and functional disorders causing hyperinsulinism. However, in our patient a laparotomy was not considered justifiable as irreversable cerebral

damage had occurred before adequate plasma glucose levels were established and no improvement was seen in his intellectual development when these were maintained.

The use of diazoxide in the management of hypoglycaemia of infancy is now established (Baker et al, 1967; Erhich and Martin, 1969; Marks and Samols, 1968). The condition remains, however, extremely difficult to treat satisfactorily. Early correction of the plasma glucose remains of major importance in preventing severe brain damage. Diazoxide is perhaps the agent most likely to achieve this. Drash et al (1968) report many complications of diazoxide including hyperglycaemia, ketosis, hirsutism, hyperuricaemia and electrolyte abnormalities. They do not record the hyperosmolar condition described here but this has been reported in adults (Charles and Danforth, 1971). Correction of this hyperosmolar state is not difficult if diazoxide is withdrawn and adequate intravenous fluids administered, insulin was probably not essential in our patient. The possibility of this potentially lethal complication requires regular monitoring of the serum electrolytes and plasma glucose during the early days and weeks of treatment. Prevention depends on the use of minimum effective dose of diazoxide which is probably 7.5 to 12.5 mg/kg per day. Hirsutism is an unfortunate but unavoidable complication.

SUMMARY

A 16 week-old infant presented with severe prolonged symptomatic hypoglycaemia resistant to the treatment with intravenous dextrose. The aetiology of the condition was established as hyperinsulinism and treatment was initiated with diazoxide 15 mg/kg per day, in 3 divided doses. This was shown to be successful in correction and maintainance of plasma glucose levels initially but led to the development of a hyperosmolar non-ketotic hyperglycaemic state on the 10 th day of treatment.

This was readily corrected by discontinuing diazoxide administration, intravenous infusion of 0.45 per cent saline solution and subcutaneous insulin. Subsequent reduction of diazoxide therapy to 9 mg/kg per day prevented recurrence of this dangerous complication.

Residual cerebral impairment due to the initial prolonged hypoglycaemia led eventually to the child's death.

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ANALYSIS OF AMPUTATIONS DUE TO CIVIL DISTURBANCE IN BELFAST FROM 1969 TO 1975

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THIS article describes the contribution of civil disturbance injuries to the amputation rate since the onset of the troubles in Northern Ireland in August, 1969.

PATIENTS AND METHODS

All patients undergoing amputation at the Royal Victoria Hospital from August, 1969 to July, 1975 have been included. The 286 amputations were performed by the casualty, general, orthopaedic and vascular surgeons. They were divided into minor and major; minor amputations being the loss of one or more digits and major amputations those at a more proximal level. The causes were classified as civil disturbance, accident and peripheral vascular disease.

RESULTS

Approximately three-quarters of all amputations occurred in males; 53 per cent followed peripheral vascular disease, 31 per cent accidents at work and on the roads and 16 per cent bomb blasts and gunshot wounds. It was particularly in the over 60 age group that peripheral vascular disease predominated, being responsible for 115 of the 136 amputations, and approximately 70 per cent were above the knee.

There were 14 men and 12 women who had bilateral lower limb amputations. Peripheral vascular disease accounted for 15, bomb blasts for eight and accidents for three. One lady had two legs and one arm amputated and one man had an arm and a leg amputated following exposure to bomb blast.

Bomb blasts resulted in major upper limb amputations to eleven men and two women, in contrast to five from accidents and one from peripheral vascular disease. Upper limb amputations dominated the under 30 age group, while most lower limb amputations occurred in the older age group.

Minor amputations accounted for 40 per cent of the total, being commoner in males because of the high incidence of work accidents and peripheral vascular disease. Bomb blasts and gunshot wounds played little part in minor amputations and were responsible for only seven of the 116 performed.

There were 36 hospital deaths in patients undergoing amputation for peripheral vascular disease. Multiple injuries accounted for most other deaths, five being due to bomb blasts, four to accidents and one to gunshot wounds.

DISCUSSION

Civil disturbance in the form of bomb blasts and gunshot wounds has contributed significantly to amputations in Northern Ireland since 1969. It has affected all age groups due to the random placing of bombs and has more than doubled the major amputation rate due to trauma. Many of the bomb blast victims sustained multiple injuries of all viscers, thorax and head as well as their limb injuries. Many were found to have traumatic amputations on admission which determined the subsequent level of amputation. Gunshot wounds caused less generalised limb damage, major amputation being necessary only because of major vessel injury. Most amputations following road traffic accidents were preceded by severe compound long bone fractures. Road traffic accidents and peripheral vascular disease more commonly involved the lower limbs, whereas bomb blasts involved both upper and lower limbs. Mortality was generally due to concurrent disease in the peripheral vascular disease group, and multiple injuries in the accident and bomb blast group.

SUMMARY

During the last six years civil disturbance in Belfast has contributed 24 per cent of the 170 major amputations at the Royal Victoria Hospital, Belfast; peripheral vascular disease 56 per cent and accidents 20 per cent. Thirty-six resulted from bomb blasts and gunshot wounds contributed only five. Bomb blasts caused the loss of 13 upper limbs, more than twice the number due to other causes. Eight of the 26 bilateral amputations resulted from bomb blast injuries. The troubles have, therefore, more than doubled the number of amputations due to trauma putting a greater work load on the limb fitting, physiotherapy and other departments concerned with amputees. In contrast, most other amputations were due to peripheral vascular disease in the toes and accidents to the fingers at work.

ACKNOWLEDGEMENTS

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BOOK REVIEWS

ANDREW MALCOLM OF BELFAST: PHYSICIAN AND HISTORIAN. By H. G. Caldwell (pp. xvii + 138; illustrated + facsimile of The History of the General Hospital by A. G. Malcolm, pp. 139 + xxxii; £6.00). Brough, Cox & Dunn for Royal Victoria Hospital, Belfast. 1977. (Copies from Belfast booksellers or Unit Administration, Royal Victoria Hospital.)

THIS book is in two parts: a biography of Malcolm (134 pages) and a facsimile reproduction of his *History of the Belfast General Hospital and the Principal Medical Institutions of the Town,* first published in 1851 (by S. & G. Agnew) but long out of print and now rare. Both are welcome; their publication in one well-produced and comparatively inexpensive volume is particularly appropriate. Those interested in medicine and its institutions, philanthropy and the history of this city generally owe a debt to author, sponsors and publshers alike.

The Royal Victoria Hospital "charity" can trace an unbroken lineage from the founding of the Belfast Charitable Dispensary in 1792 and the opening of its associated six-bed hospital in 1797 in what is now Berry Street. The only source for the history of its early years other than some fragmentary documents and, from 1817, the *Annual Reports,* is Malcolm's *History,* and this has always given the book a unique importance. This republication, added to Allison's *Seeds of Time* (1850-1903) and Marshall's *Fifty Years on the Grosvenor Road* (1903-1953), brings the complete historical trilogy within the reach of all. But Malcolm was much more than a provincial physician and chronicler and his story more than that of the growth of a hospital; to his merical vocation he added that of educationalist, philanthropist and active promoter of social and medical well-being, especially among the underprivileged. Those, sadly all too few, who know something of his work, have long hoped he would find a biographer, and happily Dr .Hugh Calwell, who has already given us a history of the first 75 years of the R.B.H.S.C., has now obliged.

By any yardstick, Malcolm was a remarkable man, and he lived in remarkable times for Belfast and industrial society generally. Like many prominent Ulster doctors, then and now, he was a son of the (Newry) manse. He entered Inst at the age of 11, progressed to the "collegiate" section to study medicine, and took the licence of the R.C.S.(Edinb.) and M.D. (with gold medal) of Edinburgh University in 1842. He returned at once to practise in Belfast, was elected a district medical attendant of the General Dispensary and, in 1845, attending physician at the Fever (later General) Hospital in Frederick Street, and died in Dublin in 1856 of congestive heart failure, aged only 37. In his 14 years of practice he proved his acumen as a busy clinician and hygienist, which included much industrial work, published many case reports, medical monographs and some experimental work, innovated "improving" societies and edited an associated magazine, wrote from the head and heart on the public health and squalor of Belfast, was a chronicler of the cholera pandemic of 1847-49, established in Belfast through his efforts and writings a sound "British clinical method" (actually "Irish" in that it was due to Robert Graves at the Meath Hospital in Dublin (*Lond. med. Gaz. 10,* 401-406, 1832)), was a main dynamic force in local medical and philanthropic societies, wrote his *History* (perhaps in only five months), and throughout showed a scientific rigour, great compassion and imagination, sound knowledge, high qualities of intellect and character, and quite unusual drive. (As just one example: "The influence of factory life on the health of the operative as founded upon the medical statistics of this class in Belfast" (*J. Statist. Soc., 19,* 170-191 (1856)) is a minor masterpiece ahead of its time, and I well remember the amazement with which Professor Pemberton, Professor Cheeseman and myself first read it in 1960 when preparing a large-scale study on flax byssinosis. Malcolm's article was so thorough that it nearly made our task unnecessary!) The *History* itself is a loosely constructed, rambling narrative, probably hastily written, but with considerable charm, and evidencing on every page the enthusiasm and compassion of the author and his intimate knowledge of Belfast, the "'charity" and other medical and associated institutions. It is pleasant reading, but its main importance is that it is literally irreplaceable since (as noted) most of its primary sources are lost.

Dr. Calwell describes all this in 16 short chapters and a prologue, epilogue, bibliography, index and three appendixes—all in 137 pages. His role is as simple chronicler, not as commentator, interpreter or critic; events are documented in his familiar, concise, accurate and

easy style, but there is little attempt to analyse the impact or implications of Malcolm's work. Even on these terms the canvas is modest. Much of Malcolm's non-clinical work and generating energy must be seen as part of the general drive in industrial society world-wide towards economic, social and "sanitary" improvement for all, arising from a complex of social, economic, political, scientific and moral reasons. Dr. Calwell, however, does not discuss these and restricts himself mainly to the events in Belfast involving Malcolm and his circle; he treats Malcolm almost in isolation rather than one of a breed who wove the pattern of an Age, and this leads to a certain lack of perspective in places. It also sets an additional problem: since primary sources are sparse—especially with Malcolm's early death—and the canvas small, even a short book leaves the substance incomplete. Dr. Calwell has made good use of papers, especially private family ones, but there are inevitable and tantalising gaps and a coherent picture, despite the author's energy and skill, fails to emerge. The book is, in fact, a set of short papers set out as chapters narrating Malcolm's many activities, with certain background information, including some interesting vignettes of contemporaries; but the thread of narrative and the insight of the subject essential to a biography are missing. This is perhaps inevitable and is unimportant when set against the author's success in documenting Malcolm's multifaceted work: the reader will for the first time be able to identify Malcolm as one of Belfast's greatest doctor-citizens, a fact which R. H. Hunter (*U.M.J., 5,* 107-123 (1936)) and particularly J. S. Logan (*U.M.J., 43,* 22-32 (1974)) had previously suggested and is now confirmed. Dr. Calwell is to be congratulated on a very considerable achievement and for deploying his talents in his retirement so fruitfully in this his second important contribution to Belfast medical history and historiography. A memorial tablet to Malcolm was originally erected in The General Hospital, Frederick Street, but was later lost; its replacement is overdue.

The publication is of a good standard and generally accurate throughout. In my edition the Preface to the *History* is incorrectly placed between pp. 12 and 13 of the first chapter. This book should be on the bookshelf of all interested in Ulster medicine.

PETER FROGGATT

SOLID LIVER TUMOURS. By James H. Foster and Martin M. Barman (pp xii + 342; illustrated; £14.75). Philadelphia, London, Toronto: Saunders. 1977.

THIS monograph on solid liver tumours gives a most extensive review of the literature and clarifies the nomenclature. The data collected by the authors themselves from 98 hospitals across the U.S.A. is open to the criticisms of any retrospective chart review, but the exercise is justified in that no single clinician or hospital complex has a sufficient volume of patients with solid liver tumours from which to draw valid conclusions about therapy. Although large African and Asian series have been reported, these have concerned mainly primary tumours, often with associated cirrhosis—a very different picture to that seen in the West. About half of the book is devoted to pathology, with large amounts of statistics from their own review and from the existing literature. This rather heavy reading tends to be repetitive, but is lightened by the insertion of multiple illustrated case histories. For those who do not wish to wade through all the figures, there are useful summaries and recommendations at the end of most chapters, although abbreviations such at L.T.S., F.N.H. and L.C.A. may prove annoying. I find the separation of the tumours in under-16-year-olds into separate chapters rather arbitrary and unnecessarily cumbersome, since the only real difference from adult tumours is the rare hepatoblastoma, occurring chiefly in the under-2-year-olds. The clinical section answers for the first time many practical questions on management and displays the fallacy of a lot of time-honoured traditions. The risks of closed liver biopsy in the usually vascular primary tumours are emphasised and the errors of liver scan reports for suspected secondary tumours are noted. The chapters on practical management are essential reading for surgeons contemplating hepatic resections. Operative technique is simplified—as the authors point out: "Too much has been written about special skills, special knowledge and special tools for liver resection." They emphasise the place of blunt dissection for identification of blood vessels—a technique they attribute to Keen's description of 1891. The practical points of hepatic resection give the true ring of one who has first-hand experience of the technical problems Palliative therapy is covered briefly but presents a balanced view based mainly on the existing literature. The book should be in all hospital libraries, but it is likely that only specialists with an interest in the field will want to purchase their own copies at £14.75 each.

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J.D.B.

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This book will be of greatest value to those who already have some experience of recording M-mode echocardiograms; the novice might despair of matching the quality of the tracings, while for the expert many of the questions asked will be elementary. Those with two-dimensional echocardiographic machines will regret the lack of reference to this important development. But all concerned with the diagnosis and management of patients with heart disease will gain more experience in the few hours required to read the 53 echocardiograms in this book than they would do in reading the next few hundred unselected echocardiograms in the average cardiac unit.

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I have possessed many editions of this textbook and this edition lives up to its great reputation. I have no hesitation in recommending it to all candidates for the membership examination.

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THIS book is intended not only for medical students commencing their clinical training, but also for nurses, physiotherapists, pharamacists and medical technologists. It is asking a great deal of one book to cater for the diverse needs of such groups. Each will certainly find much to interest them, but also much to disregard. The medical student will derive most benefit from Part I, which deals with basic principles of disease. In this section the text is closely based on the well-known pathology book, "Walter and Israel", so popular with young doctors studying for their post-graduate clinical examinations. In addition to the more usual topics, there are interesting pathophysiological discourses on fluid and electrolyte balance and disturbances in temperature regulation. In Part II the author has made his selection of the important diseases affecting individual organs and has excluded the rarities. The pathology is discussed in a rather superficial manner and in a terse condensed style. There is certainly insufficient detail for those who strive to satisfy examiners in Final Part I at Queen's. On the credit side the references, though few in number, are fairly up to date and have been carefully selected for those who would probe more deeply. Another useful feature is the inclusion of questions at the end of each chapter whereby the reader may test his powers of recall.

J.D.B.

CASE STUDIES IN ECHOCARDIOGRAPHY: A DIAGNOSTIC WORK-BOOK. By Ralph D. Clark, M.D. (pp. x + 334; illustrated; £12.25). Philadelphia, London, Toronto: Saunders. 1977.

THIS book brings to life William Osler's aphorism: "Experience lies not in seeing much but in seeing wisely." Following lucid descriptions of the normal adult echocardiogram and of echocardiographic measurements and calculations, Dr. Clark presents 53 brief case histories. The relevant echocardiograms are given and the reader is invited to use them to answer several clinical, diagnostic questions. There follow the author's answers illustrated by line diagrams, and a host of useful technical hints and clinical applications. In this way the author conveys a wealth of experience, valuable both to those who record and those who interpret echocardiograms.

This book will be of greatest value to those who already have some experience of recording M-mode echocardiograms; the novice might despair of matching the quality of the tracings, while for the expert many of the questions asked will be elementary. Those with two-dimensional echocardiographic machines will regret the lack of reference to this important development. But all concerned with the diagnosis and management of patients with heart disease will gain more experience in the few hours required to read the 53 echocardiograms in this book than they would do in reading the next few hundred unselected echocardiograms in the average cardiac unit.

M.E.S.

BRAIN'S DISEASES OF THE NERVOUS SYSTEM (8TH EDITION). Revised by John N. Walton (pp. xv + 1277; figs. 170; £17.50). London: Oxford University Press. 1977.

THIS is the first edition that has been completely revised and brought up to date by Professor Walton since Lord Brain's death. It is a comprehensive modern textbook of neurology which fully justifies its popularity. I found that it clearly expresses current neurological views and teaching.

I have possessed many editions of this textbook and this edition lives up to its great reputation. I have no hesitation in recommending it to all candidates for the membership examination.

J.H.D.M.

A SHORT TEXTBOOK OF SURGERY (4TH EDITION). By Selwyn Taylor and Leonard Cotton (pp. vi + 634; figs. 97; paper £3.95; boards £7.45). London: Unibooks (Hodder and Stoughton Educational). 1977.

IT is welcome to see a fourth edition of this useful textbook for students. The authors are to be congratulated on bringing out a further edition without notably increasing the length of this book, although their efforts to condense their material do lead to some difficulty. For example, on page 92, the 13 lines devoted to the natural history of breast cancer would almost certainly lead the student to wrong conclusions and to believe that there are two types of breast cancer: one which grows rapidly and spreads late, and another which develops secondary deposits in lymph models whilst the primary tumour remains occult.

The book is illustrated with line diagrams which are in general clear and relevant to the text, although some are called upon to illustrate more than they actually do. For instance, figure 20 is stated on page 219 to show the operation for the repair of a sliding hiatus hernia, whereas it only in fact shows the different types of hernia.

Each paragraph is followed by a well-chosen suggestion for further reading, which will encourage the student to use the textbook to provide the basis for his knowledge rather than to believe it encompasses all that he needs to know.

Orthopaedics and injuries to bones and joints are included. Throughout the book there is a very pleasing evenness in the standards of the various chapters. Most are well written and easily readable. It is a pity that doctors communicate with each other in such turgid language and every time one reads a textbook directed towards students one hopes for more scintillating language. One is usually disappointed. Nevertheless, this book does maintain a high standard and can be strongly recommended to medical students as the basis for their surgical studies.

A.D.R.

ATRIOVENTRICULAR CANAL DEFECT. Edited by Robert H. Feldt (pp. xii + 145; illustrated; £18.00). Philadelphia, London, Toronto: W. B. Saunders. 1976.

THE appearance of an entire book devoted to such an apparently narrow subject as Defects of the Atrioventricular (A.V.) Canal shows the high degree of sub-specialisation existing in cardiology today. Many might question the need for this book which draws together and synthesises contributions to the subject almost all of which have been published in specialist journals. But, as Dr. Dwight C. McGoon points out in his foreword, at certain times in the development of every topic a point is reached when sufficient new knowledge accrues to give it "a certain cohesive maturity".

The organisation of the book is good. Recent contributions to the understanding of the embryology of the A.V. canal illuminate the anatomical features f the varius A.V. canal defects. In the same way, the chapter on the conduction system in A.V. canal defect illuminates the section on the electrocardiogram. Together they introduce and amplify the brief chapter on the clinical profile of the anomalies.

Appropriately, one of the longest chapters presents the echocardiographic features of the various defects. It is illustrated with numerous informative examples of M-mode records, showing clearly the apparent diastolic movement of the anterior mitral valve leaflet through the ventricular septum in the complete defect. Unfortunately, the chapter is already somewhat dated by the absence of any reference to two-dimensional echocardiography. The chapter on angiography is succinct and well illustrated. The final chapter on surgery, including post-operative prognosis, shows how dramatically the outlook for patients with these defects has improved within the past decade.

This slim book costs £18.00 and is unlikely to be bought by many British doctors. However, as a work of reference which demonstrates undoubted "cohesive maturity", it deserves a place in every medical library.

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M.E.S.

REVISION NOTES ON PSYCHIATRY. By R. T. Koshy (pp. xi +147; £1.45). London: Hodder and Stoughton. 1977.

UNLIKE most psychiatric textbooks for nurses, usually written by psychiatrists, these revision notes are written by a nurse tutor trained in both general and psychiatric nursing. The approach is problem orientated and the emphasis is on topics of practical value to nurses involved in patient care. A useful series of short selections contains sound advice on how to handle difficult types of patient. A team approach to the management of psychiatric patients is advocated and the functions of the various therapeutic team members are clearly defined. Brief notes are provided about many, though not all, modern developments in patient care. The common psychiatric syndromes are described in note form. A reading list is provided at the end of each section as well as a number of revision questions. The text is clear and concise, though necessarily condensed. Inevitably a number of inaccuracies of fact appear. Nevertheless, this book can be recommended to nurses as a useful short revision text.

G.W.F.

CORONARY ARTERY DISEASE. By Richard Gorlin (pp. xii + 317; illustrated; £13.50). Philadelphia, London, Toronto: Saunders. 1976.

THIS monograph, which is one of a series on different topics in medicine, is written by one of the most respected and leading experts in the field of coronary disease. In the preface the author states: "It is the purpose of Coronary Artery Disease to marshal in one place the majority of the available information concerning the current practice of coronary heart disease," and he succeeds not only in doing this, but in presenting it in a concise and interesting fashion.

The early chapters cover such topics as methods of investigation, pathogenesis of atherosclerosis and the anatomy and physiology of the coronary circlulation. Later chapters are devoted to current views on the medical and surgical treatment of obstructive coronary disease and the material is presented in a well-balanced form.

At £13.50 the book is expensive, but it can be strongly recommended to all physicians involved in treating patients with ischaemic heart disease. J.G.M.

RABIES—THE FACTS. Edited by Colin Kaplin (pp. 116; plates 12; £0.75). London: Corgi Books. Also in hardback at £1.95 (London: Oxford University Press). 1977.

THE claim on the dust cover of this book states that it is "a full presentation, in accessible and largely non-technical language, of the biological and medical details of rabies, together with a discussion of present policies, in the U.K. and elsewhere, for its prevention and elimination". Eight authors have written seven chapters on different aspects of the rabies problem in man and in animals which do much to substantiate the above claim. However, because of the multiple authorship, some unevenness in style is evident and there is overlap in information, particularly in chapters 4, 5 and 6, which deal with animal rabies and the red fox. The information in the book is up to date, e.g., a map of the spread of rabies in France on page 16 shows the posititon on 10th September 1976. Many intriguing facts and statistics are presented throughout the book, but unfortunately there are no references. The last chapter deals with rabies vaccines and antirabies serum, but the useful details of the various rabies immunisation schedules are not given. The book is printed clearly, the index is adequate, and the text, with rare exceptions, would be readily understood by non-medical readers. The plates are black-and-white photographs and include cases of human and animal rabies. Doctors and medical students will learn a great deal about rabies on reading this little book, and, considering the price of medical books today, both editions are cheap.

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J.H.C.

OBSTETRIC ANAESTHESIA AND ANALGESIA. By Donald D. Moir (pp. 298; figs. 27; £8.00). London: Bailliere Tindall. 1976.

TWENTY years ago obstetric anaesthesia was frequently delegated to the inexperienced junior anaesthetist who was ill-equipped to deal with many of the problems he encountered. Since then intensive training, research and the appointment of consultants with a special interest in obstetric anaesthesia has led to a rapid improvement. Moir has played a major role in this development and his book gives a balanced view of the anaesthetist's part in modern obstetric practice. Some of the chapters: The Physiology of Pregnancy and Labour, The Pharmacology of Drugs used in Labour, and Neonatal Resuscitation, are lacking in depth but all have an extensive and up-to-date bibliography allowing the enquiring reader to pursue each subject in greater detail.

General anaesthesia for operative delivery of the infant is described and discussed at length, the author favouring endotracheal anaesthesia for almost every situation. He stresses the importance of routine oral antacid therapy during labour, the lateral position to avoid supine hypotension and pre-oxygenation prior to induction of anaesthesia. The suggested induction dose of 200-250 mg of thiopentone sodium may be insufficient to guarantee unconsciousness if intubation is difficult and indeed may contribute to intubation difficulties in the resistant patient. The problem of "failed" intubation receives little attention.

The chapter on regional analgesia and anaesthesia contains many details of great practical value. It emphasises the importance of co-operation between obstetrician, midwife and anaesthetist to guarantee a successful extradural analgesic service. The author recommends a resident anaesthetist for all large obstetric units, whose duties should include the practice and maintenance of extradural blocks. Possible obstetric causes for persisting neurological deficit following regional anaesthesia are discussed and the references will be of interest to obstetricians. There are some criticisms of this section. Few anaesthetists would use the prone position in a "full-term" patient when establishing a caudal block. The dose of bupivacaine suggested for extradural anaesthesia for caesarean section may be too small to guarantee sufficient upward spread of the sensory blockade. The author does not emphasise gentle handling of tissues by the surgeon when operating on the conscious patient, a factor which contributes greatly to the mother's comfort and satisfaction.

This book can be highly recommended to both obstetricians and anaesthetists. Trainees of both specialties will find it of great value when preparing for higher qualification.

J.M.

AN INTRODUCTORY TEXTBOOK OF MEDICINE. By J. J. Connon (pp. 373; figs. 20; £4.75). London: Lloyd-Luke (Medical Books) Ltd. 1977.

THIS new book comes between the smaller books giving advice about history-taking and clinical examination and the larger textbooks in medicine, many of which are well known and excellent. The intention of the author is to provide a concise overall view of medicine for the students who are already trained in the basics of the clinical methods.

The book emphasises the clinical manifestations of disease and outlines the underlying physiology and pathology. In this way it sets out to provide a concise overview of medicine which undoubtedly should be useful to students during their clinical years as an introduction to a deeper acquaintance with one of the standard medical texts. It does not pretend to be comprehensive for, although it contains the principles of investigation and of therapy, it does not go into any detail about these.

There are eight chapters embracing diseases of the cardiovascular system, the respiratory tract, kidneys, metabolism, gastrointestinal tract, locomotor system, blood and reticular system and, finally, the nervous system. There is also an excellent appendix containing in telegraphic style the aetiology and manifestations of common disorders. This text should fill the gap in the reading relating to general medicine and should be of great use to all medical students during their clinical years. It is a soft-cover book of some 370 pages, is very good value for money nowadays and is thoroughly recommended.

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THIS book by 20 eminent American contributors is intended as a practical guide to those responsible for the immediate care of severe accidents on arrival in hospital. To achieve this end the authors have adopted a method of presentation which relies heavily on numbered lists, either of possibilities in diagnosis or steps in treatment. One advantage of this method is that, in spite of having many contributors, the style of the book is fairly uniform throughout. This style does not make for stimulating reading. But in a crisis it is likely that one could find the right section of the book and understand the advice given quite quickly. The editors have been largely successful in avoiding unnecessary repetition.

The term "early care" is taken mainly to apply to steps that would be taken in an accident and emergency department. Some contributors describe operations which would be carried out. Coming from the committee on trauma of the American College of Surgeons, it is not surprising that the outlook is more that of the accident surgeon than the specialist in accident and emergency medicine.

Seven general chapters on topics like cardiopulmonary resuscitation, infection and anaesthesia are followed by fifteen chapters on injuries of different regions. A chapter on legal aspects, while American in emphasis, is largely applicable in the United Kingdom. The book ends with a short chapter on disaster planning.

Few accident and emergency departments can afford to be without a copy of this book.

W.H.R.

INFECTIONS AND INFESTATIONS. Edited by A. T. Proudfoot (pp. 126; illustrated; £3.00). Edinburgh: The Royal College of Physicians of Edinburgh. 1976.

THIS collection of ten essays from the December 1975 Symposium of the Royal College of Physicians of Edinburgh is welcomed. Dr. Horne summarises admirably the present-day approach to Therapy in Tuberculosis, and in the next essay Dr. Ironside adds support—and it is still needed—for the use of chloramphenicol in typhoid fever, but he does not clearly emphasise the futility of specific treatment for bacillary dystentery.

Dr. Arniel has wise words on urinary tract infections, but why is "plain" offered as "plane" twice on page 28? Perhaps his attitude towards ampicillin as a first-line antibiotic in latent urinary tract infection (page 32) has been modified by the introduction of talampicillin.

Dr. O'Grady gives a masterly presentation of "The Principles of Antibiotic Resistance" and the final sentence of his contribution—"It may be worth reflecting the next time you propose to give an antibiotic to a patient that it is not only his life but our germs that are in your hands"—leaves me with the mutual (?) depression that his is yet another voice crying in the wilderness of clinical ignorance.

The late Dr. Reid's contribution on the epidemiology of respiratory infections is of the high standard one expected from such an international authority.

Twenty years ago one would have been mildly surprised at the inclusion in an Edinburgh Symposium of Chevalier Gilles' paper on malaria, but it serves to emphasise the epidemiological contraction of the earth and updates clinicians working in temperate climates. (One of the very few editorial errors in the volume is the irrelevant "J" in Dr. Gilles' initials in the table of contents.)

The four other contributions deal with skin infestations, sexually transmitted diseases, pathogenesis of gastroenteritis and hepatitis-B in the hospital setting, and all are informative, although the content of the final essay has been updated by a recent article from Professor Marmion's team in the Journal of Hygiene.

R.R.G.

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Dr. O'Grady gives a masterly presentation of "The Principles of Antibiotic Resistance" and the final sentence of his contribution—"It may be worth reflecting the next time you propose to give an antibiotic to a patient that it is not only his life but our germs that are in your hands"—leaves me with the mutual (?) depression that his is yet another voice crying in the wilderness of clinical ignorance.

The late Dr. Reid's contribution on the epidemiology of respiratory infections is of the high standard one expected from such an international authority.

Twenty years ago one would have been mildly surprised at the inclusion in an Edinburgh Symposium of Chevalier Gilles' paper on malaria, but it serves to emphasise the epidemiological contraction of the earth and updates clinicians working in temperate climates. (One of the very few editorial errors in the volume is the irrelevant "J" in Dr. Gilles' initials in the table of contents.)

The four other contributions deal with skin infestations, sexually transmitted diseases, pathogenesis of gastroenteritis and hepatitis-B in the hospital setting, and all are informative, although the content of the final essay has been updated by a recent article from Professor Marmion's team in the Journal of Hygiene.

R.R.G.

MEDICAL PARASITOLOGY (4TH EDITION). By Edward Markell and Marietta Voge (pp. viii + 393; figs. 1611; £11.50). Philadelphia and London: Saunders. 1976.

THIS is an excellent book although unhappily the only coloured plates concern artists' impressions of various Plasmodia; there is available, however, a set of 180 colour illustrations which can be obtained separately, but the reviewer did not have the pleasure of seeing these.

It must be added that many of the black-and-white illustrations given in the text are of outstanding quality; several modern laboratory techniques have been introduced in this edition and there has been an up-dating of virtually every chapter.

Whilst one would not expect it to be compulsory reading for the senior clinical undergraduate, the continuing increase in what used to be regarded as exotic tropical infections now occurring in Britain demands that this book should be available for immediate reference when one is faced with a pyrexia of uncertain origin or other apparently baffling clinical situations in a patient who has been abroad at any time in his life.

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THE ACUTE ABDOMEN (AN APPROACH TO DIAGNOSIS AND MANAGEMENT). By Thomas W. Botsford, M.D., F.A.C.S., and Richard E. Wilson, M.D., F.A.C.S. (pp. xvi + 325; illustrated; £7.00). Philadelphia and London: W. B. Saunders Company. 1977.

THE acute abdomen has been a favourite subject for several authors and most have succeeded fairly well in producing books which are of value to students or practising physicians. This present volume in its second edition comes from Boston as a compact paperback which would certainly slip easily into a pocket. The layout is attractive in six sections. Section 1 discusses the various diagnostic tools which are available, including the clinical approach to the acute abdomen. Sections 2, 3, 4 and 5 discuss the various categories of the acute abdomen, while Section 6 concludes the book by discussing the management of the post-operative abdomen. The book is easily read and the line diagrams are well chosen and illustrate each point with clarity. Some useful x-rays are included and also well-chosen ultrasonagrams.

Detailed operative treatment is not included but the principles of such treatment are well discussed and this book would be useful to those whose responsibility it is to diagnose the acute abdomen but perhaps not to operate on it. The chapter on anaesthesia seems rather out of place as it is unlikely to be a source of reference for the anaesthetist and would not be of direct interest to the surgeon.

In a book like this which concerns itself with a common clinical problem there are bound to be shades of opinion which would disagree with some of the statements that are made. I would disagree with the statement on page 10 that vomiting without pain or that has preceded the pain for a considerable period of time probably is not associated with a surgical lesion, as I think it is common for children with acute appendicitis to present with vomiting and to vomit for a considerable period before pain may necessarily be complained of. However, these are matters of opinion and in general I think this book gives a very balanced account of these common clinical problems.

The book is probably too detailed for the average medical student, although any medical student who felt he had a particular interest in surgery would be well advised to read it. It would certainly be suitable for the postgraduate student in surgery, providing he had another source of reference for operative detail. In the country of its origin I am sure it is of considerable value to physicians working on their own who might carry out occasional surgical procedures. I would, therefore, recommend this book to the student who is particularly interested in surgery, to the postgraduate in surgery and to the general practitioner who wishes to have a concise reference to the problems involved in the diagnosis and management of the acute abdomen.

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THIS is the eleventh in a series of monographs dealing with various aspects of radiology. The book is of special interest since Dr. Davidson from Mount Zion Hospital, San Francisco, an authority on renal disease, wrote most of the text while on sabbatical leave in London, under the critical eye of his British contemporaries. The radiologic assessment of renal parenchymal disease is discussed on the basis of pathologic anatomy and physiology.

The introductory chapters concern radiographic technique, renal anatomy and embryology. Pathological processes are discussed in "Diagnostic Sets" based on the size and shape of the kidneys on the plain film and intravenous pyelogram. While this is a practical approach, and useful for reference purposes, the natural evolution of disease and clinico-pathological correlation are necessarily rather disjointed as similar conditions must be included in several of the eight "Diagnostic Sets".

The excellent illustrations demonstrate the value of properly supervised intravenous pyelography, especially the use of tomography to enhance detail. The role of renal arteriography and venography and the value of ultrasound in the evaluation of renal mass lesions is well documented. In a book devoted to renal disease it is surprising to find no discussion on the value of radioactive isotopes, while cysto-urethrography is given scant mention. Another criticism is the apparent acceptance of simple retrograde pyelography as a valuable and acceptable technique.

With a comprehensive bibliography, this is a good reference book for the radiologist or urologist, and for those training for F.R.C.R. distils much useful information. J.P.B.

MUNRO KERR'S OPERATIVE OBSTETRICS (NINTH EDITION). By P. R. Myerscough (pp. 896; figs. 310; colour plates 9; £15.00). London: Balliere Tindall.

THE ninth edition of this famous text-book appears nearly seventy years after its first publication (Operative Midwifery by J. Munro Kerr, 1908). It still remains the standard British text and is essential reading for the postgraduate preparing for higher degrees. The book is primarily concerned with the techniques and operative procedures of obstetric care but includes the whole range of obstetric complications which call for operative intervention. During the past decade there have been great changes in many aspects of labour ward management, with a new and more critical appraisal of many operative procedures and their effect on the newborn infant and its subsequent development. The use of the partogram, selective augmentation and electronic monitoring of labour are fully discussed and reflect important changes in management. A new chapter on anaesthesia and analgesia have been introduced, with particular reference to the nerve-blocking procedures. The text contains details of many obstetric manoeuvres which are now rarely, if ever, used in current obstetric practice in this country, but, as the author points out, he is aiming to serve a world-wide readership. In many parts of the Third World it may be necessary to achieve vaginal delivery in spite of increased maternal risk, for resort to caesarean section can have serious implication, social and medical, for the patient concerned.

Inevitably, many passages dealing with historical topics have had to be sacrificed, along with interesting case histories by Munro Kerr and Chassar Moir, which undoubtedly made the book more readable. Widespread and important references are listed at the end of each chapter and these will prove most useful to the postgraduate student.

In spite of the inclusion of many new topics, reflecting advances in care, the size of this edition, when compared with its predecessor in 1971, is not greatly increased. Unfortunately, the same cannot be said for the price and, despite this, the paper is thin enough to allow the print to show through on both sides. Otherwise the production is satisfactory and the author is to be congratulated on a fine achievement. W.T.

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CLINICAL METHODS—VOL. 1: THE HISTORY, PHYSICAL AND LABORATORY EXAMINATIONS. Edited by H. Kenneth Walker, M.D., F.A.C.P., W. Dallas Hall, M.D., F.A.C.P., and J. Willis Hurst, M.D., F.A.C.P., F.A.C.C. (pp. xi + 420; £7.50). London: Butterworths. 1977.

THERE have been several books of this type which are designed to help those who are starting medicine and who need to know what is meant by clinical skill and how to acquire it. This particular volume not only deals with history-taking and examination, but also with laboratory methods; it has various chapters on psychiatry, allergy, birth control and immunisation, and attempts to include much of clinical medicine as well. The result is rather indigestible and not entirely satisfactory, in my view, for the average British student. It somehow succeeds in becoming neither fish nor fowl nor fine fresh herring! J.V.O.

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THERE are few practising clinicians who can be unaware of or have not consulted a previous edition of this book. The title and its status suggest that it is a text-book of therapeutics, but this is a misconception. It is certainly not a classical therapeutic text-book for undergraduates or academic therapeutic teaching. It is essentially a voluminous, sophisticated, up-to-date guide for the practical and practising clinician. In the situation of "office practice" in North America the clinician has many instant personal decisions to make on mode of therapy for the individual patient and primary care physicians in that environment often undertake complex therapeutic decisions without referral or second opinion. The need is therefore for an up-to-date authoritative reference. To this end, Current Therapy is now published yearly. The panel of authors is wide and authoritative. Of approximately one hundred and eighty authors, one hundred and seventy are North American. The transatlantic flavour of therapy is occasionally (only occasionally) disconcerting, partly because United States Pharmacopea and British National Formulary names are not always synonymous. Also, even though modern therapy throughout the Western world is much in step, the philosophy of the American Federal Drug Administration is essentially, and rightly so, "careful", there are occasional time "gaps" in drug usage on either side of the Atlantic. It is fascinating to recognise that propranolol in the only β-blocker available in the U.S.A.; also cromoglycate and beclomethasone are described as very recent advents to the therapy of asthma. In general, sophisticated advice is found throughout the text; for instance, the two discussions on staging and therapy of Hodgkin's disease. Generally, the authors are impressive—again an instance, Nicoloff, Oppenheimer and Volpé each write separate sections on thyroid disease.

Due to the eminence of the authors there is a tendency for each chapter to be its own authority, but some of the treatments have been pioneered by other workers and it would be helpful to have references to the original work for more detailed consultation. References to original source work or the treatments discussed are universally omitted throughout the book and this is a considerable disadvantage.

Where or for whom should this book be bought in the U.K.? There are strong arguments for all ward units and health centres possessing up-to-date therapeutic reference sources. Every ward could well possess, firstly, the National Formulary (which all wards do) but supplemented by copies of Laurence and Avery and, I suspect, with advantage, Conn's Current Therapy—1977. J.W.

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