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# THE ULSTER MEDICAL JOURNAL

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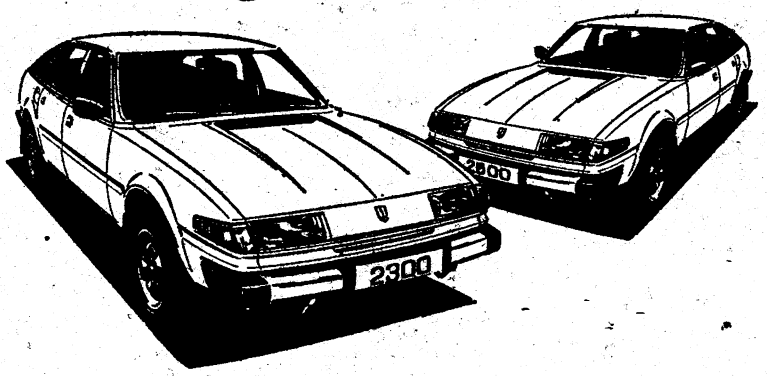


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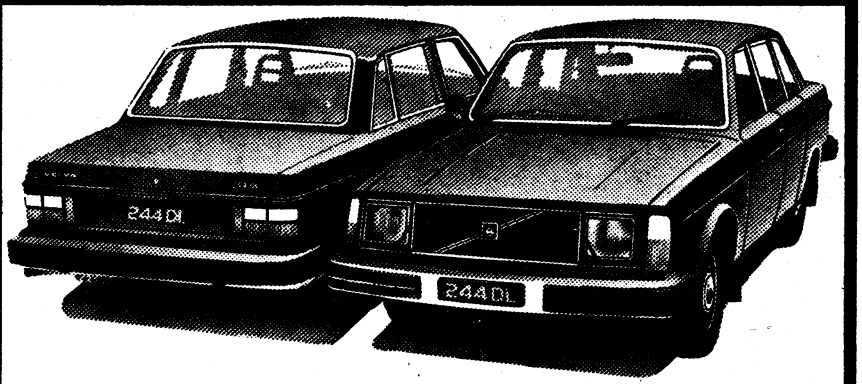


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4. Scientific measurements should be given in SI units, but blood pressure should be expressed in mmHg and haemoglobin as g/dl. Traditional units may usefully be given in parenthesis and conversion factors may be stated, especially with tables and illustrations.

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BELFAST CITY HOSPITAL,
BELFAST BT9 7AD.

.....19.....

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VOLUME 47 1978 No. 2

# EMERGENCY ADMISSIONS TO A GERIATRIC MEDICAL UNIT

**R. W. STOUT, M.D., M.R.C.P.**
**L. A. HOBSON, M.B.**
**ANONA E. WALMSLEY, M.B., D.R.C.O.G.**
Geriatric Medical Unit,
Belfast City Hospital.

DIRECT admission of patients from home is the predominant method of admission to geriatric medical units. Admission may take place as the result of a telephone consultation with the general practitioner or, in less urgent cases, following a domiciliary assessment visit by a member of the medical staff of the unit. However, in recent years the pattern of referral to hospitals in Belfast has changed. This has been brought about by the simultaneous development of general practitioner deputizing services and the emergency bed service. As a result, many more elderly patients are admitted from the casualty department without direct contact between the family doctor and the hospital medical staff. As it has been the custom for general medical units to accept all medical admissions from the casualty department, this has resulted in a change in the pattern of admission to both the geriatric medical and general medical units. To take account of this change in referral pattern it was decided to start a system of direct admissions from the casualty department to the geriatric medical unit of the Belfast City Hospital. This paper describes the results of the first year's working of this system.

## METHOD

One of the features of geriatric medicine is that it provides a continuing commitment to a defined section of the elderly population. This is organized on a geographical basis. The wards of the Geriatric Medical Unit, Belfast City Hospital provide the hospital facilities for Geriatric Sector A which is mainly located in South Belfast and corresponds to postal districts 2, 6, 7, 8 and 9

(Adams, 1969). It also provides part of the services for Geriatric Sector B, mainly West Belfast, postal districts 10, 11 and 12. On the other hand, general medical emergency admissions are shared between the Belfast hospitals on time based criteria. This results in the Belfast City Hospital accepting all emergency medical admissions from the Greater Belfast Area on Sunday, Wednesday and Friday of each week. Hence, on these days, elderly patients requiring emergency admission come to the Belfast City Hospital even if their homes are outside the parts of Belfast served by the Geriatric Medical Unit of this hospital.

A system was started in which all patients requiring emergency medical admission who were over the age of 75 and whose homes were in Geriatric Sectors A and B, were admitted direct from the Casualty Department to the Geriatric Medical Unit. The criteria for admission were the same as those for admission to the general medical wards. For practical reasons, patients were admitted directly from the Casualty Department during the day, but at night and week-ends they were admitted to the general medical ward and transferred to the Geriatric Medical Unit the following day. The only exceptions were patients who were too ill for transfer. The number, diagnosis and fate of all the admissions from this source in 1977 were recorded. The system started with the Friday take-in on December 1976, the Sunday take-in was included in April 1977, and the Wednesday take-in November 1977.

## Results

In 1977 there were 128 emergency admissions via the Casualty Department. In the same year 424 patients were admitted direct from home or transferred from other wards or hospitals. The fate of the patients coming from the two sources of admission is shown in Table 1. The mortality of those admitted as

Table 1

*Fate of Patients Admitted to Geriatric Medical Unit,* 1977

| Fate | Admissions via casualty | | Admissions by other routes | |
|---|---|---|---|---|
| | No | % | No | % |
| Total number | 128 | — | 424 | — |
| Discharged | 66 | 51.6 | 215 | 50.7 |
| Deaths | 45 | 35.0 | 81 | 19.1 |
| Continuing care | 10 | 7.8 | 63 | 14.9 |

emergencies is predictably higher but the number of patients requiring continuing hospital care is much less. The figures, of course, are not comparable as the planned admissions are a selected group of elderly patients.

The average age of the 128 patients was 81.4 years with a range of 75 - 94, and 62.5 per cent were female. The age and sex distribution and the fate in relation to age are shown in Table 2. Apart from the very small number of patients over 90 years old, there is, as expected, a trend towards a higher proportion of deaths and requirement for continuing care in the older age groups.

TABLE 2

*Fate of Emergency Admissions in Relation to Age*

| Age | No. (no. females) | Discharges | | Deaths | | Continuing Care | |
|---|---|---|---|---|---|---|---|
| | | No | % | No | % | No | % |
| 75 - 79 | 49(28 | 24 | 49.0 | 16 | 32.7 | 3 | 6.1 |
| 80 - 84 | 45(30 | 25 | 55.6 | 14 | 31.1 | 4 | 8.9 |
| 85 - 89 | 28(18) | 12 | 42.9 | 13 | 46.4 | 3 | 10.7 |
| 90 - 94 | 6(4) | 5 | 83.3 | 1 | 16.7 | 0 | 0 |

The major diagnosis at the time of admission is shown in Table 3. The one

TABLE 3

*The Most Common Diagnoses on Admission*

| Diagnosis | Males | | Females | |
|---|---|---|---|---|
| | No | % | No | % |
| Respiratory Disease | 20 | 41.7 | 22 | 27.5 |
| Cardiovascular Disease | 9 | 18.8 | 15 | 18.8 |
| Stroke | 11 | 22.9 | 13 | 16.3 |
| GIT Disease | 1 | 2.1 | 6 | 7.5 |
| Anaemia | 1 | 2.1 | 6 | 7.5 |

most important diagnosis was chosen for each patient, and the five most common diagnoses are shown in the table. The commonest diagnosis was respiratory disease, usually bronchopneumonia or an infective exacerbation of chronic obstructive airways disease. Cardiovascular disease and cerebrovascular disease were also common reasons for admission. There was no difference in the average age of patients in the various diagnostic categories.

The fate of the patients admitted with different diagnoses is shown in Table 4. The mortality was highest in the patients with cerebrovascular disease and these patients also provided the highest proportion of patients requiring continuing hospital care. The average length of stay of all patients was 40.7 days. There

TABLE 4

*Fate and Length of Stay in Relation to Diagnosis*

| Disease | Discharges | | Deaths | | Continuing care | | Average length of stay (days) | | |
|---|---|---|---|---|---|---|---|---|---|
| | No | % | No | % | No | % | total | dis-charges | deaths |
| Respiratory disease (42) | 19 | 45.2 | 17 | 40.5 | 3 | 7.1 | 36.4 | 41.3 | 12.3 |
| Cardiovascular disease (24) | 13 | 54.2 | 10 | 41.7 | 0 | 0 | 24.4 | 21.1 | 27.7 |
| Stroke (24) | 7 | 29.0 | 12 | 50.0 | 4 | 16.7 | 56.1 | 28.5 | 24.5 |
| GIT disease (7) | 5 | 71.4 | 1 | 14.3 | 1 | 14.3 | 42.1 | 9.8 | 28.0 |
| Anaemia (7) | 5 | 71.4 | 2 | 28.6 | 0 | 0 | 21.7 | 26.4 | 10.0 |

were no important differences in length of stay of patients in the different diagnostic categories.

## Discussion

It is notable that the majority of elderly patients who have severe enough illnesses to require emergency admission to hospital are able to return home again. There is, nevertheless, a fairly high mortality. However, the proportion of patients requiring continuing hospital care for a prolonged period is small.

Admission via the casualty department accounted for 23 per cent of total admissions to the geriatric medical unit. This is in contrast to the 90 per cent emergency admission rate in the general medical wards of the Belfast City Hospital (Grant, 1975). The length of stay of the patients is considerably longer than that of patients admitted to the general medical wards. The average length of stay of our patients was 40.7 days whereas the average length of stay of patients in general medical wards is between 11 and 14 days. However, the figures for admissions to the Geriatric Medical Unit are weighted by a relatively small number of patients who spend a long time in hospital. Nevertheless, it is one of the features of medicine in the elderly that recovery is slower, rehabilitation is more prolonged and length of stay in hospital is increased.

It was unexpected that such a large proportion of admissions should be due to respiratory disease. It is sometimes suggested that severe respiratory disease is a disease of middle aged adults and that chronic respiratory disease is incompatible with survival to advanced age. This is clearly not the case. It seems that measures to prevent respiratory disease, such as discouraging smoking and avoiding industrial exposure to air polution will have beneficial effects in the elderly as well as patients in other age groups.

After the scheme in the Belfast City Hospital had started a paper appeared describing a comprehensive geriatric medical service in Hull (Bagnall et al, 1977). The principles used were similar to those in the Belfast City Hospital. The geriatric department offered to admit directly all medical emergencies aged 75 or over. Additionally the unit undertook to readmit any patient previously treated by it and those patients of 74 and below whose circumstances made it likely that they would benefit from their first treatment being in the department. As in the Belfast City Hospital, non-transfer of patients within the geriatric medical unit was the policy and commitments for long-term care and intermittent admission for social and holiday relief were maintained within the same admission wards. The results for a much larger number of patients are very similar to those reported in this paper. Of these admissions 28 per cent were aged 75 - 79, 28 per cent between 80 and 84, 19 per cent between 85 and 90, and 10 per cent over 90. The average duration of stay was 30 days but 80 per cent of all admissions were emergencies. Only 1.8 per cent of all admissions remained in hospital for six months or more.

A comprehensive system of care for the elderly sick is a logical way of developing geriatric medicine. The age limit of 75 years is arbitrary and was chosen mainly because of the availability of resources. However, in practice it

proved to be a good indicator of need for the specialized care of the geriatric medical unit. This is supported by the fact that in the Belfast City Hospital requests for transfer from other medical wards have been negligible since the direct admission scheme was introduced. As the over seventy-fives are the section of the population which is going to increase in number most rapidly in the next decade it seems reasonable to concentrate the resources of geriatric medcine on this age group. Further development of this system in Belfast is hindered by the present system of general medical emergency admissions. A geographically based medical admission system would make possible much closer cooperation between the general medical and the geriatric medical services. Such cooperation is essential if the increasing numbers of elderly sick are to be properly managed in hospital.

We thank Dr. J. A. C. Ball for permission to include his patients in this survey and the physicians of the Belfast City Hospital for their co-operation in this scheme.

## References

ADAMS, G. F. (1969). Review of Geriatric Services in Northern Ireland Hospitals. A report to the Northern Ireland Hospitals Authority.

BAGNALL, W. E., DATTA, S. R., KNOX, J. and HORROCKS, P. (1977). Geriatric medicine in Hull: a comprehensive service. *British Medical Journal*, **2**, 102.

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**ERRATA**

**"Nosocomial Rotavirus Gastroenteritis in a Neonatal Nursery" by J. F. T. Glasgow, B. G. McClure, J. H. Connolly and H. J. O'Neill. This volume (47) pages 50-56.**

**In this article the authors' legend of Table II was omitted. The maximum number of cots in each of the six cubicles was indicated by the number in brackets. Rd indicated a rotavirus infection with diarrhoea; R rotavirus infection with no diarrhoea; d diarrhoea without confirmation of a rotavirus infection. The dates gave the time of onset of illness or recovery of the virus.**

**On page 52 "Laboratory Studies" paragraph 2, line 16 'aggravated' should read 'aggregated'.**

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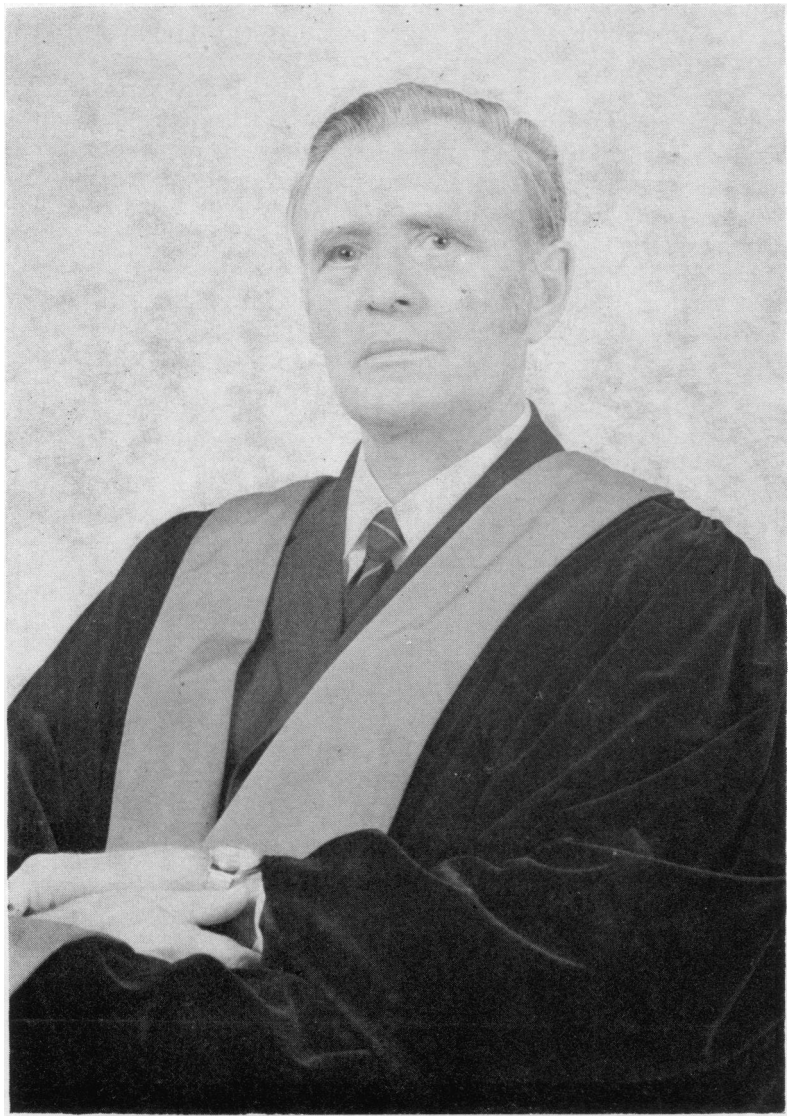

R. J. KERNOHAN, M.D., F.R.C.P., F.R.C.P.(I.), D.P.H., D.C.H., 1919-75
*(By courtesy of Van Büren, and Mrs. R. J. Kernohan)*

# A CASE OF THE CARDIO-AUDITORY SYNDROME (LONG QT INTERVAL AND PROFOUND DEAFNESS) DIAGNOSED IN THE PERINATAL PERIOD AND KEPT UNDER SURVEILLANCE FOR TWO YEARS *

by

**P. FROGGATT**
Vice-Chancellor's Office, The Queen's University, Belfast

and

**A. A. J. ADGEY**
Cardiac Unit, The Royal Victoria Hospital, Belfast

## PROLOGUE

I first met Bert Kernohan in the spring of 1964. He was keen to enrol the help of my senior colleague John Pemberton (then Professor of Social and Preventive Medicine) with some work he was planning in the Ballymena area into the aetiology of ischaemic heart disease and the early detection (in school-children) of hypertension with a view to an intervensionist study: the general concern of the profession allied to his own developing interest stimulated the former;the incrimination of hypertension in ischaemic heart disease and the recent marketing of suitable corrective drugs, mainly beta-adrenergic blocking agents, focussed his attention on the latter. I fancy Pemberton was somewhat sceptical; he couldn't believe that a physician remote from a teaching centre and running a busy consultant practice could organise and supervise the necessary large-scale studies on these complex subjects which were at that time attracting some of the best brains and the heaviest funding in the medical world. But he was sympathetic — he was after all the biographer and former assistant of Will Pickles (Pemberton, 1970), the country doctor who was an ideal prototype for Samuel Smiles who had added significantly to our knowledge of *inter alia* infectious hepatitis and Bornholm disease from observations made in his single-handed practice in Wensleydale. He asked me if I knew Kernohan: Bert and had not then met, but I knew his reputation by the tongue of good report — a busy and esteemed physician with a first-rate mind (he had graduated in 1941 with first-class honours and in three post-RAMC years had collected the MD, MRCP, MRCPI, DPH and DCH(Eng.) ) and who had published widely, remarkable for one unconnected with a major teaching hospital or medical school. When Bert arrived Pemberton and myself were quickly convinced by

*This material comprised much of the first Kernohan Memorial Lecture given at the Postgraduate Centre, Waveney Hospital, on 18th October 1977 by one of us (P.F.) who is, however, solely responsible for the Prologue.

his knowledge, drive, and above all sheer enthusiasm, and but for the facts that Pemberton was already conducting a study of his own into deaths from coronary disease in Belfast (which became one of the important pioneer epidemiological works in this field in the 1960s (McNeilly and Pemberton, 1968)) and the notorious unreliability of blood pressure readings "in the field", he would I believe have been pleased to co-operate in the proposed Ballymena studies. Though he had not received tangible help, only encouragement, Bert and I at once became friends. About this time two articles of mine on certain cardiac conduction anomalies and their genesis were published (Fraser *et al,* 1964a,b) and from that time we added a common interest to our friendship and we used to sit and and talk about electrophysiology of the heart, a subject about which I knew, and know, very little, and he knew even then quite a lot and came to know even more. I hope I don't delude myself too outrageously in believing that Bert's increasing interest in cardiac dysrhythmias (Kernohan, 1966a,b; Grant *et al,* 1966) owes something to those days.

In 1971 I became Dean of the Faculty of Medicine : Bert's congratulatory note was among the first I received. He was then as he remained post-graduate, and to some extent medical, Pooh-Bah at the Waveney Hospital but unlike his fictional prototype he was courageously making a great success of his many activities including the postgraduate centre (Biggart and Kernohan, 1974), and when the hospital came to be more closely connected with Queen's in the developing undergraduate teaching and attachment programmes Bert became a member of the University Faculty of Medicine and until his death rarely missed a meeting. In 1973 he was appointed Clinical Lecturer and Examiner in Medicine (for final MB) and discharged his duties with customary skill and gusto and a certain modest regard for convention. He contributed frequently and constructively to Faculty business, took a deep interest of all aspects of medical education, and I believe cherished these links with his old University and Medical School as deeply as he cherished his distinction in being examiner, and latterly senior examiner, for the Royal College of Physicians of Ireland.

About this time Bert helped me in a more personal way : he asked me if I wished to be proposed for *ad eundem* Fellowship of the Dublin College. The occasion of the invitation, if not his invitation itself, was of some moment. We were staying overnight in Dublin in Buswell's Hotel in Molesworth Street and this, as it turned out, gave us a ringside seat for the great Sinn Fein march on the Dail to protest against the emergency anti-terrorist measures which the Fianna Fail government of 1972 was introducing in its dying days. The crucial debate and division were to take place that very evening and trouble was widely forecast: even an attack on Leinster House itself was only ridiculed by the over-confident or the under-informed! Molesworth Street was soon packed with a lusty placard-bearing and shouting mob which rushed in from Dawson Street and was only stopped by a massive police barricade which stretched from the hotel to, appropriately perhaps, the headquarters of the Masonic Order in Ireland (Irish Constitution)! Speeches were made from the back of a slogan-bedecked lorry by Bernadette Devlin and colleagues, and things looked ugly for a time, but eventually the crowd was part broken-up by the Garda, part dispersed, and

left Molesworth Street, Leinster House, Buswell's Hotel, and the State intact. (Earlier, while parking my car in Merrion Square, the street lights were extinguished and a dozen or so tenders of fully-accoutred troops passed my car and entered Leinster House from the rear, a reminder of how seriously Dublin at that time took the Sinn Fein threat!) This vision of *Götterdämmerung* seemed an appropriate backdrop for my entry to this new stage in my career, and so I agreed to Bert's suggestion. He at once went ahead, successfully as it turned out. He then even more daringly proposed my name to the Censors of the London College for election to their Membership under bye-law 117 — election through the evidence of published work. (He spared my blushes from likely failure by keeping this initiative to himself!) Surprisingly he was again successful and he attended the ceremony in London making the journey for this sole purpose, a gesture completely typical of this warm-hearted man. All this he did through altruism and genuine friendship: he sought from me no favour for I had none to give; he was not advancing a protégé for I was not that; he was not acting on my wink or nod because, although I greatly respect and enjoy my connections with these great Colleges, I am immodest enough to believe that my career, such as it was, had not suffered from their lack. Bert also invited me to speak at post-graduate meetings and symposia and we always kept in touch on unusual cases of cardiac arrhythmias, and during all this time I came to esteem him highly for his wide knowledge, his compassion, his vitality, and above all for his complete commitment to his profession and to those he served. By force of knowledge, energy, character, and personality he dominated his local scene to a degree that, without disrespect to his colleagues, Bert and Waveney medicine became almost synonymous. I last saw him a month before he died: typically he had driven from Ballymena to my house late one evening after a full day's work to tell me some follow-up facts of a case we had reported (Kernohan and Froggatt, 1974). His sudden and untimely death removed an outstanding doctor, one of Ulster's best physicians and a man I was proud to call my friend.

A lecturer in a memorial series often tries to assess the place his subject occupied in his discipline and his profession. I think it is too proximal to Bert's death to be able to present a balanced perspective: some later lecturer will I hope attempt the task. Furthermore, though Bert published regularly and, for a busy physician, also extensively, his greatest legacies are outside the covers of journals — the strength and reputation of the Waveney, its postgraduate centre, and the admiration and thanks of thousands of patients who worshipped him. Bert's major clinical and research interest was cardiology and I hope I may adequately serve his memory if I offer as a personal *Festschrift* a hitherto unreported case of a syndrome on which he and I had previously published (Kernohan and Froggatt, 1974), about which he was intensely interested, and which a decade before I had helped to delineate (Fraser *et al,* 1964a,b) and the unusual aspects of which had I believe done something to stimulate Bert's interest in cardiac dysrhythms all those years ago. Much of the clinical work in this case is due to my colleague, Dr. Jennifer Adgey, consultant cardiologist at the Royal Victoria Hospital, who appropriately appears as joint author.

## THE HEREDITARY QT PROLONGATION SYNDROMES

In the 1950s a brief case abstract (Möller, 1957) and two detailed reports (Jervell and Lange-Nielsen, 1957; Levine and Woodworth, 1958) were published from Scandinavia and America describing in all six children (in three sibships) who were severely deaf from infancy and had had recurrent syncopal attacks during which four had died suddenly. This combination of profound "congenital" deafness, syncope, and sudden death in a child had only once been previously reported — by Meissner (1856) in anecdotal form in a lengthy book (Fraser *et al,* 1964(b). The electrocardiogram (ECG) was unique and characterised by a grossly prolonged QT (or QU) interval and certain TU wave changes (mainly biphasic or alternating polarity, and high voltage on the unipolar chest leads) most especially following emotional disturbance, and (frequently) sinus bradycardia. The clinical picture is fully reviewed by Fraser *et al* (1964a) and Jervell (1971). Later studies (e.g., Jervell and Sivertssen, 1967; Olley and Fowler, 1970) showed the syncope (and sudden death) to be due to ventricular fibrillation or asystole : the prolonged QT interval whatever its cause (it was then assumed to be due to a cellular biochemical anomaly), indicates a myocardium unusually vulnerable to minor supraventricular aberrant rhythms and dysrhythmia-triggering mechanisms generally which would be harmless in a normal heart. Associated and unusual pathology in the blood vessels and neural elements in the sinus node (Fraser *et al,* 1964a) and inner ear (Friedmann *et al,* 1966, 1968) of equivocal significance were also reported. The condition segregated in families as an autosomal recessive trait (Fraser *et al,* 1964b). Six years after the first reports two other families were described with affected members displaying all the above features except that they heard normally (Romano *et al,* 1963; Ward, 1964), the pattern of inheritance being autosomal dominant with varying expression. Since then well over 100 families have been described world-wide of either the rarer cardio-auditory syndrome or the commoner Romano-Ward syndrome (see Schwartz *et al* (1975) for review) and further cases are regularly documented. Research has mainly aimed at (a) delineating the syndromes and searching for any genetic connection, or linkage with other identifiable genes, (b) elucidating the cause of the QT prolongation and TU changes with a view to rational treatment or correction, (c) identifying the mechanisms triggering and self-limiting the potentially lethal ventricular arrhythmias, (d) introducing an effective therapeutic regimen to reduce the number and length of the attacks of syncope and hence reduce mortality, (e) instigating basic biochemical and pathophysiological research into possible underlying mechanisms and the mode of gene action which produces the pleotropic stigmata of the syndromes, and (f) investigating whether these or any associated syndromes could account for a significant proportion of cases of unexplained death in childhood or "cot death" (Froggatt and James, 1973).

This paper describes a case of the cardio-auditory syndrome which exhibits some important features not previously described and which provides information under (a), (b), (d) and (f) above. It has been referred to briefly in another context (Froggatt and James, 1973). Discussion and recent reviews of these syndromes are in Schwartz *et al* (1975) and Vincent *et al* (1974a).

## CASE REPORT

Gerard S. was born in the Royal Maternity on 18th May, 1971. At 37 weeks maturity an amniocentesis had been carried out (because of maternal Rhesus iso-immunisation) during which foetal bradycardia, taken as indicating foetal distress, was noted and a lower section was performed. Birth weight was 2.6kg; Apgar score 5; heart rate 160 per min; no cardiac murmurs; haemoglobin 13.2 g/dl; liver and spleen enlarged; direct Coombs' test positive. There were no other significant findings. At age four days exchange transfusion was initiated. Bilirubin was 350 $\mu$mol/l (20.4 mg/100 ml); heart rate 116 per min. After 30 mins (with 135 ml of blood withdrawn and 125 ml replaced) the child became cyanosed and "quiet". Heart rate was 80 per min and noted as "irregular". Exchange transfusion was stopped, the clinical picture improved but bradycardia persisted at 80-100 per min and an ECG was taken. This showed a prolonged QT interval (Fig. 1)* and was provisionally attributed to

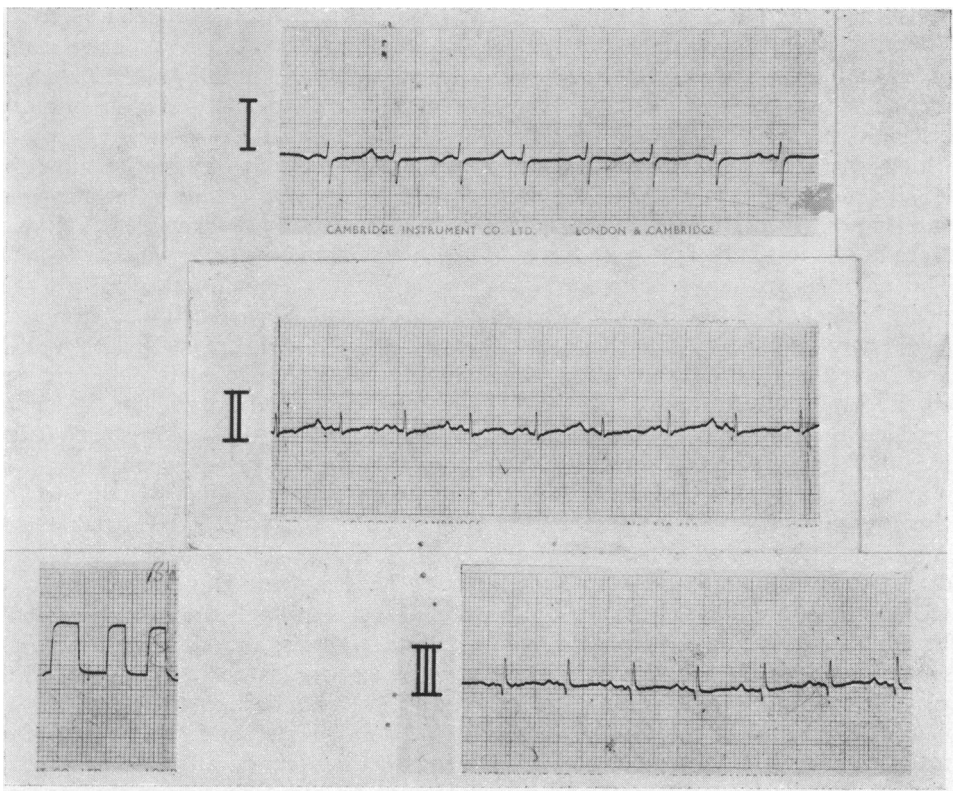


FIG. 1: Gerard S. age 4 days (22nd May, 1971). Note the grossly prolonged QT interval (RR = 0.53 secs., $QT_o$ = 0.43, $QT_c$ = 0.36, $QT_o - QT_c$ = 0.13, ($P < 0.001$)) and TU wave anomalies including alternating polarity of the T waves in the lead I strip. (In all tracings in this article each small square represents 0.04 secs.).

* The parameters and notation used in the text and figure captions with reference to measurement of the QT interval are explained in Appendix B.

electrolyte imbalance: potassium was 5.60 mmol/l (=Eq/l), calcium 1.62 mmol/l (6.50 mg/100 ml), magnesium 0.70 mmol/l (1.65 mg/100 ml), and bilirubin 217 μmol/l (12.70 mg/100 ml). Calcium gluconate and magnesium sulphate improved the electrolyte picture and a second exchange transfusion was successfully completed. Four days later blood electrolytes were considered normal (particularly: potassium was 5.80 mmol/l and calcium 2.08 mmol/l) but the QT prolongation and TU changes persisted. The child was discharged on 31st May and the paediatric registrar (the late Dr. Cynthia Steele) referred the case to one of us (P.F.) as possibly a QT prolongation syndrome. On 7th July the child was found to be totally unresponsive to sound and a provisional diagnosis of the cardio-auditory syndrome was made.

*First admission.* This was on 2nd August 1971 to the Cardiac Unit, Royal Victoria Hospital (AAJA). Examination showed an alert child of normal-for-age physique. Heart rate was 120 per min and there was an ejection systolic murmur at the left sternal edge. The ECG was as previously with characteristic TU wave changes now marked (Fig. 2). Results of all the other extensive range of special tests and investigations were unremarkable. Continuous ECG oscilloscope monitoring with hourly print-outs was carried out for one month and disclosed permanent though variable QT prolongation and aberrant TU waves which characterise these syndromes, several short episodes of self-terminating nodal bradycardia, and several single late cycle ventricular ectopics (see Froggatt and James, 1973, Figure 2). Sequential stellate ganglion blockade (with xylocaine) of the left and right ganglion as a trial therapeutic measure was performed. The results were equivocal: there was no important effect on the QT interval or TU appearance but neither was there an ipsilateral Horner's. Repeat trial was postponed (see later). On the experience of Jervell and Lange-Nielsen (1957) and Jervell *et al* (1966) the patient was digitalised and, though remaining prolonged, a persistent shortening of the QT interval compared to previous tracings resulted (e.g. on 2nd September: RR=0.480 sec, $QT_o$=0.344 sec, $QT_c$=0.284 sec; ($QT_o$—$QT_c$)=0.060 sec (P=0.001). (For explanation see Appendix B). It is impossible to say how much of this improvement was unequivocally due to the therapy since the QT interval in these syndromes is remarkably variable (see Appendix A), but the more favourable picture persisted and the child was discharged on digitalis on 11th September, 1971. Frequent ECGs over the next 15 months showed maintenance of the digitalised, seemingly improved, pattern. In October 1971, aged 5 months, while taking digitalis, the child had his first serious syncopal attack characteristically while annoyed at being constrained at play. It followed the classic pattern of "severe" attacks described by e.g., Fraser *et al* (1964a) and Jervell (1971). In April 1972 he had a second similar one after a tantrum, and in September a third. During all this time he attended as an outpatient for check assessments and was judged to be regularly taking the medication.

*First re-admission.* This was on 23rd January 1973. Continuous ECG monitoring was re-commenced, digoxin was discontinued, and assessment of other relevant cardio-active drugs which had been previously described as efficacious in these syndromes was initiated *viz* sodium diphenylhydantoin (Dilantin;

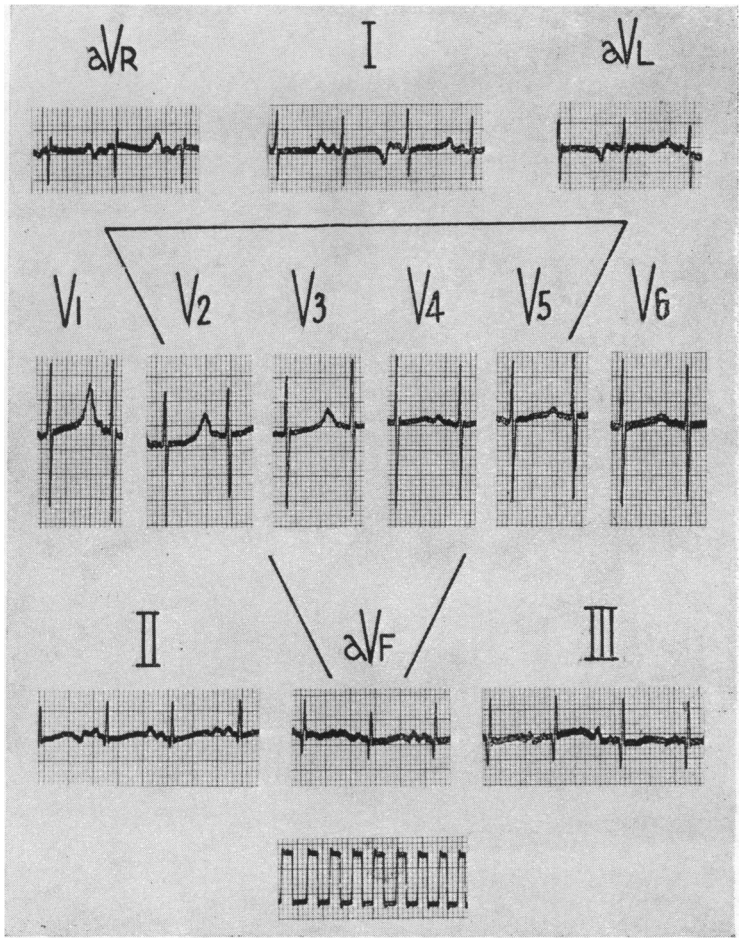


FIG. 2: Gerard S. age 11 weeks (2nd August, 1971). Similar to Fig. 1. This ECG picture characterises the two recognised prolonged QT syndromes. (Reproduced from *Ulster Medical Journal*, **42**, 140 (1973), by courtesy of the editor).

Epanutin) as a single intravenous bolus of 36 mg; isoprenaline (or isoproterenol) (Saventrine) 5 mg *qid* for 3 days; and practolol (Eraldin) 10 mg *qid*. Dilantin and Eraldin, but not Saventrine, decreased the degree of QT prolongation and were later therapeutically used. (The assessment of these drugs is confounded by the often marked variation in the QT prolongation and TU complex changes from one time to another which occur in this syndrome necessitating detailed statistical analysis to isolate any drug effect. This is explained in Appendix A and illustrated in Fig 3). During the insertion of the intravenous cannula into the child's arm for Dilantin injection he became very distressed, the QT interval elongated further and the T wave (precordial monitor lead) became prominent

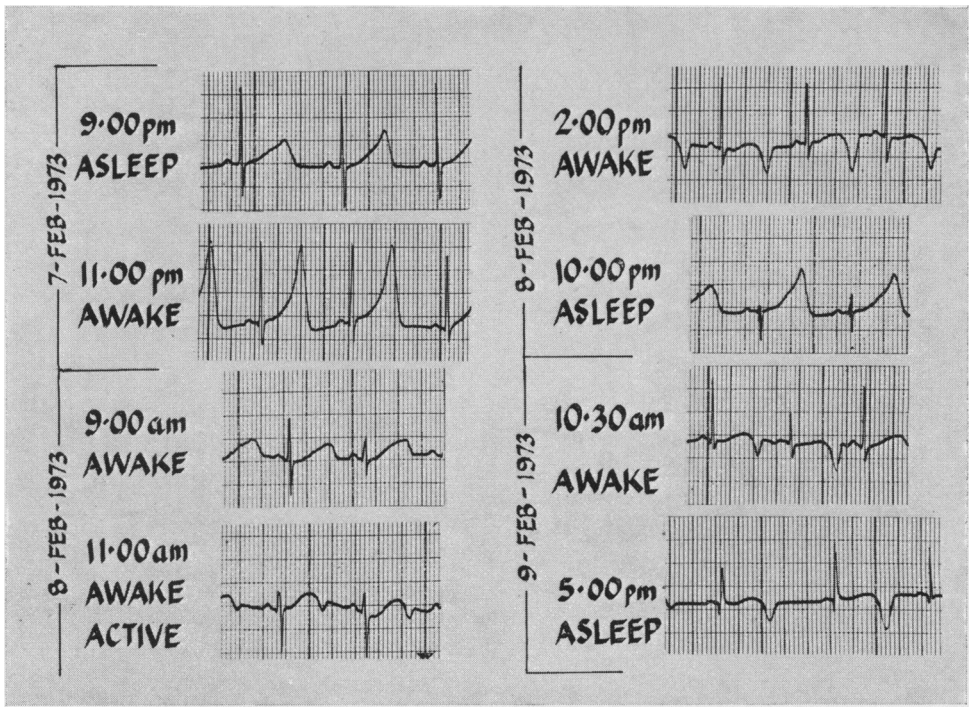


FIG. 3: Gerard S. (7th February, 1973). The tracings are from the monitor lead and cover 44 hours. Note the variability in the TU wave pattern unrelated to medication and wakefulness.

and inverted, and ventricular tachycardia and fibrillation (VF) ensued which was terminated by a "precordial thump" to the lower end of the sternum. In all, five such episodes of VF were documented: each was terminated in the same way (see later), Sinus rhythm returning usually after several beats of AV nodal rhythms (Figs. 4 and 5). Of the drugs therapeutically tested Eraldin had the most beneficial effect, though not as marked on the ECG as was digitalis, and the patient was discharged on 14th February on 10 mg *qid*. The parents were instructed how to thump the lower end of the sternum during a syncopal attack. The child was regularly reviewed and the Eraldin reduced to 10 mg *tid* because of complaints of "staggering" and "dulness". Audiogram confirmed severe bilateral perceptive deafness most marked in the higher tones. No further attacks were noted until 7th September when the child, now 28 months old, had a severe one and another three days later. The mother thought her "chest thumping" had stopped the second and possibly also the first.

*Second re-admission.* This was on 11th September. Continuous ECG monitoring was recommenced and Eraldin discontinued. On 28th September a left cervical sympathetic block at the level C6/C7 was effected using xylocaine. The following day he had a further episode of VF immediately preceded by R on T ectopics.

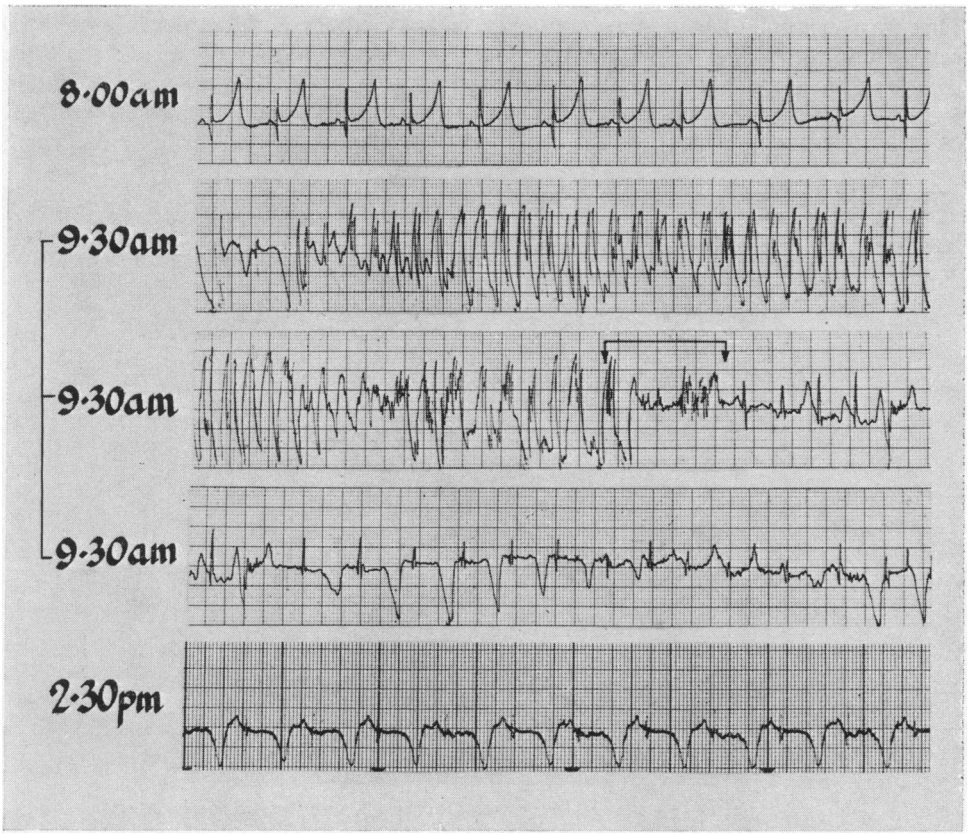


FIG. 4: Gerard S. (31st January, 1973). Note the run of ventricular tachyarrhythmia which reverted after a precordial "thump" (arrowed in third strip).

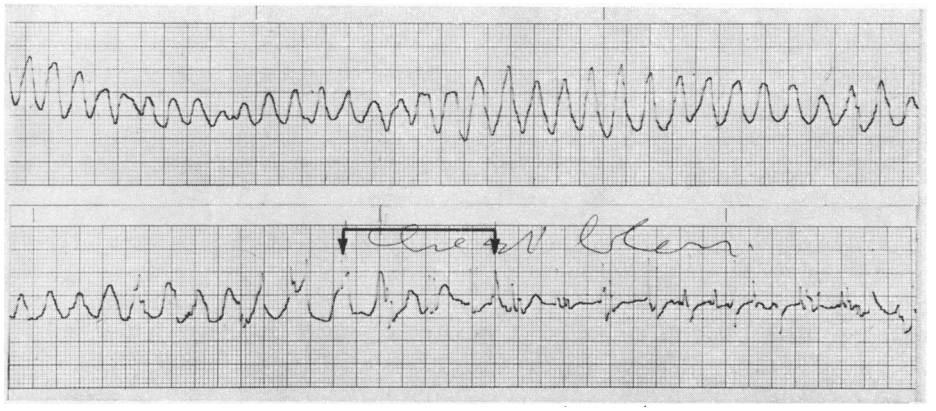

FIG. 5: Gerard S. (29th September, 1973). An episode of unequivocal ventricular fibrillation terminated by a precordial "thump" (arrowed on second strip).

This was terminated by a chest thump. On 1st October a right block (as above) was carried out. The results of these two blocks are in Figs 6 and 7: they are discussed in detail later but they appeared to effect a dramatic improvement in the ECG picture both on the length of the QT interval and on the TU complex. On 3rd October a self-terminating episode of ventricular flutter was recorded,

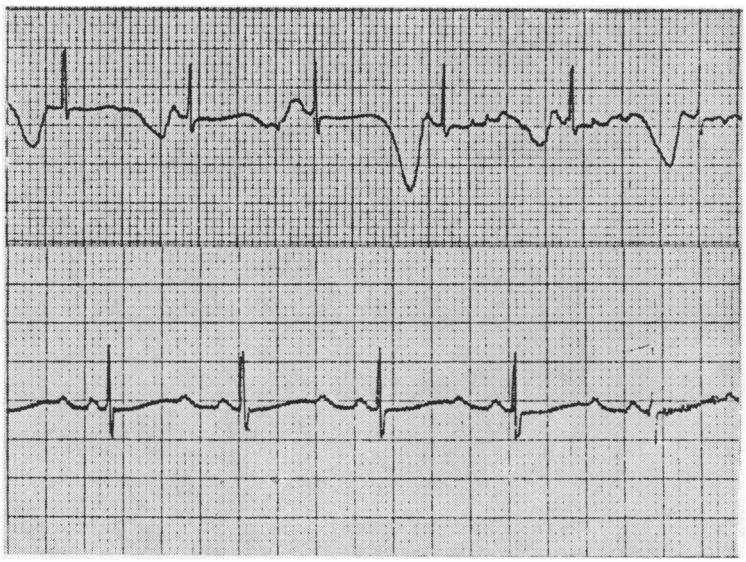

FIG. 6 Gerard S.: Left stellate ganglion blockade (28th September, 1973). The top tracing (lead II) was recorded several minutes before blockade; the lower tracing 11 minutes after the start of blockade procedure and at the appearance of an ocular Horner's. Note improvement in the ECG picture, post-blockade readings being (10 complexes): RR = 0.71 secs., $QT_o$ = 0.44, $QT_c$ = 0.33, and ($QT_o$–$QT_c$) now 0.11 secs. ($P < 0.001$).

but there were no further attacks and the patient was discharged on 7th October on Dilantin, digoxin and Nacton to be re-admitted a week later for permanent cervical sympathetic block. Unfortunately on 9th October he had a further syncopal attack at home which proved refractory to parents' precordial "thump ing". A post-mortem was not obtained.

*Family information.* The patient was the younger of two children (1F; 1M) born to healthy unrelated parents. Information covering kinships up to the third degree gave no history of syncope, fits, significant deafness, or unexplained or untimely sudden death. Audiograms on parents showed, for the father, bilateral loss up to 30 db at 4000-8000 Hz, and for the mother, left unilateral loss up to 55 db at 8000 Hz. Using Ljung's (1949) formula for estimating $QT_c$ in adults, ECGs of first-degree relatives of proband (mother, father, sister) were normal. Blood grouping (ABO, Rhesus, K, k, $Kp^a$, $Fy^a$, $Jk^a$, $Le^a$, MNS, Pi, $Di^a$) did not

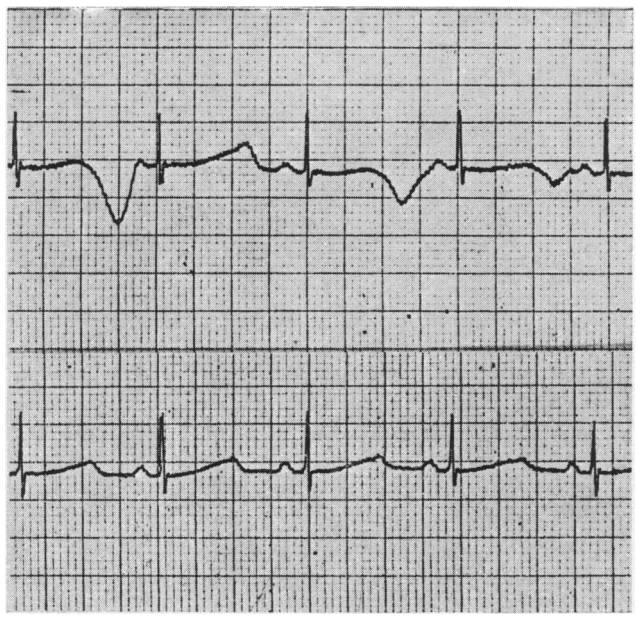

FIG. 7: Gerard S.: Right stellate ganglion blockade (1st October, 1973). Procedure as in Fig. 6, the lower tracing being 9 minutes after the start of blockade: RR = 0.76 secs., $QT_o$ = 0.42, $QT_c$ = 0.34, ($QT_o$ –$QT_c$) = 0.08 ($P < 0.001$).

discredit the suggestion of Friedmann *et al* (1968) of possible close linkage of the determinant gene with the cde allele though the $C^w$ allele, segregating in two other Northern Ireland families containing members with this syndrome (Friedmann *et al,* 1968) was not identified.

## DISCUSSION

This case of the cardio-auditory syndrome presents some unusual or previously unreported features of therapeutic value, as follows.

### *Early diagnosis*

In this syndrome the first syncopal attack usually occurs in childhood but rarely as early (5 months of age) as was the case in this patient (of the 203 cases of the long QT syndromes collected by Schwartz *et al* (1975) only six had attacks recorded so young): and diagnosis has been made in only four patients prior to the first attack of syncope — all were close relatives of probands and investigated routinely (Schwartz *et al,* 1975). Our patient is only the second child

reported in which the cardiac anomaly has been demonstrated in the perinatal period (first week of life) and the first to be diagnosed so early: the other (Langslet and Sorland, 1975) had an ECG taken two hours after birth because of foetal cardiac distress during labour though the significance of the documented abnormality was not recognised at the time. The presence of the cardiac anomaly at birth confirms what was previously only speculation, is of embryological and developmental importance, and provides a basis for postulating that the QT prolongation syndromes can contribute to infant mortality over its full age range (birth to one year) and possibly also to stillbirths and foetal loss.

### *Therapy*

This is aimed at (a) decreasing the myocardial vulnerability by shortening the (prolonged) QT interval and stabilising the TU complex, (b) reducing the number and severity of VF-triggering arrhythmias (premature and ectopic beats, etc), (c) reducing those factors known to enhance myocardial vulnerability and VF-triggering arrhythmias in these conditions e.g., fright, emotional stress, severe physical exertion, water immersion as in swimming, and (d) terminating, as an emergency, any potentially lethal ventricular dysrhythmia which arises. New evidence is provided here on (a) and (d), as follows.

*Stellate ganglion block.* Evidence, both hypothetical and experimental, has recently accumulated to suggest that the conduction disturbance in the long QT syndromes may be due to asymmetrical cardiac sympathetic innervation or imbalance rather than to metabolic disturbance at the cellular level *per se.* (i) Most victims have their attacks of syncope during periods of emotional or physical stress, or bathing, when neural influences will be marked and these have been shown also to worsen their ECG picture (e.g., Fraser *et al,* 1964a, Figure 11). (ii) Postmortem cardiac anomalies — focal neuritis and neural degeneration within the sinus node, AV node, bundle of His, and ventricular myocardium — are concentrated in cardiac neurological tissue and have been accepted as determinants of, or at least correlates with, the clinical cardiological findings (James, Froggatt, *et al,* 1978). (iii) Experimentation has demonstrated that asymmetrical sympathetic neural control of the heart may cause anomalies in myocardial repolarisation (Yanowitz, *et al,* 1966; Abildskov, 1972) and left side sympathetic stimulation, or right side block, produces ventricular tachyarrhythmias including VF in certain instances particularly with a damaged or vulnerable myocardium (see Schwartz *et al* (1975) for review). (iv) Beta-adrenergic blockade has had a putative efficacy in alleviating symptoms (Schwartz *et al,* 1975). (v) Atrial pacing studies in some cases show QT shortening without T wave inversion as in normal subjects (Roy *et al,* 1976). (vi) T wave polarity alternation, common in this syndrome and marked in the present case, can also be obtained by sequential unilateral stellate ganglion stimulation (Schwartz and Malliani, 1975). (vii) Cerebrovascular accident and central nervous system disease may produce lengthening of the QT interval and large T waves (Burch *et al,* 1954; Hugenholtz, 1963). (viii) Direct interference with the existing cardiac neurological control in

QT prolongation syndromes affects the electrical conduction picture: thus several authors have demonstrated QT shortening in the Romano-Ward syndrome (prolonged QT interval without deafness) by stellate ganglion pharmacologic blockade and/or surgical ablation either of the left side (Moss and McDonald, 1971; Schwartz and Malliani, 1975), the right side (Ramon *et al,* 1972), or after both separately (Vincent *et al,* 1974b), though the longer-term persistence of the improvement is not yet established (Moss, 1973; Schwartz *et al,* 1975); others have found no change (Dear, 1975; Curtiss *et al,* 1978); and in the case of Ratshin *et al* (1971) the QT prolongation was increased after both right and then left side blockade. In the present case, seemingly the first patient with the cardio-auditory syndrome to be so treated, both left and then right side blockade shortened the QT interval and normalised the TU complex (Figs. 6 and 7) but unfortunately the patient died before the planned unilateral surgical stellate ganglion ablation or functional destruction could be performed. The dramatic response to stellate blockade — which waned as the ganglion recovered — was more marked than with practolol therapy and, in the overall picture, at least as well marked as with digitalis, and although no final decision had been reached on which side to operate (the literature at the time was unhelpful in that Moss and McDonald's (1971) patient's QT interval improvement after left stellectomy later regressed and the patient of Ramon *et al* (1972), after right stellectomy, died within six months despite an initial favourable response) it seemed the treatment of choice. This finding further confirms the common pathogenesis in these two QT prolongation syndromes.

*Precordial "thump pacing" and "thump version".* Patients with QT prolongation syndromes have self-terminating episodes of cardiac arrest (mainly VF) which may be frequent. It is not known why any particular episode persists and proves fatal while others spontaneously revert. It is clearly advisable to terminate such an episode as an emergency procedure and with a minimum of trauma. Pennington *et al* (1970) first showed that "precordial thumps" could revert ventricular tacharrhythmia, as well as (more commonly) asystole, to sinus or AV nodal rhythm by evoking a premature depolarisation of a re-entry pathway. If necessary the procedure could be continued rhythmically as "thump pacing" and is less traumatic than external cardiac massage. One of us (AAJA) terminated several documented VF attacks in our patient by "thump version", the first time in these syndromes that this has been described (Figs. 4 and 5).

### *Association with sudden unexpected death in infancy*

The perinatal diagnosis of our patient allowed us to monitor his progress over the first two years of life: this included the period (2-5 months) when sudden unexpected death in infancy ("cot death") is most frequent. Ever since an early communication (Fraser and Froggatt, 1966) the possibility has been considered that QT prolongation and related syndromes could comprise a significant proportion of the "cot death" entity: sudden and unexpected (or unexplained) death through cardiac arrest such as had been documented in these syndromes. Pioneer

work by James (1968) indicated a basis for theorising enhanced dysrhythmic potential mediated through certain physiological maturation processes in the cardiac conduction system during the first year of life and which could lead to lethal arrhythmias in normal hearts and, *a fortiori,* in a vulnerable myocardium such as in the QT prolongation syndromes, and in 1973 Froggatt and James (1973) developed the hypothesis fully. Since then it has attracted considerable attention both critical and supportive (Valdes-Dapena, 1973; Valdes-Dapena *et al,* 1973; Maron, *et al,* 1975; James, 1976; Froggatt, 1977), and Schwartz (1976) has even speculated that cardiac adrenergic imbalance may play a role in sudden infant death as it might do in producing QT prolongation. Crucial evidence on the hypothesis is missing, or by its nature unobtainable: one finding which would help is — do we observe, in the first year of life and particularly at 2-5 months *pari passu* with the histomorphological changes in the conduction system first described by James (1968), an increased incidence of potentially lethal cardiac dysrhythmias? If these do not exist in the QT prolongation syndromes they are unlikely to exist to any extent in infants generally. Until the present case no such ECG monitoring of a QT prolongation child had been carried out.

The findings are equivocal. During the peak "cot death" age group (2-5 months) the only rhythm anomalies recorded were runs of self-terminating nodal bradycardia and sporadic late cycle ventricular ectopics such as previously reported in immature infants (e.g., Church *et al,* 1967) and which did not lead to syncope. However, from the age of about five months attacks of VF occurred any of which could have been fatal; and this is still well within the "cot death" modal age of risk. The (seeming) immunity of the very young infant both to "cot death" and, in the QT prolongation syndromes, to syncope bears further investigation: one, no doubt of several common factors, is that cardiac sympathetic innervation normally does not reach full maturation until as late as six months of age (Hirsch, 1970). Our results leave the status of the cardiac conduction hypothesis in "cot death" more or less as before.

## SUMMARY

This article describes a case of the cardio-auditory syndrome (QT prolongation and severe deafness), the first to be diagnosed in the perinatal period and kept under surveillance and ECG monitoring over two years which included the "cot death" modal age range (2-5 months). Attacks of ventricular fibrillation were recorded and these were terminated by a precordial "thump", the first time the success of this measure has been documented in the (often self-limiting) episodes of VF in this syndrome. Assessment was made of the efficacy of sodium diphenylhydantoin, digitalis, practolol, isoprenaline, and unilateral stellate ganglion blockade, and the authors conclude that in this patient digitalis or stellate ganglion blockade seemed the treatments of choice. Unfortunately the patient died before unilateral stellectomy could be performed. The findings add further information concerning the status of the cardiac conduction hypothesis in "cot death".

## APPENDIX A

Many claims have been made for the efficacy of various cardio-active drugs in the QT prolongation syndromes based on reduction in the number and severity of the syncopal attacks and/or improvement in the ECG picture, *viz* shortening of the QT interval and normalising of the TU complex. Both of these criteria are difficult to assess, the former because of the rarity (in statistical terms) of the syncopal attacks in most cases and the difficulty in adequate patient follow-up, and the latter because of the marked variation in relevant ECG parameters from time to time in the same patient which is a marked feature in these syndromes (Fig. 3) and which is often associated with emotion e.g., fear at time of drug administration, or physical state e.g., sleep. Furthermore, any improvement resulting from treatment is often undramatic — an added difficulty in assessment. In this study we measured the effect, primarily on the length of the QT interval, of digitalis, isoprenaline, practolol, and sodium diphenylhydantoin. Digitalis clearly and consistently shortened the QT interval; sodium diphenylhydantoin and practolol appeared to do so also but to a minor degree; and oral isoprenaline had no important effect. In the second instance, to judge whether any improvement was attributable to the drug or to some extraneous factor (as above) we proceeded as follows.

Ten consecutive sinus rhythm complexes from ECG tracings at five different times before therapy (50 readings in all) yielded measurements which were used to establish reliable averages, and estimates of within-subject and between-complex variation, for the subject's QT and RR intervals. With *practolol*, 10 mg *tid* was administered orally and ten consecutive sinus rhythm complexes measured every six hours for 24 hours and then (at 10 mg *qid*) every six hours for four days. Regression and covariance analyses show a significant ($P<0.001$) shortening of the (prolonged) QT interval, independent of heart rate (RR interval) in its linear and quadratic form, compared to the pre-therapy level and unaffected by whether the subject was asleep or awake. Maximum improvement was from the third day. In absolute terms the improvement was modest but perhaps important though any benefit should be set against the other known effects of beta-adrenergic blocking which may *a priori* have a dysrhythmic potential in these patients, e.g., slower heart rate less responsive to adrenergic stimuli. With *sodium diphenylhydantoin,* a single bolus of 36 mg was administered intravenously with the subject sedated and again ten consecutive sinus rhythm complexes measured this time every 90 seconds for 15 minutes. Regression and covariance analyses as before again show a true shortening of the QT interval though more modest ($P<0.01$) than with practolol. The maximum effect was nine minutes after drug administration.

The independent effect of sleep — as a binary factor 'asleep"/"awake" — was tested because of its importance as a risk factor in "cot death", its role in further prolonging the QT interval in one other case described in Froggatt and James (1973), and its dysrhythmic role in other analogous conditions (Johanssen and Jorming, 1972; Wellens *et al,* 1972). Similar analyses as above with 22 time-

points two hours apart (10 sleep; 12 awake) showed no significant difference in QT interval length ascribable to being "asleep" or "awake".

The multi-factor analyses used in the above do not easily permit meaningful absolute measurements of pre- and post-drug QT intervals to be given. Complete results are available on request to one of us (P.F.).

## APPENDIX B

Prolongation of the QT interval is clearly the crucial diagnostic discriminant in the QT prolongation syndromes: its accurate measurement and comparison with "normal" values are therefore important. In this paper the QT interval is measured from the start of the Q wave to the final return of the T wave to the isoelectric line, the average of at least five consecutive complexes being taken. This is designated $QT_o$ for the subject examined.

The length of QT varies with heart rate curvilinearly (rather than linearly) and in children this relationship varies with age and sex. To establish an appropriate "expected" value for QT ($QT_c$) i.e., the value QT would 'expect" to take in a normal person for a particular heart rate and given age and sex, to compare with $QT_o$, it is necessary to standardise for these variables. Extensive studies by Fraser *et al* (1964b) established appropriate population regression equations, the one used here being

$$QT_c = 0.132 + 0.388\ (RR) - 0.157\ (RR^2) + 0.0017\ (age)$$

where RR is the length of the cardiac cycle of the subject in seconds,

$RR^2$ is its square,

age is the age of the subject in years.

Comparison of $QT_c$ with $QT_o$ will establish the degree of $QT_o$ prolongation if any.

Fraser *et al* (1964b) also showed that normal theory was applicable and that the standard error (S.E.) of $QT_c$ was 0.02 seconds. This means that the extent of $QT_o$ prolongation can be expressed in conventional probability terms i.e., where (approximately)

$(QT_o - QT_c) > 0.04$ secs, then $P < 0.05$

,, $> 0.05$ secs, then $P < 0.01$

,, $> 0.06$ secs, then $P < 0.001$

In the case presented in this paper the degree of prolongation of QT in the untreated patient is extreme (e.g., Figs. 1 and 2) and requires no sophisticated statistics: the importance of accurate assessment is in judging the effect of therapy.

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# THE HEALING SERPENT — THE SNAKE IN MEDICAL ICONOGRAPHY

by

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THE SIR THOMAS AND LADY DIXON MEMORIAL LECTURE

*The world's great age begins anew*
*The golden year's return*
*The earth does like a snake renew*
*Her winter weeds outworn.*

When Shelley invoked the snake symbolically in this fashion he was hardly doing anything new. The snake's association with death, rebirth and the cycle of nature is practically universal. For the ancient Egyptians the snake was the life of the earth, and there are texts from as early as 2300 B.C. referring to the Quroborus or tail eating serpent, the symbol of the cyclical nature of the cosmos. In Egyptian medicine we clearly find the snake's most important attribute – its dualistic nature – the snake that kills is the snake that cures. The Egyptian snake Goddess *Meresger* could inflict disease on those who offended her yet was invoked to protect against snake bites. Snake amulets in turn could protect against disease. In the very ancient papyrus Ebers the fat of the black snake is found as a part of the materia medica.

The Asklepian symbol of the entwined rod and serpent does not, as far as I know, occur in Egypt before the Alexandrian period. However, it does in Mesopotamia. The libation cup of King Gudea of Lagash, made of steatite and dating from about 2000 B.C., shows the great serpent god Ningishizda as two snakes coiled round an aixial rod. The epic Gilgamesh indicates its significance. Gilgamesh, an early legendary ruler of Uruk dived to the bottom of the primaeval sea in search of the herb that bestowed eternal life. On his return he stopped to bathe. Meanwhile a cunning serpent stole the herb and, by casting off its skin, came into possession of eternal life. Man on the other hand was condemned to sickness and death. From then on the serpent was invoked as protector against disease. The myth of rejuvenation and its symbolic association with the snake's ability to shed its skin was almost ubiquitous in the ancient world.

In ancient Greece the serpent appears in multiple roles, nearly always associated with divinity and symbolizing fertility and death. Examples easily come to mind: Medusa the snake-haired gorgon, the serpent that guards the golden apples of Hesperides, the Apollonian python, the death of Laocoon and the struggles of the infant Hercules. In the mysteries of Dionysus the women ran frenzied through the streets with snakes in their hair, and perhaps most important, the snake was an attribute of the earth, personified in Demeter, the earth-mother.

The most famous Greek healing snake is, of course, the one associated with Asklepios the God of Medicine. Around 500 B.C. he was a little known Thessalonian deity; by 400 B.C. he had become the pan-Hellenic God of Healing. The first mention of Asklepios is in the *Iliad,* he is mortal, a local chieftain; Homer calls him 'blameless physician'. He has two sons, Machaon who cures the Greeks of their wounds and later becomes the father of surgery, and Podalarius who becomes the patron of dietary medicine.

How this obscure character became deified and later universally acclaimed the god of medicine is a source of some contention. Whatever the reason, by the fifth century, shrines dedicated to him appear all over Greece. The most famous at Epidaurus. Fortunately there is a superb account of the buildings and ritual of Epidaurus; for Pausanias visited it in the second century A.D. when it was still flourishing. At the centre was the temple in which stood a statue of the god in ivory and gold made by Thrasymedes.There is still a ramp visible at the site of the temple for the bed-ridden to be wheeled in. The temple was surrounded by other buildings, gymnasia, baths and a stadium, and most important of all the abaton or incubation hall.

The temples of Asklepios were essentially sites of miraculous healing. The sick, if they were fortunate, were visited in dreams by the divine physician, often as a serpent, and either immediately cured or instructed how to receive a cure. In cases of successful cure, and there were many recorded, grateful patients left votive offerings, many of which represented their diseases. Incubation, or temple sleep, was not original to the Greeks, they probably imported it from Egypt. It was certainly practised in Mesopotamia, for when Alexander the Great fell sick at Babylon his generals slept for him in the temple of Marduk. Dreams were closely associated with the earth or chthonic deities and consequently were associated with healing, for it is the earth which produces curative herbs.

There are other important centres at Athens, Cos, the home of Hippocrates, Eleusis, and Pergamon the birthplace of Galen. Galen, the most rational of physicians, tells us how he himself was cured by a visitation. He talks of

> 'The ancestral God Asklepios, of who I declare myself to be a servant since he saved me when I had the deadly condition of abcess.'

Rational and religious cures were quite at home together in the Greek world.

In 295 B.C. Asklepios came to Rome from Epidaurus after the Roman citizens sought his aid during the visitation of a devastating plague. He came in the form of a serpent and rested at the Tiber island where an Asclepion was built. The rod and serpent are still visible. Asklepios became one of the most revered of Roman deities and for a while was an important rival to Christianity.

It is of course the serpent which is his constant companion and indeed can stand in place of him. The snake is almost certainly identifiable as Elaphe longissima. Besides its association with divinity the snake appears in Classical medicine in a much more material fashion. In the Hippocratic corpus snake in

wine, taken orally, is recommended for retained placenta, serpent grease is incorporated in a pessary for infertility and viper's broth is recommended for skin disease. Celsus, the Latin writer, prescribes snake for scrophula, and Dioscorides, the compiler of the greatest pharmacopoeia of antiquity, recommends serpents for quick eyesight and grief of nerves.

The most renowned snake therapy of the Ancient World was the substance known as theriac. Before pursuing this, however, it is necessary to turn to the most famous snake of all, the serpent in the Garden. Fortunately, there is no need to pursue the complex iconology surrounding this event except to note that it presents the dark side of the serpent. With the expulsion of Adam and Eve from the Garden came disease and death. But this was not the last appearance of the snake in the Bible and the next time it appears in its healing role. When the Israelites were wandering in the desert complaining of their miserable food God visited fiery serpents upon them and many died. When the people repented, at the Lord's command Moses set up a serpent of brass on a pole. Those who had been bitten looked on the serpent and were healed. In the Middle Ages the brazen serpent became a powerful symbol of healing and during severe epidemics of plague Thalers were struck depicting the serpent.

The brazen serpent was, of course, a prefiguration of the crucifixion and in this sense Christ and the healing serpent are one. As Augustine says 'What is the serpent lifted up? The death of the Lord on the cross'. Christ was, of course, the divine healer and his identification with the serpent was frequently made. The Ophites, the early Christian heretical sect, worshipped Christ in the form of a snake.

At this point it is possible to turn back to the panacea of the ancient world – theriac. Mithridates the VI, who came to the throne of Pontus in 111 B.C., lived in constant fear of being poisoned. To thwart any such attempt he concocted an antidote; so effective was this, however, that when he finally desired death by suicide he had to ask his servant to slay him, self-poisoning being of no avail. The antidote or mithridate came into the hands of Nero whose court physician Andromachus improved on the fifty-four existing ingredients and arrived at a new total of seventy-four. The remedy was extolled by Galen, which was perhaps sufficient to ensure its subsequent success. It became one of the most sought after drugs in Medieval and Renaissance Europe. For various commercial and geographical reasons Venice became the centre of the theriac trade and indeed they ran their own serpent farms, breeding the particular species of viper required. Serpents are frequently found figured on theriac jars. The remedy had a long life but gradually came under fire in the late seventeenth and eighteenth century during the revolt from Galenism and polypharmacy.

More significant, however, is that theriac, the panacea, became a symbol of the supreme remedy, Christ himself. Schouten (1967) describes a small panel by Van-Eyck dated 1442. It shows St. Jerome in his study; in the corner is a theriac jar with an apple on the lid. The meaning is clear. The apple in Christian art symbolises the fall, brought about by the serpent. Theriac, the serpent's flesh, the symbol of Christ the healer, represents redemption. The dualistic nature of

the serpent could hardly be more apparent. It was the fall initiated by the snake that brought disease into the world. Grunewald's picture of the tresspassing lovers covered with snakes brings out all too clearly the motifs of the serpent, the fall, sin, disease, and punishment.

If then Christ became the healer for the Middle Ages and Renaissance, what became of the healing God Asklepios? The cult of Asklepios reached its zenith in the second century A.D. and presented a serious contender to Christianity, for in one aspect at least, Asklepios presented the same message as Christ. The God came under heavy fire in the patristic literature and, though temporarily revived by Julian the Apostate, he eventually went underground. Many pagan gods never truly disappeared but were subsumed under Christian saints in the same way that amulets and talismen lived on as saintly relics possessing healing power. Asklepios was certainly subsumed in part under Christ himself though he was also strongly linked to the two Christian patron saints of medicine, Cosmas and Damian. In many accounts these saints were reported to heal the sick by appearing to them in their dreams. The connection with Asklepian incubation is clear. Perhaps the most famous miracle is the one frequently depicted in which the two saintly physicians exchange the healthy leg of a dead Moor for the diseased leg of a priest.

If Asklepios assumed another form during the Middle Ages, the snake retained all its pristine healing power and this was transmitted through scholastic and popular culture. For instance Avicenna the Arabic physician whose *Canon* was the major medical text of the Middle Ages, recommended snake for leprosy. Snake remedies were ubiquitous in the orthodox medicine of the Middle Ages. In the Renaissance snake preparations were much sought after as promoters of rejuvenation and beauty treatments.

Not only did snakes heal, they still retained their malevolent power. Topsell in his *Historie of Serpents* of 1608 records that in mid-sixteenth century Hungary 'many serpents and lizards bred in the bodies of men' and caused about 3,000 deaths. With the birth of the new experimental science in the seventeenth century, the serpent lost none of its healing power. Its traditional qualities were soon redescribed in the new language of chemistry. Charas (1673) subjected the viper to innumerable experimental investigations and concluded they were valuable remedies for itch, erysipelas, measles, smallpox, leprosy and were a valuable adjunct to the production of a beautiful skin.

His most interesting section is that on theriac. The initial remarks are sceptical of that famous remedy, not however that he doubts the wondrous efficacy of viper, it is because he considers that in preparation the essential salts were lost. A careful method was necessary to produce the quintessential volatile salt. The snake's healing power had survived revolutions of theory before and it was not to be eclipsed by something so trivial as experimental investigation. The snake was more than just an ingredient of medicine however, it has always been a powerful symbol of healing itself.

At the time of the Roman Empire there was a central Italian tribe know as the Marsians, famous for their knowledge of snakes. Galen himself tells us how he ventured into the hills to learn from them. Their tradition still lives on at Cocullo in the Abruzzi mountains. Here the shrine of the tenth century Saint Domenico of Foligno, famous for its healing cures, has an annual serpent festival on the first Thursday in May. The term Marsians in the Ancient World came to mean anyone with power to handle snakes for as Firmicus, the fourth century astronomer says:

> 'In the first degrees of Capricorn rises the snake handler. Those born when this constellation runs will be Marsians who charm poisonous snakes by sleeping spells or charmed herbs'.

The constellation Ophiucus or the serpent-handler was also called Asklepios in the Ancient and the Medieval world. Snake-handlers then were more than just charmers and sellers of poisons and antidotes, they were also the public vendors of drugs and remedies. The handler of snakes in the market place was the quack, the mountebank and the medicine seller. An illustration in a fifteenth century manuscript, *The Dresden Galen,* shows an itinerant medicine vendor at work, with his accompanying snakes.

The association did not only exist in the popular arena, for the symbolism was the same in high renaissance culture. When Duke Federigo Gonzaga of Mantua decorated he Palazzo del Te with astrological symbols, he chose to illustrate the quotation from Firmicus in the same manner. The tradition did not die with the birth of the modern world. There are engravings from the nineteenth century showing quacks with snakes as their symbol.

I have discussed so far the single snake of Asklepios as the symbol of medicine. But also familiar is the double snake as the symbol of healing. This is the caduceus of Mercury. Hermes was the messenger of the gods and the guide of departed souls. In antiquity the caduceus was the symbol of the messenger and it ensured him unmolested passage. I know of one possible example of its association with medicine in antiquity, that described by Hast (1972). This is an oculists stamp from the third century A.D. On the top surface are said to be four lightly scratched caducei joined at the centre to form a cross. The origin of this lone association is a mystery but it may arise from the fact that Homer describes the caduceus as being able to charm the eyes of men.

The next time the caduceus is found as a symbol of medicine is in the sixteenth century. In England the caduceus was used by Sir William Butts, physician to Henry VIII and by John Caius who presented the Royal College of Physicians with a caduceus in 1556. In the Philadelphia Museum is a picture described as a portrait of an elderly physician, a copy after an original of 1500-1510. He is shown holding a caduceus (Szancer and Szancer 1971). If this is so it is the earliest post-classical example existing. However, it is possible that the man has been identified as a physician because he is holding a caduceus, he could equally well be a hermetic philosopher.

It is hard to fault Schouten's explanation for the association in the Renaissance of the caduceus and medicine. The transfer was almost certainly made by way of alchemy. The Egyptian God Thoth, the giver of wisdom, was identified by the Greeks with Hermes. In the first centuries after Christ a large alchemical and astrological literature developed under the name of Hermes Trimegistus. The Renaissance accepted Hermes as a real person of great antiquity and the source of profound knowledge. One of the texts in the Hermetic corpus is known as the *Asklepios* and the knowledge in it is imparted by Hermes to Asklepios as master to pupil. Renaissance philosophers knew their symbols and it is hardly likely they confused the caduceus and the rod and staff of Asklepios. Rather the caduceus of Mercury the symbol of transmuting power, was adopted by the physicians who practised alchemy. Whatever the true reason the caduceus soon became a medical symbol. It can be found on the frontispiece of medical texts, pharmacopoeias, perhaps in its most famous form as the official insignia of the U.S. Army Medical Department.

I have briefly reviewed a mere fraction of the many manifestations in medicine of this remarkable beast and have confined myself largely to European culture, neither have I made mention of the snake's association with medicine in primitive societies. I want, however, to finish with an example from current anthropology for it permits me to speculate a little on what is clearly the recurrent feature of serpent symbolism – its dualistic character – the rich imagery of health and disease, life and death always associated with it.

Animals, it has been suggested, are a primordial metaphor through which men came to define their own humanity. In all cosmologies there is an explicit assumption of order in the universe. It is this after all that allows man to demarcate himself from animals. In primitive cosmologies the classification of animals parallels the divisions of society. Among the Nuer people, animals, like men are organized on the lines of descent groups. Among the Benin peoples animals are classified by the domains they occupy, and this in turn is an invocation of the natural order to sanction the maintenance of social station. There are animals of the sky, land, day and night, just as there are kings, warriors and magicians. Each knows his place.

There are some animals, however, that nearly always fall in the cracks, for they are neither one thing nor the other. It is always at the boundary lines too, that there exist the greatest dangers and the most powerful natural forces. These are the areas of greatest avoidance and ritual (witness the forces, now but a parody, that are unleashed at the transitional time of Halloween). For the unwary they are fatal areas. Yet in all societies certain individuals can master and control these forces and use them for good or evil. The animals which dwell at these intersticial areas are likely to be powerful symbols of the most profound natural forces. By its very nature the snake is an animal that is potentially anomalous in any classification system. It is, after all, a creature that lives on land yet has no legs, that swims in the water yet has no fins, that dwells in trees but has no wings. It is an abomination, in the categories of Leviticus, 'a swarming thing'. Among the Benin peoples the snake holds such an anomalous position. In Benin society only two categories of people can harness the most powerful

natural forces there are, the witch and the divine healer. Like the snake in nature, these individuals in society fall outside the normal social groupings. The one however, can control the boundary forces for the production of evil, the inflicting of disease, the other for good, for healing. I use the example of the Benin for one symbol of the medicine man is his staff and on it is entwined the most powerful and dangerous of all animals, the snake (Ben-Amos 1976).

The association of the snake and medicine, with the life and death, good and evil is thus no accident. It stands as a natural symbol of the most powerful forces in the cosmos. For us who live in a universe where animals are classified by evolutionary descent the snake no longer holds this ambiguous position, the symbol has become a badge. There is no reason, though, why we should not recast its old meaning in modern terms, for we are all very much aware that medicine today stands guard over some of the most powerful forces ever discovered by men and these too have the capacity for evil as well as good.

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# DISEASE IS GOOD FOR YOU

by

**IAN FRASER**

We have all been conditioned over the years by every form of audiovisual aid to believe that Guinness is good for you, and indeed we see an extensive field trial of this beverage being carried out daily by many of our friends, and so it may seem somewhat of a paradox to find a paper entitled 'Disease is Good for You'. I, however, would like to support the unorthodox idea and show that some diseases that afflict mankind can be beneficial. I shall endeavour, for example, to show that the world was a more exciting place with more originality when the bacillus of tuberculosis and the spirochaete of syphilis were given free range. We must ask ourselves if the easy and rapid and effective treatment of tuberculosis and syphilis, which in the case of the latter disease has prevented that late, interesting and stimulating complication known as general paralysis of the insane (G.P.I.), has made the world a less exciting place in which to live. Is the absence of these diseases the cause of so much mediocrity among artists, politicians, and leaders in business and society? They no longer display the flair and originality they used to have. They are a pedestrian group playing for safety rather than success.

Perhaps my title is too broad. Certain diseases must be excluded – the incurable diseases, the painful ones, the debilitating ones, all of which make a man an introvert rather than outward looking. In this connection I must mention an occasion when some years ago I was talking to Sir Stanford Cade – London's leading cancer expert at that time. He produced from his pocket photographs of two politicians who had come under his care. One of these he pointed out to me was a British Prime Minister of Ulster descent, who, he said, although involved in major political problems probably had as his main personal worry and anxiety whether he would be able to swallow his own saliva; it will be remembered that Bonar Law at that time was suffering from a cancer of the throat. The other picture was that of Neville Chamberlain holding a famous piece of paper in his hand with a promise of 'peace in our time', and yet, said Cade, Chamberlain was probably more worried as to whether his colostomy would suddenly act at the wrong moment. Cade had operated on him not long before for a cancer of the rectum. Anthony Eden never knew when his cholangitis with high fever would confine him to bed just at a critical moment when he was faced with an important international decision.

A book has just recently been published in Switzerland describing in detail the ill health of many of the great world leaders – e.g., Stalin, Hitler and Mussolini: there are many similar examples and there will always be the problem of when one's health and one's ability to do the job come into conflict. Who is to tell the doctor, for example, when he is no longer capable? The

decision cannot be left to the individual but to the clear impartial judgement of friends. In politics and in medicine more than in any other walk of life is there the necessity of *mens sana in corpore sano.*

Every man has two separate parts in his make up, one is the artistic side and the other the scientific, mathematical, computer side. It is the artistic side only that can be involved and stimulated by tuberculosis and syphilis. We cannot see the computer being involved or affected by either. In the extensive literature on the subject we find few bank directors, business tycoons, atom splitters, or professors of mathematics mentioned as having gained anything from these diseases. In medicine the skill of diagnosis and the care and treatment of the sick patient are a combiination of art and science. The average doctor is vain enough to think he has in his own make up these two ingredients in the right proportion.

## TUBERCULOSIS AND GENIUS

Moorman (1939) gave a long list of people, mostly writers, poets, musicians, sculptors and painters (Appendix 1) to support the views expressed in such quotations as 'The best recipe for producing the highest type of creative mind is an initial spark of genius plus tuberculosis', or 'The decline in tuberculosis coincides with the decline in creative writing' or 'By way of compensation for good health we may have to forego the pleasure of certain cultural joys'. Ebstein (1932), too, maintained that tuberculosis does not cause genius but may fan into flames a dormant spark.

Moorman suggested that we all have a dual personality. One part is conventional and restricted by established habits and customs; the other part, which, although held in check, can with the right stimulus be released to show the person's real ego. The stimulus may be alcohol, tuberculosis, or syphilis. He described in detail the lives of R. L. Stevenson, Schiller, Voltaire, Molière, Shelley, Keats, St. Francis of Assisi, Marie Bashkirsteff (The Russian child Prodigy), Katherine Mansfield (The New Zealand novelist), and of Francis Thompson, of Preston, who wrote 'The Hound of Heaven' said by some to be the greatest ode in the English language. He was able to list 80 others all of whom added much to the artistic side of British culture. In his book on much the same subject Ebstein (1932) went far back into history ending up with Klabund in 1928. He gives short notes of each of his 133 cases and covers a vast field – Russia, Germany, France, including such well known names as Chopin, Paul Ehrlich, Goethe, Gorski, Laënnec, Rousseau, Schiller, Attila (King of the Huns), Fontaine (of the fables), Goldsmith, Washington Irving, D. H. Lawrence, Rudolf Wagner and many others. Both of these books were published before 1945, and before tuberculosis started to disappear. Penicillin, a forerunner of streptomycin, had just been introduced a few years earlier.

It was said of Tom Hood that as his health declined from tuberculosis his poetical fire seemed to burn more brightly. 'The Song of the Shirt' came from a man on his death bed. Chopin created his greatest masterpieces when his tuberculosis was most active. Aubrey Beardsley knew he was doomed and so

with feverish energy he tried to put a lifetime into each twelve months. Keats obviously felt that time was running uot when he wrote – 'When I have fears that I may cease to be before my pen has gleaned my teeming brain'. He clearly hoped to have time to put on paper all the ideas that were filling his brain at the moment. The idea of haste is often mentioned but the work that actually has been produced rarely shows any signs of rush or hurry.

When Ernest Henley wrote in 'Invictus'

*It matters not how strait the Gate*
*How charged with punishment the scroll*
*I am the master of my fate*
*I am the captain of my soul.*

he had had one leg amputated because of tuberculosis and his lungs were now affected. With the spread of the disease to his other leg he went to Edinburgh on crutches to see Sir Joseph Lister who was ushering in the dawn of antiseptic surgery with his carbolic acid treatment. Fortunately after two years in hospital he was discharged a relatively fit man. During this time he wrote his well known poem 'In Hospital' and also made close contact with another consumptive Robert Louis Stevenson. Stevenson was able to produce many works of literary genius which still delight us, right up to the moment when he finally succumbed to the disease in Samoa. Elizabeth Barrett Browning was long confined to bed with tuberculosis of the spine, and yet was able to share one of the most romantic marriages of all time. Her husband Robert once said of her 'She has a soul of fire in a shell of pearl', and later when she was dying of tuberculosis he wrote 'As the disease advances it gives its victims ever increasing beauty; passion is increased; desire more elegant; and finally a wonderful happiness, an ecstasy of hope and confidence – all will be well soon – and then the brief candle is blown out'. Elizabeth Barrett Browning wrote one of her own poems to George Sand whom she greatly admired, and it was the latter who nursed that master of music Frederick Chopin until his death at the early age of 39.

In a useful paper on Chekov and his chronic tuberculosis the late Dr. Brice Clarke of Belfast gives the interesting history of the life of this Russian doctor and writer who, when he coughed up some blood for the first time exclaimed 'this is the visiting card of tuberculosis'. He survived it for many years. He was at his very lowest ebb when he wrote 'The Cherry Orchard', but when this play was produced for the first time in the theatre in 1904 he himself appeared on the stage and received a tremendous ovation. He died a few months later.

The Brontë family present a good example of eccentricity and of disease and genius. They were riddled with tuberculosis. Although their father coughed on with his 'chronic bronchitis' until the age of 84; Anne died at the age of 29, Emily at 30, and Charlotte at 39. The two last named displayed great literary talent. Their brother Branwell too was tuberculous and whilst having no literary ability whatsoever, was a painter of some merit.

Bochaelli (1960) showed that doctors suffering from tuberculosis have themselves been pioneers in advances in the treatment of the disease. In this context

he mentioned the work of Dett Weller, Paul Ehrlich, Koch, Karl Turbân, Parrot and Cornet. One can trace all the advances prior to the discovery of specific chemotherapy in their published papers. Turbân was the first to perform a thoracoplasty by rib resection. Tuberculin was discovered by Koch and self administered when he discovered that he himself had tuberculosis. Laënnec is always remembered as the inventor of the stethoscope but he himself died very early from tuberculosis.

## OTHER CAUSES OF GENIUS

Other causes of genius have been advanced. My friend Sir George Pickering, until recently Regius Professor Medicine at Oxford, wrote 'Creative Malady' a book which I greatly enjoyed because I disagreed with most of it. He tried to establish that often genius has resulted from the presence of psychoneurosis – and it was this that created the urge to do something. He analysed the life and life cycle of several well known people – Charles Darwin, Florence Nightingale, Mary Baker Eddy, Sigmund Freud, Marcel Proust and Elizabeth Barrett Browning. He maintained that illness may be an evil episode but occasionally it can be of benefit not only to the victim but to society. The psychoneurotic is able to escape into privacy; in fact he himself was forced to go to bed on account of a pain in his hips caused by advanced osteoarthritis. He thus had time for thought, reflection, and writing. Now since he has had a successful hip joint replacement and is free from pain he has lost the excuse for solitude. He pointed out what we all know, that creative works usually appear unsought in periods of leisure. Newton was in his garden when the apple fell; Archimedes was in his bath. Poincaré was just putting his foot on a bus, and Darwin was in his carriage and in fact could remember the very spot on the road where he suddenly discovered with great joy his solution to the problem of evolution, even though it took him another twenty years to complete his work on the subject. These and many other discoveries, the result of so called serenpidity, all appeared when the mind was at rest.

The mind like the heart has two phases, a systole and a diastole. When at work it is cut off from thought but when it is at rest the big ideas appear. How many of us at school were unable to answer the examination paper at the critical moment but saw all the answers clearly when in our bath or going to bed? An alternative to illness for some people was prison, where Bunyan, Bertrand Russell and others did such valuable work. Some like Milton found peace in blindness. Pickering in his list of psychoneurotics includes Mary Baker Eddy, the founder of Christian Science. When she died in 1910 she was one of the richest women of the day, and yet for years had had to be carried up and down stairs. At the end she was a frail elderly old woman pursued by terrors of persecution. She survived, however, three husbands, and died at the age of 89. So psychoneurosis has obviously something to be said in its favour. Sigmund Freud developed the idea and technique of psycho-analysis in 1892; he tried to oversimplify the problem in relating nearly everything to sex and the oedipus

complex. He said on one occasion – 'I cannot be industrious when I am in good health. On the contrary I need a certain degree of discomfort that I want to get rid of'. To him *mens sana in corpore sano* did not make sense. He died at the age of 83 in 1939. It is interesting to see how long these psychoneurotics can live enjoying their ill health. Although some of them have been described as men of genius Keats was probably more correct in describing them as 'men of achievement'. Pickering suggested the name of 'creative malady' for a disease with a useful end-product or at least a by-product.

W. R. Bett wrote a book in 1952 which he called 'The Infirmities of Genius' and differed from Pickering who had at least tried to find in psychoneuroses a common denominator. Bett, on the other hand, in giving the detailed life history of fifteen people, found a different disease in each. These people all suffered, as the general public does, from a mixed bag of diseases so that we can find no common bond linking them together. Two of his cases, however, were relevant to my way of thinking; one was John Keats, who had tuberculosis and syphilis; and the other was Charles Baudelaire, who openly admitted that his syphillis was the cause of his driving force.

Recently I received an article from Dr. Rentchnick in Geneva called 'Les Ophelins Menent Le Monde' – which could be loosely translated 'if you want to get to the top it is best to be an orphan'. Rentchnick, it would appear, following the death of Monsieur Pompidou, decided to look into the family and personal history of some 350 people who had reached the top especially in the field of politics, army, arts and law. It is interesting and amusing reading, but when he brings in the kings and queens one must disagree. They reached their positions in no way through their own efforts 'Some are born great, some achieve greatness, etc.'. I am afraid Oscar Wilde also would have disagreed with this. He said 'For anyone to lose one parent may be regarded as a misfortune, but to lose both looks like carelessness'.

## SYPHILIS AND GENIUS

Any one doctor over his entire professional life sees very few cases of general paralysis of the insane (GPI) and will in the years to come see still fewer. This interesting disease with its grandiose delusions can at times have been the stimulus for certain ideas that would not have been thought of otherwise, and in the list of names that follow in Appendix 2. I feel that there is a definite relationship between their achievements and the disease. The productive period of the disease is a short one before the inevitable final in insanity. As Thomas Osbert Mordaunt puts it 'One crowded hour of glorious life is worth an age without a name'.

I remember one personal case very vividly. I was doing one of my few – alas too few – locums in general practice. This was in Co. Londonderry. I was called out to see a well-to-do farmer who had been for a time after leaving school a student in Edinburgh University before coming home to take over his father's quite extensive estate. It was while he was a student that he had made contact

with the spirochaete. He was happily married, and on the day before I saw him he had told his wife that he was going to the local fair to buy some 20-30 cattle. Some hours later she was somewhat disturbed when she saw some 300 head of cattle being driven into the yard, and when he returned in the evening he told her that this was just the beginning and he hoped to have 2,000 or 3,000 more tomorrow. The onset of his grandiose delusions had been very rapid – he was in a Belfast nursing home next day, and in Purdysburn Hospital a few days later. The suddenness of this is well exemplified in another case often quoted by Sir William Thomson (Professor W.W.D.) – that of a well known high court judge – a man of fastidious tastes and immaculate manners – who, while hearing an important case in the High Court, had a sudden desire to pass his water. He proceeded to do this in a crowded court in full view of all concerned – and he was rapidly replaced in his post. Many people of my vintage in Belfast have in their homes paintings by an artist who turned out a great number of attractive oil paintings now much sought after. He had a short very productive very exciting spell during the stimulating period of his GPI before finally he died in the mental asylum.

When I was a student in London I remember a well known and brilliant ENT surgeon, who had been getting more and more eccentric and irrational, committing the final act which put him in the asylum. He was performing a mastoid operation and the ear flap kept falling back over his operation wound; after this had happened four or five times he could stand it no longer and cut the ear off. It is always said that Germany's chief thoracic surgeon had GPI and that towards the end of his life when a blood vessel began to spurt he used to try to catch the stream in mid air with his forceps rather than stop the bleeding point on the artery itself. On a more positive side, perhaps, is Cecil Rhodes, who it is alleged would never have had the magnificent conception of the Cape to Cairo Railway or the imagination to create Rhodesia without the help of the spirochaete.

GPI came as a rule some twenty years after the original infection: its victims were in the prime of life, often in responsible positions and often of high intelligence; sadly the end was a degrading one for such men. At first they were figures of fun with their delusions of grandeur and unpredictable impulses of behaviour, ending sadly, as one man put it 'As gibbering idiots awaiting a death of humiliation'. It must be remembered that GPI was a scourge in Victorian and Edwardian society and deaths from it ran into thousands each year. Wagner-Jauregg, later Wagner Von-Jauregg, in 1927 was awarded a Nobel prize for his original work on its treatment with malaria. This treatment was slow in being accepted as indeed was penicillin which replaced it. I suppose it is sad to think that in 1943 with the discovery of penicillin, this exhilarating disease was killed for ever. I am afraid I did not think of this when I was carrying out the pioneer trials in Sicily of research into the drug. Syphilis will go on, naturally, as long as man exists, but no longer will it show the late complications, since the disease can so easily be wiped out in its early stages. Have our doctors reduced the power of creativity and originality among the artists to the level of circles, squares, dots and blobs?

Dickson Wright in 1971 wrote a very good article on 'Venereal Disease and the Great' with a vast number of references. Discussing the church he points out that Cardinal Wolsey, and also three Popes, had been infected – no one is left unscathed, and this article has just a touch of pornography as one would expect from Dickson Wright. Regrettably, from our point of view, he does not separate gonorrhoea from syphilis, for I consider the former to have been an unproductive disease, doing neither patient nor his country any good whatsoever – no fringe benefits. It is said that Lord Cardigan was in considerable discomfort with his infection, which made him ride with less than his usual dash when he led the Light Brigade at Balaclava. Perhaps leading his men from behind may, in fact, have saved his life.

Syphilis has influenced the life and work of many well-known literary personalities. Daudet who, although he was also addicted to cocaine, and morphia, finally died from GPI. George Meredith also had GPI but struggled on to a ripe old age, going about in his bath chair drawn by his famous donkey 'Picnic'. Guy de Maupassant, described by some as 'a man of unbridled appetite' died of GPI at the age of 43, having stimulated many others to follow his example. Molière for the last eight years of his life was a chronic invalid from syphilis. He hated doctors and they hated him, but they got their own back on him, as he died in the theatre during the fourth performance of his famous play 'Le Malade Imaginaire' – a satire on doctors – when his syphilitic aneurysm ruptured. Heinrich Heine left Germany to live in Paris, where he changed from the Jewish religion and where he got his syphilis: he died at the age of 57 but had been bedridden for the last eight years of his life and was nursed through them all by his devoted mistress. He is said to have produced the most beautiful poems ever written in the German language. Oscar Wilde got his syphilis from a lady known as 'Old Jess' – said to be the only working harlot in Oxford when he was there: to her he dedicated a poem, which was very kind of him. He was disgusted with the mercurial treatment as it spoiled, he said, his nice teeth. Whether the cerebral abscess from which he died in Paris can be attributed to his syphilis or to the fall he had had in Reading Goal has never been solved.

Baudelaire was not only a syphilitic but an opium eater as well, and his most brilliant works were done under the influence both of the drug and the infection. It is often suggested that Dean Swift had cerebral syphilis to which his poem to Celia refers. In a play in London last year called 'Yahoo' it was openly stated that Gulliver's Travels could only have been conceived by a man with all the grandiose delusions of general paralysis of the insane. In the world of music Beethoven's deafness was said to have arisen from his having had syphilis. Schubert at the early age of 24 got syphilis but he in fact died quite young, most probably from tuberculosis and poverty, although some say that syphilis did shorten his days. Lorenzo de Ponte, the librettist of the Marriage of Figaro, had syphilis and later GPI and he actually died from it. Donizetti died relatively young at the age of 50. He had spent his last seven years declining slowly from GPI. Though he could still compose he could not any longer conduct. In his last stages the famous duet from Lucia de Lammermoor, which was one of his

masterpieces, was bawled into his ear as he lay dying in bed, but even that apparently produced no reaction.

Doctors did not often appear in the list of syphilitics. Finsen the Dane, a Nobel prinze winner and famous for his lamp, died in 1904 from syphilis. I remember when this lamp was in daily use in The Royal Victoria Hospital for treatment of skin tuberculosis. Another was Von Behring – Koch's famous assistant, who died of GPI in 1917 at the age of 63. He will always be remembered for his famous work on diphtheria and tetanus. It is interesting to see that it is the artist, whether in music, writing, poetry, painting or sculpture, who appears most often. Coming to the arts we find Manet, Van Gogh – who it may be remembered cut off his ear shortly before committing suicide – also Gaugin who later went to Tahiti; Goya struggled on until the age of 82 when he died of a stroke. He had in all twenty children; sadly all of these died except one.

In the realm of sculpture we find an interesting article by Gleen Geelhoed (1968) on Cellini and his syphilis. In his own autobiography Cellini describes how he got his syphilis at the age of 28 when he took to live with him one of his most attractive models. He soon found that he had developed the 'French Disease'. When he was in quite an advanced stage of it he had an attack of malaria which gave him a prolonged but temporary improvement. Sadly he soon reverted to his grandiose delusions. He was treated with mercury, and in his famous statue of Perseus he included 'Mercury' at the bottom, perhaps linking together the cause of the sculptor's inspiration, and the cure.

In 1926 Springer wrote 'Die Genialen "Syphilitiker".' The name might have suggested 'The Genial Syphilitic' as indeed many are, in fact, some too genial. But this book deals with the relationship between syphilis, genius and culture. It is an interesting book, not very reliable, and in certain places shows muddled thinking; but its great value is that it gives a comprehensive list of notable people in the world of art, science, politics, law, church, state, medicine, royalty, all of whom have had the disease. Springer gives an extensive list and from this and other sources Appendix 2 has been compiled. Springer it will be seen includes such people as Job – who we know had many sorrows. Some will be sad to see Good King Wenceslaus (1378-1400) also on his lift – perhaps one will sing this carol now with less than one's usual gusto. He also mentions King Philip 11 of Spain (1555-1598) and suggests that without his grandiose delusions of GPI he would not have had the courage or the audacity to risk his Armada against the British Navy.

## CONCLUSIONS

I hope I have been able with all these examples to prove to your satisfaction, as I naturally have to my own ! that disease can be good for you. Are we better to have a long-lived community of bodily healthy people, nonentities and parasites, who are giving nothing to society, or a population with some exciting if eccentric personalities? Would a little tuberculosis among our politicians be a stimulus and give us some leadership rather than drab healthy mediocrity. It is sad if good health (so called) brings such a calamity with it.

My other contention was that syphilis has its advantages. Going back to the politicians it might be said that although they show no overt signs of syphilis yet in some ways we fear at times that they have delusions of grandeur. I know all of you who have had tuberculosis or syphilis are now much happier, and those who are fortunate enough, indeed, to have had both, will look on this as an added bonus. I suppose we should congratulate those who have reached the top of the profession without any of these external (or are they internal) aids.

## Appendix1

### THE FOLLOWING SUFFERED FROM TUBERCULOSIS

Milton
Pope
Shelley
Voltaire
Hood
Keats
Walt Whitman
Elizabeth Barrett Browning
Francis Thompson
Goethe
Molière
Channing
Mérimée
Thoreau
Descartes
Locke
Spinoza
Beaumont
Samuel Johnson
Goldsmith
Sterne
De Quincey
Scott
Leigh Hunt
Jane Austen
Charlotte Brontë
Emily Brontë
Ann Brontë
Stevenson
Balzac
Rousseau
Washington Irving
Hawthorne
Gibson
Kingsley
Ruskin
Emerson
Cardinal Manning
Lanier
Marie Bashkirtseff
Robert Southey
Westcott
George de Guérin
David Gray
Amiel
John R. Green
Robert Pollok
Hannah More
James Ryder Randall
N. P. Willis
John Addington Symonds
Stephen Crane
Katherine Mansfield
Paul Laurence Dunbar
Eugene O'Neill
Novalis
Klabund
Chekhov
Llewelyn Powys
W. E. Henley
William Cullen Bryant
John Greenleaf Whittier
Maksim Gorki
Feodor Dostoevski
Aubrey Beardsley
Eugene Albrecht
Beranger
Richard Lovelace
George Ripley
Blackmore
Joseph Rodman Drake
Kirke White
Adelaide Ann Proctor
Henry Timrod
H. C. Bunner
John Sterling
Havelock Ellis
John Millington Synge
Cicero has also been listed among those who may have suffered from tuberculosis

## Appendix 2

### AUTHENTIC CASES OF SYPHILIS

Voltaire
Christopher Columbus
Socrates 470-399 BC
Caesar
Caesar Augustus 63 BC-14AD
King Wenceslaus 1378-1400
King Charles VIII 1494
King Louis XII 1498
King Francis 1515-1547
King Philip II of Spain 1555-1598
King Louis XIV 1643-1715
Sebastian Roch Nicholass Chamfort 1791
Jean François De La Herpe 1803
Napoleon Bonaparte 1822
Ludwig Van Beethoven 1827
William Hyde Wollaston 1828
August Von Goethe 1830
Christian Dietrich Grabbe 1836
Nikolaus Lenau 1850
Robert Reitzel 1898
Frederich Nietzsche 1900
Oscar Wilde 1900
Paul Gauguin 1903
Neils Ryberg Finsen 1904
Otto Erich Hartleben 1905
Hugu Wold 1907
Walter Leistikow 1908
Hans Jaeger 1910
Emil von Behring 1917
Andreas Ady 1919
Hans Paasche 1920

King Louis XV 1715-1744
King William of Prussia 1840-1861
Pope Alexander VI 1492
Pope Julius II 1503
Pope Leo X 1513
Ulrich Von Hutten 1523
Benvenuto Cellini 1571
Viscomte de Turenne 1675
Marshall Von Sachsen 1750
Jean Baptiste de Boyer 1771
Charles Von Rohan 1787
Honoré Gabriel Riqueti Grad Mirabeau 1791
Ernest Theorore Hoffman 1822
Heinrich Heine 1856
Robert Schumann 1856
Arthur Scholenhauer 1860
Henri Murger 1861
Ferdinand Lassalle 1864
Edouard Manet 1883
Hans Makart 1884
Richard Von Volkmann-Leander 1889
Karl Westphal 1890
Guy de Maupassant 1893
Alphonse Daudet 1897
Paul Desthanel 1923
Lenin (Wladimer Itjitsch Uljanow) 1924
Woodrow Wilson 1924
René Viviani 1925
Meredith
Thackeray
Molière
Baudelaire

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# CHOICE OF TREATMENT IN THE MANAGEMENT OF BLEEDING OESOPHAGEAL VARICES IN PATIENTS WITH CIRRHOSIS

by

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URGENT control of haemorrhage is a basic surgical principle, but it is not always achieved most effectively by surgery. Emergency portacaval shunt can undoubtedly control bleeding from oesophageal varices, but the huge mortality in non-selected patients, as reported by Orloff, is prohibitive (Orloff et al, 1975). The idea of selective management based on clinical and laboratory findings was first suggested by Child as far back as 1964 when he introduced his now widely used classification of patients with cirrhosis (Child, 1964). However, even if one follows his concept of reserving portal decompression for A cases, the results of shunt surgery are often disappointing. Most controlled trials have failed to show any clear-cut advantage following either prophylactic or therapeutic shunt, and thus there has followed a reappraisal of the value of shunt. Realizing that the vast majority of patients with bleeding varices will never be fit for shunt, how should these shunt rejects be managed?

First it is necessary to establish that bleeding is coming from the oesophageal varices, since it is accepted that patients with cirrhosis may be bleeding from other lesions. However, rigid adherence to the now popular policy of routine emergency endoscopy in all patients should be resisted. The pendulum has swung too far since there is no evidence that emergency endoscopy in all patients with haematemisis reduces mortality (Sandlow et al, 1974; Morris et al, 1975; Lee et al, 1977). It must also be acknowledged that it does not always provide the correct diagnosis since observer error may be as high as 30 per cent (Conn et al, 1967). The much higher incidence of acute mucosal lesions in the American series, when compared with the figures for the British Isles, may represent a higher incidence of alcoholic patients, or perhaps reflect over-vigorous lavage, which can produce artefactual bleeding. Certainly, the practice of inducing vomiting in order to displace residual clot while the endoscope is still in place in the stomach, may explain Sagawa's 15 per cent incidence of the Mallory-Weiss syndrome (Sagawa et al, 1973). The fact that varices are not actually bleeding at the time of examination does not exclude them as the source of bleeding. Indeed, it is unusual to demonstrate active bleeding into the lumen of the oesophagus, even by direct injection of contrast medium into the left gastric vein (Lunderquist, 1977). It is probably acceptable to assume the diagnosis on the basis of exclusion of other sites of bleeding, although by using a wide bore rigid oesophagoscope to distend the varices, one may demonstrate the site of bleeding when the thinner, flexible endoscope has failed to do so. All patients should have endoscopy at some stage to confirm the diagnosis, but emergency endoscopy should be selective.

Massive haemorrhage in patients with cirrhosis is generally due to varices, and in this situation, therapeutic trial using the four channel Sengstaken tube is justified. It minimizes blood loss, which is poorly tolerated by these patients, and when properly managed, oesophageal tamponade gives rise to very few of the problems listed by Conn (Conn, 1958). True, it may also control bleeding from oesophagitis or the Mallory-Weiss syndrome, but this is no disadvantage since the diagnosis will become apparent later. With the bleeding controlled, the patient can be properly resuscitated, more fully investigated, and the usual measures taken to combat coma. The next morning, when the patient is haemodynamically stable, the laboratory data available, the medical team fresh, and the theatres fully staffed, a decision is taken on the further therapy. Oesophageal tamponade is not a definitive treatment and the oesophageal balloon should be deflated within 24 hours and a careful watch kept for rebleeding. About 60-70 per cent of patients will rebleed within 48 hours, and it is therefore wise to keep the deflated tube in place during this period. Those that rebleed require immediate reinflation of the balloons and an urgent decision taken on further management. Our policy is to allocate patients to one of four treatment categories on the basis of clinical status.

## TREATMENT CATEGORIES

### 1. *Rejection*

Patients with the triad of hepatic precoma, marked jaundice and gross ascites, are not improved by any operative procedure. However, it is still worthwhile continuing with tamponade and the usual supporting measures since, surprisingly, a few patients will rally even from this perilous clinical condition. Should survival occur, further definitive measures can be considered later.

### 2. *Injection*

Even in the absence of encephalopathy, the patient with jaundice and ascites fares badly following emergency laparotomy or thoracotomy. In this situation, injection sclerotherapy using a wide bore rigid oesophagoscope controls bleeding effectively in 90 per cent of patients, and 80 per cent survive to leave hospital (Johnston and Rodgers, 1973). More recently, the flexible endoscope has been used, but although the instrument is simpler to pass, the actual injection is more difficult unless one employs an outer sheath to compress and delineate the varices prior to injection (Williams, 1977). Also, if bleeding is severe, the sucker in the flexible endoscope is insufficiently powerful to remove the accumulating blood from the lumen of the oesophagus. In addition, the flexible instrument does not prevent rapid dissemination of the sclerosant away from the injection site, and therefore presumably achieves less of the desired intimal damage that can be obtained by means of the rigid oesophagoscope (Johnson, 1977). Percutaneous transhepatic sclerosis via the coronary and short gastric veins is attractive in that general anaesthesia is not required (Lunderquist and Vang, 1974). However, the technique is not easy canulation being achieved in only 40 of 62 patients attempted (Dick, 1977). Also, there is a high incidence of technical snags and complications (Scott et al, 1976).

Due to the falling popularity of shunt surgery, there has been a remarkable upsurge of interest in injection therapy in its various forms. It is certainly the least traumatic of the available methods, but suffers from the disadvantage that sclerosis tends to be temporary and bleeding recurs as the veins recanalize. It is therefore necessary, following recovery from the acute episode, to decide whether the patient should have repeated prophylactic injections or injection therapy only when recurrent bleeding occurs. In some patients, improvement in liver function may permit consideration of subsequent oesophageal transection or very occasionally, shunt surgery.

### 3. *Transection*

Many patients with reasonably good liver function will never be suitable for shunt because of advanced years, or past encephalopathy, or the presence of diabetes, etc. In this situation, it is obviously desirable to obtain a more prolonged result than that achieved by injection methods. Since the vast majority of haemorrages occur in the 5 cm segment of the oesophagus above the cardia, direct surgery in this region seems logical. The Boerema-Crile ligation technique and the Walker mucosal transection methods of variceal obliteration, although widely adopted, require thoracotomy and carry a 30 to 40 per cent mortality in the presence of acute bleeding. The use of the Boerema Button or Prioton Clip permits full thickness oesophageal transection via the abdomen, but the high morbidity from stricture formation detracts from the undoubted simplicity and low mortality (Johnston and Kelly, 1976). Transabdominal transection using the Russian produced SPTU circular stapling apparatus, permits immediate mucosal apposition, and thus less risk of stricture (Van Kemmel, 1974; Johnston, 1977). In addittion, the abdominal approach allows ligation of the left gastric vein at the upper border of the pancreas, and division of all the peri-oesophogeal collateral vessels, thereby reducing the chance of recurrent bleeding. We have used this method in 40 patients in whom shunt was contraindicated. Fourteen were emergency transections and although bleeding was controlled initially in all instances, two patients had further serious haemorrhage within a week and both died. There were four other hospital deaths, two from septic peritonitis, one from hepatorenal failure and one from respiratory failure. In the follow-up period extending from one to 27 months, there were three late deaths, but none resulted from haemorrhage. Only two patients have had recurrent variceal bleeding and both responded to injection therapy. Although the initial disappearance of varices on barium studies and endoscopy is dramatic, one is cautious in predicting the long term results at this early stage.

### 4. *Selection*

In many clinics, portacaval shunt has been abandoned because of the high incidence of encephalopathy and unconvincing evidence of its worth in the various controlled trials. However, there is undoubtedly a place for portal systemic decompression, but perhaps we must learn to "select better who should be shunted, or to shunt better those we select", as Conn so aptly put it (Conn, 1974).

(a) *Select Better*

After the expenditure of much finance, time and energy on blood flow and pressure studies, we now know that selection on the basis of haemodynamic investigations does not improve the operative risks, the incidence of encephalopathy, or the long term survival (Smith, 1974; Bismuth et al, 1974; Burchell et al, 1974). Neither is there much truth in the old clinical adage, 'The patient who looks well and feels well does well'. End-to-side portacaval shunt, still the most commonly used anastomosis, is easy to perform and carries a low mortality, but in order to reduce the incidence of encephalopathy, the operation should be reserved for Child's Grade A patients under the age of 50 without a past history of diabetes or encephalopathy (Johnston, 1977). In addition, the presence of acute bleeding or active hepatitis should also exclude a patient from consideration for shunt.

(b) *Shunt Better*

,The effectiveness of any of the standard portal systemic shunts in preventing haemorrhage is marred by the disturbing incidence of disabling encephalopathy. In this respect, there is little to choose between portacaval, mesentericocaval or conventional splenorenal shunts. This has led to the search for more selective shunts which would effectively decompress the varices without depriving the liver of all its portal blood. In 1967, Warren introduced the exciting concept of the distal splenorenal shunt (Warren et al, 1967). It is technically more difficult than the traditional shunts and carries a significantly higher mortality, but the incidence of encephalopathy is certainly reduced (Galambos et al, 1976; Langer et al, 1977). Although workers in Lund found no improvement in the encephalopathy rates with the distal splenorenal shunt, it should be noted that they did not ligate the main coronary vein as described by Warren, and thus allowed progressively more blood to be diverted from the portal to the systemic systems (Vang et al, 1976). However, even when the identifiable collaterals are litigated, hepatic resistance tends to open up potential pathways between the hypertensive and decompressed circuits, making permanent separation difficult to obtain. Probably the delay in the onset of encephalopathy makes the Warren shunt worthwhile, though it is not an operation to be taken lightly by the occasional shunt surgeon.

The left gastric vena canal shunt may be more truly selective, but it is unlikely to be generally adopted since it is not only more difficult to perform, but it is technically impossible in 10 per cent of patients, and carries a 10 per cent thrombosis rate (Inokuchi et al, 1975).

Over the years, there has been a tendency for individual units involved in the management of bleeding varices to follow the currently popular line of treatmnt for virtually all patients. Perhaps a more wide range of the whole range of methods is desirable, selecting the best procedure for each individual patient on the basis of what limited knowledge we have. I agree with Dean Warren that 'a surgeon who does the same operation for every patient with portal hypertension does not perform optimally, no matter which operation he chooses' (Warren, 1975).

## SUMMARY

Bleeding oesophageal varices present the clinician with one of his most difficult problems in diagnosis and therapy. The need for a flexible approach in the management of individual patients is stressed. After diagnosis and initial control of bleeding, it is suggested that on the basis of clinical judgment, patients should be allocated to one of four treatment groups, namely rejection, injection, transection or selection.

## ACKNOWLEDGEMENTS

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# THE BELFAST EXPERIMENT IN DIRECT ACCESS TO CONTRAST RADIOGRAPHY

by

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The general practitioner working in his consulting room or his patient's home has a strictly limited range of diagnostic facilities available to supplement his clinical skills and experience. As long ago as 1946 the Annual Representative Meeting of the British Medical Association recommended that wherever possible, hospital departments of pathology and radiology should give direct access facilities to general practitioners. In spite of this, the 'open door' department has been slow to materialise.

In 1968 Anderson wrote: 'The start of the National Health Service in Britain coincided with a distinct hardening of the lines of demarcation between general practitioners who worked outside the hospitals, and the consultants, registrars and housemen who worked inside the hospitals. One of the manifestations of this was that access to laboratory and radiological facilities tended to be regarded as perquisites of the hospital doctors. Some general practitioners had open access to X-ray equipment at cottage hospitals, but most were obliged to refer patients to hospital out-patients clinics (or to casualty departments in emergencies). A hospital doctor then decided whether an X-ray examination was necessary and, if so, what particular examination should be carried out'. Many reasons were advanced for the failure to make progress over the years, the most often quoted being shortage of space, equipment and staff in the various departments and a fear of being inundated by a flood of unnecessary or inappropriate investigations.

There were, however, notable exceptions to the general pattern and several hospitals were pioneers in extending these facilities to family doctors. In October 1962, the Radiology Department of the Royal Infirmary, Dundee, offered direct access facilities to neighbouring general practitioners, and in January 1964 Hammersmith Hospital initiated a restricted service. In September 1964, Guy's Hospital introduced a limited service to 'practitioners believed to be interested'. In the following month, the diagnostic X-ray department of the Middlesex Hospital notified two hundred doctors in the area that they were offering direct access facilities for X-rays of the chest, skeleton and paranasal sinuses. Within a year this service was extended to include all investigations suitable for out-patients with the exception of barium enemas, as it was felt that adequate preparation of the patient might prove a difficulty. In 1966 facilities became available at King Edward VII Hospital, Windsor.

It was not until the end of 1972 that Belfast was to attempt a pilot scheme on these lines. At that time there was in existence a number of 'teaching practices' established by the Northern Ireland Council for Post-Graduate Medical Education for the purpose of vocational training in general practice. Arrangements were made between the Council and the Department of Radiology of the Royal

Victoria Hospital, and a series of familiarisation meetings was held. Dr. E. M. McIlrath, Consultant Radiologist at the department, discussed the various indications and precautions, and the necessary administrative details were agreed. The department offered initial facilities for carrying out ten barium meals, ten cholecystograms and five intravenous pyelograms per week. Normally reports were to be sent back to the referring doctor, but the radiologist reserved the right to intervene and refer a patient directly for consultant opinion if the X-ray appearances warranted.

This paper reviews the work which has been carried out during the three years since the scheme became operative. I hope to show how much the service has been used, how many of the examinations have proved positive, and what general conclusions may be reasonably drawn.

## RESULTS

Table 1 shows the number of examinations carried out each month from 1973 to 1975. There were 56 examinations in the first year and 88 in the second year, a considerable increase, suggesting that the scheme was proving popular

TABLE 1: NUMBER OF INVESTIGATIONS CARRIED OUT EACH MONTH

| | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1973 | 3 | 1 | 8 | 2 | 6 | 6 | 6 | 2 | 7 | 5 | 3 | 7 | = | 56 |
| 1974 | 8 | 11 | 14 | 8 | 8 | 4 | 0 | 5 | 5 | 4 | 16 | 5 | = | 88 |
| 1975 | 6 | 2 | 9 | 10 | 5 | 4 | 2 | 3 | 10 | 3 | 9 | 5 | = | 68 |

and useful. Unfortunately, the total for the third year dropped to 68, implying that factors were at work rendering the service less acceptable. I believe the principal factor was the civil unrest and violence in Belfast and the fact that the Royal Victoria Hospital is sited in an area of the city which is considered unsafe by some members of the public.

Table 2 shows the type of investigation requested. These consisted of 117 barium meals, 56 per cent of the total. There were 56 cholecystograms (27 per

TABLE 2: RADIOLOGICAL INVESTIGATION REQUESTED

| | | |
|---|---|---|
| Barium meal | 117 | (56 per cent) |
| Cholecystogram | 56 | (27 per cent) |
| Intravenous pyelogram | 37 | (17 per cent) |
| Total | 210 | |

cent) and 37 intravenous pyelograms (17 per cent). In addition, there were a small number of barium enemas, X-rays of the chest and spine carried out when requested, even though these investigations had not been offered to the participating doctors at the inception of the scheme.

Table 3 shows the incidence of radiological abnormalities or positive findings. Of 117 barium meals 75 were abnormal, an incidence or 'strike rate' of 64 per cent. Of 56 cholecystograms there were 19 positive (34 per cent) and there were 13 positive out of 37 intravenous pyelograms (35 per cent).

TABLE 3: INCIDENCE OF ABNORMAL X-RAY FINDINGS ("POSITIVE")

| | *Number of investigations* | *Positive findings* | *per cent* |
|---|---|---|---|
| Barium meal | 117 | 75 | 64 |
| Cholecystogram | 56 | 19 | 34 |
| Intravenous pyelogram | 37 | 13 | 35 |
| Total | 210 | 107 | 50.9 |

Table 4 is a comparison of results of the Belfast practitioners with those of other hospital centres and our RVH consultant colleagues. The positive strike rate for barium meals and cholecystograms is marginally higher in the case of the teaching practices than in any other group. That for IVP's is appreciably less than the RVH consultants and the Royal Infirmary, Dundee, but comparable with the figures from the Middlesex Hospital, and the Student Health Service at Queen's University, Belfast.

TABLE 4: COMPARISON OF BELFAST RESULTS WITH OTHER GROUPS

(per cent)

| | *Belfast teaching practices* | *RVH consultants* | *Royal Infirmary Dundee** | *Middlesex Hospital** | *Student Health Service, QUB* |
|---|---|---|---|---|---|
| Barium meal | 64 | 54–60 | 60 | 44 | 62 |
| Cholecystogram | 34 | – | 30 | 19 | – |
| Intravenous pyelogram | 35 | 46 | 48 | 23 | 33 |

* G.P. referrals

Table 5 shows the additional work undertaken in the Radiology Department as a result of this scheme. It can be seen that GP referrals formed approximately 1 per cent of the three investigations carried out in the department during the period under review.

TABLE 5: ADDITIONAL WORK UNDERTAKEN IN THE RADIOLOGY DEPARTMENT R.V.H. DURING ACCESS BY TEACHING PRACTICES 1973-1975

| | *Total hospital tests (approximately)* | *From GP's* | *Per cent of G.P* referrals of total *work load* |
|---|---|---|---|
| Barium meal | 15,000 | 117 | <1 |
| Cholecystogram | 5,000 | 56 | >1 |
| Intravenous pyelogram | 5,000 | 37 | <1 |

## DISCUSSION

In 1966 Cook reviewed the first year of the 'open door' X-ray facility at the Middlesex Hospital and wrote 'There can be no doubt that the open access policy is right in principle. The quality of the requests, the incidence of positive findings and the rapidly increasing demand all point to this'. Similarly, Anderson (1968) when describing the first three years of the experiment in open access at Guy's Hospital found that general practitioners are no less discriminating in their referrals (as judged by positive results) than the consultant staff in the out-patient departments.

Steiner (1965) reviewed the first ten months of the service offered by Hammersmith Hospital. He wrote, in a refreshing spirit of camaraderie: 'We have tried to develop a system which in a small measure should be of help to our general practitioner colleagues within the area of the hospital'. His conclusion read as follows: 'There is no doubt that open access for general practitioners to hospital X-ray departments is a step in the right direction. With time the service will probably expand and co-operation between the hospital diagnostic service and general practitioners will improve. In many cases the service avoids delay. When patients are sent to out-patients for consultation, some of the necessary X-ray examinations have already been carried out. In some instances, the management of the patient is left entirely to the practitioner, and hospital referrals are not necessary'. It is my own opinion that a further bonus would accrue in that by freeing the consultants from many routine and repetitive investigations they would have more time for the elucidation and management of more obscure problems.

The figures given indicate that the pilot scheme in Belfast has produced results comparable with those from other centres, and therefore that their conclusions are just as valid here. I would hope that the facilities could be extended and expanded in the direction of other hospitals, for example, the City Hospital, the Mater Hospital and the Ulster Hospital, and I am confident that they would be used intelligently and with discrimination. Perhaps the most telling argument in support of this goal is the fact that the vocational training schemes for general practice will produce doctors who for two of their three years in training will have access to all investigative procedures in hospital. Dare we then deny them these facilities once they take their place in the primary care team?

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# SOURCES OF HLA TYPING SERA

by

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## INTRODUCTION

Antibodies to antigens of the HLA system are formed by a proportion of women during a pregnancy and sometimes after blood transfusion. The gestational antibodies are of no significance to the pregnancy and in most cases they are thought to disappear from the serum a few weeks after termination of the pregnancy. They are, however, of great value as HLA typing reagents and most tissue typing laboratories (including our own) rely heavily on pregnancy sera as their source of HLA antisera. Blood samples from many mothers during their pregnancies are sent to the Northern Ireland Blood Transfusion Service for red cell antibody screening and aliquots of these sera are also examined for HLA antibodies. When a serum is found to contain a monospecific antibody of potential value for tissue typing, the patient and/or her family doctor are contacted and arrangements are made to take a further 50 ml sample of blood. This serum is sufficient for our own needs but in order to facilitate the interchange of sera with other laboratories both in the United Kingdom and abroad larger volumes of sera are necessary. It is inappropriate to ask for a full standard donation of blood from a mother a short time before or after the end of a pregnancy. Large volumes of serum can be obtained by plasmapheresis, a procedure which entails no loss of red cells by the patient, but because of the time involved it is often inconvenient for the mother of a new baby to attend hospital (or the transfusion service building) to give plasma by this means.

We have therefore considered a different approach for obtaining large volume supplies of HLA typing sera. In some women, HLA antibodies may persist for years after pregnancy (Tongio, Berrebi and Mayer, 1973) and therefore a proportion of female blood donors might be expected to have these persistent and stable antibodies. It would not be difficult to obtain 'dry bottle' donations from selected regular blood donors at their next visit to the transfusion centre.

With a view to obtaining HLA typing sera in this way we screened blood samples from a group of female blood donors. This paper reports our findings.

## MATERIALS AND METHODS

Blood samples (2 ml) were obtained from 7,230 female blood donors for HLA antibody screening. To simplify administrative procedures no attempt was made

to select married woman donors who had been pregnant. The sera were separated and stored at –20°C for up to three weeks before screening against panels of lymphocytes selected to include all the known HLA-A and -B locus antigens. A standard two-stage microcytotoxicity test at 22°C was used throughout.

Sera showing HLA activity were, if necessary, further tested to identify monospecific antibodies. A simple questionnaire was sent to the blood donors found to have antibodies. In it we asked whether or not they had ever had a blood transfusion and/or pregnancy and if so, the dates thereof.

## RESULTS

Table 1 summarises our findings in the blood donors and compares them with the results of routine screening of ante-natal sera. Of 220 pregnancy/transfusion questionnaires issued 172 (78 per cent) were returned. The answers are summarised in Tables 2 and 3.

TABLE 1: HLA ANTIBODIES PRESENT IN SERA FROM BLOOD DONORS AND ANTE-NATAL SAMPLES

| | *Blood donors* | *Ante-natal* |
|---|---|---|
| No. of samples tested | 7230 | 4756 |
| No. with HLA antibody | 220 (3.04%) | 956 (20.1%) |
| No. with monospecific antibody | 25 (0.35%) | 44 (0.93%) |

TABLE 2: SUMMARY OF REPLIES TO PREGNANCY/TRANSFUSION QUESTIONNAIRE

| *History of Blood Transfusion* | *History of Pregnancy* | | |
|---|---|---|---|
| | *Yes* | *No* | |
| YES | 34 | 0 | |
| NO | 120 | 18 | |
| | 154 | 18 | 172 |

TABLE 3: INTERVAL SINCE LAST IMMUNISING STIMULUS

| *Years* | *Pregnancy Alone* | *Pregnancy and Transfusion* |
|---|---|---|
| 10+ | 31 | 8 |
| 5-10 | 25 | 10 |
| 2-5 | 41 | 8 |
| 0-2 | 13 | 7 |
| Pregnant at time of sample | 3 | 0 |
| Reply unclear | 7 | 1 |

## DISCUSSION

The proportion of blood donors with HLA antibodies was, as expected, much smaller than the proportion of ante-natal sera with anti HLA activity (3.04 per cent as compared with 20.1 per cent). The yield might have been improved if we had selected only blood donors who had been pregnant; our figures might then have approached those of Rodey, Anderson and Aster, (1976) who found HLA antibodies in 18.7 per cent of non-pregnant multiparae with a history of four or more pregnancies.

The replies to our questionnaire indicated clearly that transfusion alone is not a common stimulus to the production of persistent antibodies; and almost 90 per cent of the blood donors with antibodies had been pregnant at some time. Their antibodies are remarkably long lived: 74 of 154 women with antibodies (48.1 per cent) had not been pregnant nor had transfusion for 5 or more years. In Rodey's (1976) series the corresponding figure was 64 per cent, presumably due to the greater (4 or more) parity of his donors.

We define an antibody to be potentially valuable for tissue typing if it is adequately avid and if it appears to be monospecific. Ante-natal sera often contain multispecific antibodies and only a small proportion (44 of 956 = 4.6 per cent) are potential tissue typing sera. On the other hand, antibody containing sera from blood donors yield a much higher proportion of "clean" HLA antibodies (25 of 220 = 11.36 per cent) probably because the weaker and cross reacting antibodies have declined in activity to undetectable levels.

Our finding of HLA antibodies in a significant number of female blood donors confirms the possibility of obtaining HLA typing sera from this source. The vast majority of donors give blood regularly and it is a simple administrative matter to arrange for the taking of "dry bottle" donations from specially identified donors. As an alternative plasmapheresis could be considered although this would often entail a special visit to the transfusion centre and we feel it important to avoid, as far as possible, interference with the routines of blood donation and collection. In order to reduce unproductive screening of negative sera, multiparous donors could be chosen for testing and we feel that this particular group represents a viable alternative to pregnant mothers as a source of typing sera, especially for HLA laboratories located within transfusion centres.

We would like to thank Col. T. E. Field and Mr. K. McLaughlin of the Northern Ireland Blood Transfusion Service for obtaining the blood donor samples. One of us (J.M.) is in receipt of a grant from the Northern Ireland Kidney Research Fund.

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# DRUG OVERDOSAGE: A STUDY AT THE ACCIDENT AND EMERGENCY DEPARTMENT OF THE ROYAL VICTORIA HOSPITAL, BELFAST

by

**DIANA S. M. HADDEN**

Reports from various centres have shown that drug overdose is an increasing medical problem (Ghodse, 1977, Holding et al 1977). The number of patients presenting at the Casualty Department of the Royal Victoria Hospital with drug overdose has been recorded over the past four years for the information of the Northern Ireland Liaison Committee on the Misuse of Drugs. The present paper records this information and compares the experience of the hospital with published records from London and Edinburgh.

## PATIENTS AND METHODS

The records of all patients recorded by the medical staff as 'overdose' or poisoning in the Accident and Emergency Register at the Royal Victoria Hospital, Belfast from 1973 to 1976 were personally studied by the author. Any records not fitting the diagnosis were discarded. Information on age, sex, drug taken, drug combination or combination with alcohol was obtained retrospectively from the patients' accident and emergency notes. An attempt was also made to determine the proportion of patients who had taken a previous drug overdose, and to evaluate the motive for the overdose; these figures were less reliable as only the information recorded could be analysed.

## RESULTS

The number of overdoses each year has increased over the period under review (Table 1). The monthly figures were also determined but no definite pattern throughout the year could be ascertained. The annual number of new attendances

TABLE I

Numbers (percentage in brackets) of male and female patients with drug overdose and total new attendance at Accident and Casualty Department.

| | *TOTAL* | *Males* | *Females* | *Sex Unknown* | *Ratio F: M* | *Total New Attendance* |
|---|---|---|---|---|---|---|
| 1973 | 385 | 128 (33.3) | 247 (64.2) | 10 | 1.93 | 43,716 |
| 1974 | 428 | 153 (35.8) | 257 (60.0) | 18 | 1.68 | 43,090 |
| 1975 | 464 | 156 (33.6) | 300 (64.7) | 8 | 1.92 | 42,858 |
| 1976 | 459 | 173 (37.7) | 278 (60.6) | 8 | 1.61 | 41,938 |

at the Accident and Emergency Department remained approximately the same. The overall female: male ratio can be seen to remain approximately the same throughout the four years. The monthly numbers of females and males showed no definate pattern of variation, nor was there any definite pattern in sex ratio in different age groups. In general females were approximately 60 per cent of the total.

The number of overdoses occuring in each decade has been reviewed. Patients under the age of 13 are not seen at this Department. The number of overdoses increased very rapidly from the 13-15 age group to a high level in the 15-19 age group. The first three years of the survey showed a peak incidence in this 15-19 group whereas the fourth year (1976) showed a peak in the 20-24 age group. The fall away from the peak was fairly steady in all years, reaching very low levels in the sixth decade.

The drugs taken were classified into 5 groups (Table II). Group 1, the antidepressants, forms a small percentage but this has doubled over the period. Group 2, the non-barbituate tranquilliser/hypnotics (in particular the benzodiazapine compounds) forms the major section of the drugs taken as overdoses.

TABLE II

TYPES OF DRUGS TAKEN IN OVERDOSAGE

The percentage figures in brackets are percentage values of that drug out of the total number of known drugs taken in that year. They are not percentages of patients taking that drug. The figures were calculated in this way because of the large number of patients who took more than one drug in their overdose.

| | 1973 | 1974 | 1975 | 1976 |
|---|---|---|---|---|
| 1. Antidepressants | 20 (4.8) | 40 (9.2) | 45 (8.9) | 44 (7.7) |
| 2. Non-barbiturate Major and Minor tranquililser/hypnotics | 189 (45.5) | 211 (48.6) | 290 (56.2) | 283 (49.8) |
| 3. Barbiturates | 64 (15.4) | 52 (12.0) | 41 (8.1) | 51 (8.9) |
| 4. Analgesics | 58 (13.9) | 48 (11.1) | 62 (12.3) | 88 (17.9) |
| 5. Miscellaneous | 84 (20.2) | 83 (19.1) | 69 (13.8) | 104 (18.3) |
| Total Known drugs | 415 (100) | 434 (100) | 507 (100) | 570 (100) |

The benzodiazapines expressed as percentages of the total, totalled 40.2 in 1973, 42.4 in 1974, 50.1 in 1975 and 45.3 in 1976. They have therefore remained fairly constant over the four year period. Group 3, the barbiturates, shows conversely a decrease over the period, falling from 15.4 per cent in 1973 to 8.9 per cent in 1976. Group 4, the analgesics, have increased over the four years. When the analgesics were analysed it was found that salicylates had decreased from 5.5 per cent (1973) to 4.7 per cent (1976), paracetamol had remained approximately the same at 3.4 per cent in 1973 and 3.0 per cent in 1976, but dextropropoxyphene

and paracetamol in combination (Distalgesic) had increased markedly from 0.7 per cent in 1973 to 5.0 per cent in 1976. Miscellaneous drugs and substances remained approximately the same at 20.2 per cent (1973) and 18.3 per cent (1976).

The number of patients who took a combination of drugs or a combination of drug(s) with alcohol was calculated from the total number of patient overdoses in each year (Table III). Both types of combination overdoses have

TABLE III

DRUG/ALCOHOL COMBINATIONS

| | 1973 | 1974 | 1975 | 1976 |
|---|---|---|---|---|
| Total | 385 | 428 | 464 | 459 |
| Drug combination | 70 (18.0) | 72 (17.0) | 89 (19.0) | 120 (26.0) |
| Combination with alcohol | 78 (20.0) | 91 (21.0) | 154 (33.0) | 151 (33.0) |

increased. The drug combinations have increased by approximately one half from 1973 to 1976 but overdoses taken in conjunction with alcohol have increased even more from 20.0 per cent in 1973 to 33.0 per cent in 1976.

Some estimation of the number of patients who had taken a previous overdose was attempted. From 1973 to 1975 this varied from 5 to 10 per cent: in 1976 it was 14 per cent.

An attempt was also made to classify the overdoses into (a) suicidal, (b) accidental or (c) those which were intentional but which did not intend suicide. The percentage in the intended suicidal group were 6.0 in 1973, 6.0 in 1974, 9.0 in 1975, 12.0 in 1976. Accidental overdose percentages were 2.0 in 1973, 1.0 in 1974, 2.0 in 1975 and 4.0 in 1976. The figures may be inaccurate: the groups tend to overlap and the patients tend to be confused in their motives. Drug abuse with narcotic drugs was a very small group, approximately 1-2 per cent. Therefore more than 90 per cent of the patients analysed in this study would fall into the third group.

## 'DISPOSAL' OF PATIENTS FROM ACCIDENT AND EMERGENCY UNIT

The majority of 'overdose' patients are admitted to the observation word. This indicates the probability of discharge from hospital the next day. However, should the patient's condition necessitate it the patient may be admitted to a general medical ward or psychiatric ward the next day. Table IV only shows disposal from the Accident and Emergency Department and does not indicate subsequent disposal of the patient from the observation ward.

The number of patients admitted to the observation ward rose from 173 (44.9 per cent) in 1973 to 262 (57.1 per cent) in 1976, whereas the number of patients going home (a small number, approximately two per month, leave without consent) fell from 71 (18.4 per cent) in 1973 to 59 (12.9 per cent) in 1976.

TABLE IV

Initial disposal (during the first twenty four hours) of Overdose Patients presenting at the Accident and Emergency Unit.

Numbers involved in brackets are percentages)

| DISPOSAL | 1973 | 1974 | 1975 | 1976 |
|---|---|---|---|---|
| Home | 71 (18.4) | 49 (11.5) | 58 (12.5) | 59 (12.9) |
| Observation Ward | 173 (44.9) | 178 (41.6) | 214 (45.3) | 262 (57.1) |
| Medical Ward | 104 (27.0) | 136 (31.8) | 145 (31.6) | 103 (22.4) |
| Psychiatric Unit | 5 (1.3) | 14 (3.3) | 15 (3.2) | 5 (1.1) |
| Intensive Care Unit | 15 (3.9) | 32 (7.8) | 19 (4.1) | 20 (4.4) |
| Unknown | 16 (4.2) | 20 (4.7) | 12 (2.6) | 10 (2.2) |
| Died in Accident and Emergency Unit | 1 (0.26) | — | 1 (0.2) | — |
| TOTAL | 385 | 429 | 464 | 459 |

Patients admitted to a medical ward or Psychiatric unit increased from 1973 to 1974 and thereafter fell to reach a level below the 1973 level in 1976. The patients admitted to intensive care increased sharply from 1973 to 1974 (3.9 per cent to 7.8 per cent) but, although the numbers did fall the figure in 1976 is maintained at 4.4 per cent. 'Intensive Care' includes respiratory intensive care for depressed respiration, cardiac monitoring for possible dysrhythmias (for example in tricyclic antidepressant overdose), or specialised care in a renal unit (for example in paraquat poisoning). The number of deaths indicates only the number dying actually in the Accident and Emergency Department.

## DISCUSSION

Overdoses are common in the Casualty Department and becoming slightly more common. The figures approximate 1.25 per day in 1976 with an average female: male (F: M) ratio of 1.8: 1 These results support findings of other workers in Belfast (Lyons and Bindal, 1977) in that the majority of patients who take overdoses are young women. The greater female: male ratios tended to be in the younger age groups. Previous studies have shown an even higher proportion of female patients and Ghodse (1977) showed a F: M ratio of 2.2: 1 in London.

The peak age of overdoses was in the 15-19 group in 1973, 1974 and 1975 and in the 20-24 group in 1976. This confirms other studies which show a peak in the younger age group although the 15-19 years peak is younger than most. Although the number of overdoses has increased the number of patients actually intending suicide remains low. Recorded suicides inNorthern Ireland were reduced by half from 1964 to 1970 (Lyons, H.A., 1972).

The commonest type of drug taken in overdose in Belfast remains the minor non-barbiturate tranquillizer or hypnotic, the main group being the benzodiazepines. Barbituates and salicylates have fallen, paracetamol maintains a low percentage, while "Distalgesic" has increased markedly in incidence.

Drugs taken as overdoses are those which are available. Hypnotics are commonly prescribed and are therefore easily available. Elmes et al, (1976) found an increase in the prescribing of hypnotics in Northern Ireland from 30 daily doses per 1000 persons on doctors' lists per day in 1966 to 44.3 daily doses per day in 1974. Despite this there was a reduction in the prescribing of barbituates from 80 to 45 per cent of all hypnotic prescribing. This decrease in availability barbiturates has undoubtedly been the cause of the reduction of incidence of barbiturates overdosing.

Both drug combinations and combinations of drug (or drugs) with alcohol have increased greatly in frequency over the four year period. Drug combinations increased from 18 to 26 per cent, but drug and alcohol combinations increased from 20 to 33 per cent. The reasons for this may be that more alcohol is being consumed by the population in general, and more is being consumed by the younger age groups. In 1973 the average weekly household expenditure on alcohol was £1.22 (beer 67p, wines/spirits 38p, not defined 17p) and in 1974 £1.93p (beer 83p wines/spirits 55p, not defined 54p). This was a 58 per cent overall increase in expenditure. The price of beer in 1973 was 14.5 per bottle and in 1974 18.0p per bottle (24 per cent increase). Spirits ($\frac{1}{2}$ glass) cost 22p in 1973 and 24p in 1974 (9 per cent increase). The overall increase in the price of alcoholic drinks during this period was thus 15 per cent. The increase in expenditure is therefore greatly in excess of the increase in prices and must reflect a true increase in alcoholic consumption per household. One cause of increased consumption may be the fact that the price of alcoholic beverages relative to other food has decreased recently. It has been estimated that the number of minutes work required for a male manual worker to pay for a large loaf ($1\frac{3}{4}$ pounds), 1 pint of beer and a bottle of whiskey have changed from 9, 23 and 659 respectively in 1950 to 11, 12 and 209 in 1976 (Spring and Buss, 1977). Increased alcoholic consumption may be reflected in the driving offences involving alcohol or drugs and these have increased steadily, 980 in Northern Ireland in 1974, 1210 in 1975 (personal communication from Dr. R. B. Irwin).

If there is an increase in alcoholic consumption in the population as a whole, there will be an increase in the younger age group. But there has probably been a relatively greater increase in the consumption of alcohol in the younger age groups. Advertising is aimed more and more at this age group, which is more susceptible to pressures both from advertising and social popularity. The same type of individual tends to abuse alcohol and drugs. Alcohol is itself a drug and the same effect can be had from both sources, individually or in combination.

## SUMMARY

Drug overdoses seen at the Accident and Emergency Department, Royal Victoria Hospital during the years 1973-1976 were analysed. The total number of overdoses increased from 385 in 1973 to 459 in 1976, the ratio of females to males being approximately 2: 1 and the peak incidence being in the 15-24 age range. The drugs taken were mainly tranquilliser/hypnotics, with benzodiazapines being by far the most common. A fall in incidence of barbiturate overdosage was noted but a rise in overdosage by dextropropoxyphene with paracetamol (Distalgesic). Drug combinations increased from 18 per cent to 26 per cent over the four years, and combinations with alcohol increased even more from 20 per cent to 33 per cent. Disposal of patients from the accident and emergency department was analysed.

### ACKNOWLEDGEMENTS

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# HLA ANTIGEN FREQUENCY OF NORTHERN IRELAND BLOOD DONORS

by

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HISTOCOMPATIBILITY (HLA) typing is primarily used to match kidney donors with awaiting recipients. However many studies have been carried out to determine the frequency of the HLA antigens in various diseases.

In this laboratory we have been requested to carry out such studies in several diseases, e.g. diabetes, ankylosing spondylitis, farmer's lung, Plummer-Vinson stricture and flax byssinosis. In order to compare the antigen frequencies in these diseases with those of a normal healthy population we decided to type 200 blood donors. Obviously there are drawbacks to using blood donors as controls as their health is better than average and their age is not of either extreme. However, using blood donors provides a simple way to obtain the blood sample required for our testing and also gives a cross-section of social status within the population. One interesting and very important offshoot of this study is that we have 200 tissue-typed blood donors who could, if the need occurred, be used for platelet transfusion if their type was identical to that of a patient requiring platelets.

## MATERIALS AND METHODS

Two hundred blood donors (125 male, 75 female) born in Northern Ireland were tissue typed for HLA–A and –B locus antigens. The number of blood donors from each county was proportional to the total population of that county. An extra 10 ml of blood from suitable donors was taken at the donor sessions into sodium citrate. The blood donors were typed within one day of bleeding.

A total of 72 Sera defining the following specificities were used:
HLA – A1, A2, A3, A9, A10, A11, A28, A29
HLA – B5, B7, B8, B12, B13, B14, B15, B17, B18, BW22, B27, BW35, B.40.
The sera were either supplied by the National Tissue Typing Reference Laboratory, Bristol, or were sera from our own laboratory which have been tested for their activity both here and in Bristol. Typing was by a two stage

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microlymphocytotoxicity test at 22°C (Nelson and Middleton 1975) and at least 3 sera were used to define each specificity.

The antigen frequency of the Northern Ireland blood donors was compared with the antigen frequency in 1,036 blood donors from Bristol, in 342 blood donors from Glasgow and in 453 blood donors from Eire using a Yates' corrected chi-squared analysis, with a correction for the number of antigens tested (Grumet et al, 1971).

The gene frequency of each of the antigens in the Northern Ireland blood donors was calculated using the formula $p=1-$ (sq. rt.) $1-f$ where p denotes the gene frequency and f the frequency of the corresponding antigen.

The tissue types of the Northern Ireland blood donors were analysed to find out if there were any differences in the antigen frequency due to sex, age or place of birth. In the latter analysis only blood donors born in Co. Down ($n=43$), Co. Antrim ($n=48$) and Belfast ($n=42$) were considered, as the number of blood donors born in Counties Derry, Tyrone, Armagh and Fermanagh were considered too small for statistical analysis. For the purpose of assessing the effect of age on HLA antigen frequency we divided the blood donors into two groups, 119 aged 16-35 and 81 aged 36-65.

## RESULTS

Table 1 shows the frequency of HLA antigens in blood donors from Northern Ireland compared with the antigen frequency in blood donors from Bristol, Glasgow and Eire. Statistical differences at the 5 per cent level were found in the following antigens HLA – A1,-B7,-B8,-B14 and -B18 with Bristol, -A11 with Glasgow and -B12 with Dublin. Only one difference, HLA -B14 in the comparison with Bristol blood donors, is still significant after multiplying the initial P value by a factor off 21, the number of comparisons made between the two populations.

TABLE 1

*Frequency of HLA antigens in blood donors from Northern Ireland, Bristol, Glagow and Eire*

| HLA Antigen | N. Ireland Bl. Donors (n=200) | | Bristol Bl. Donors (n=1036) | | Glasgow Bl. Donors (n=342) | | Eire Bl. Donors (n=453) | |
|---|---|---|---|---|---|---|---|---|
| | No | % | No | % | No | % | No | % |
| 1 | 86 | 43 | 348 | 33.6[a] | 138 | 40.4 | 210 | 46.4 |
| 2 | 91 | 45.5 | 536 | 51.7 | 163 | 47.7 | 217 | 47.9 |
| 3 | 53 | 26.5 | 265 | 25.6 | 78 | 22.8 | 97 | 21.4 |
| 9 | 31 | 15.5 | 190 | 18.3 | 60 | 17.5 | 61 | 13.5 |
| 10 | 20 | 10 | 87 | 8.4 | 21 | 6.1 | 35 | 7.7 |
| 11 | 28 | 14 | 106 | 10.2 | 26 | 7.6[f] | 55 | 12.1 |
| 28 | 10 | 5 | 38 | 3.7 | 31 | 9.1 | 34 | 7.5 |
| 29 | 16 | 8 | 78 | 7.5 | 16 | 4.7 | 41 | 9.1 |
| 5 | 13 | 6.5 | 87 | 8.4 | 21 | 6.1 | 26 | 5.7 |
| 7 | 67 | 33.5 | 265 | 25.6[b] | 93 | 27.2 | 124 | 27.4 |
| 8 | 69 | 34.5 | 260 | 25.1[c] | 105 | 30.7 | 156 | 34.4 |
| 12 | 54 | 27 | 254 | 23.7 | 114 | 33.3 | 163 | 36 [g] |
| 13 | 5 | 2.5 | 45 | 4.3 | 15 | 4.4 | 9 | 2 |
| 14 | 30 | 15 | 72 | 7 [d] | 34 | 9.9 | 47 | 10.4 |
| 15 | 9 | 4.5 | 50 | 4.8 | 29 | 8.5 | 31 | 6.8 |
| 17 | 18 | 9 | 79 | 7.6 | 26 | 7.6 | 46 | 10.2 |
| 18 | 16 | 8 | 35 | 3.4[e] | 19 | 5.6 | 34 | 7.5 |
| 22 | 8 | 4 | 55 | 5.3 | 13 | 3.8 | 16 | 3.5 |
| 27 | 11 | 5.5 | 77 | 7.4 | 27 | 7.9 | 26 | 5.7 |
| 35 | 16 | 8 | 114 | 11 | 29 | 8.5 | 54 | 11.9 |
| 40 | 20 | 10 | 116 | 11.2 | 30 | 8.8 | 39 | 8.6 |

Listed below are the chi-squared values greater than 4 when the HLA antigen frequency of Northern Ireland donors is compared with that of Bristol, Glasgow and Eire. P values in brackets have been corrected for the number of antigen frequencies compared.

a. $chi^2 = 6.108$ $p = 0.0129$ (0.27)
b. $chi^2 = 4.958$ $p = 0.0246$ (0.516)
c. $chi^2 = 7.115$ $p = 0.0075$ (0.158)
d. $chi^2 = 13.305$ $p = 0.0004$ (0.0084)
e. $chi^2 = 7.921$ $p = 0.0050$ (0.105)
f. $chi^2 = 5.067$ $p = 0.0231$ (0.485)
g. $chi^2 = 4.648$ $p = 0.0294$ (0.617)

In Table 2, which shows the gene frequencies of HLA antigens in Northern Ireland blood donors, $X_1$ and $X_2$ indicate the gene frequencies of antigens which we have not been able to detect.

No significant difference in antigen frequency was found between male and female donors. The frequency of HLA -A10 differs significantly with the age of donor. Seventeen blood donors (14.3 per cent) aged 16-35 were HLA -A10

TABLE 2

*Gene frequencies of HLA antigens in* 200 *Northern Ireland Blood donors*

| *HLA Antigen* | *Gene frequency* |
|---|---|
| A1 | .2450 |
| A2 | .2618 |
| A3 | .1427 |
| A9 | .0808 |
| A10 | .0513 |
| A11 | .0726 |
| A28 | .0253 |
| A29 | .0408 |
| $X_1$ | 0.797 |
| | 1.0000 |
| B5 | .0330 |
| B7 | .1845 |
| B8 | .1907 |
| B12 | .1456 |
| B13 | .0126 |
| B14 | .0780 |
| B15 | .0228 |
| B17 | .0461 |
| B18 | .0408 |
| BW22 | .0202 |
| B27 | .0279 |
| BW35 | .0408 |
| B40 | .0513 |
| $X_2$ | .1057 |
| | 1.0000 |

positive compared to three blood donors (3.7 per cent) aged 36-65 ($p=0.0257$). There were seven blood donors from Co. Antrim (14.6 per cent) who were HLA -A10 positive whereas all of the Belfast donors were HA -A10 negative ($p=0.0275$). However these differences are no longer significant after correction for the number of comparisons made. Detailed tables of the analysis of the Northern Ireland blood donors on the basis of place of birth, age and sex are available from the authors.

## DISCUSSION

We have compared the frequency of 21 HLA antigens in Northern Ireland blood donors with that of blood donors from Bristol, Glasgow and Eire. In the latter two comparisons only one antigen frequency in each, HLA -A11 and -B12 respectively, was significant at the 5 per cent level. By definition, out of 20 comparisons, on the average, we would expect one of them to be significant at the 5 per cent level. When we multiplied the initial P value for the two significant comparisons by a factor of 21 (the number of camparisons made) we found that in neither case was it still significant. However in the comparison of HLA antigen frequency in donors from Northern Ireland with those of Bristol we found that five antigen frequencies HLA -A1,B7,-B8,-B14 and -B18 differed significantly. One of these, HLA -B14, was still significant after correction for the number of comparisons made. These differences are unlikely to be due to the sera which have been well defined both here and at the National Tissue Typing Reference Laboratory, Bristol. Our number of blood donors tested (200) is much smaller than the number tested in Bristol (1,036) and this could be one of the reasons for the difference in frequencies between the two centres.

Our finding that a blood donor population from Northern Ireland has a very similar HLA antigen frequency to a blood donor population from Glasgow and from Eire but varies significantly in five antigens from a Bristol blood donor

TABLE 3

*ABO distribution in blood donors from Northern Ireland, Bristol, Glasgow and Eire*

| *Area* | *Group O* | *Group A* | *Group B* | *Group AB* |
|---|---|---|---|---|
| N. Ireland* | 54.74 | 32.97 | 9.65 | 2.63 |
| Bristol* | 43.54 | 45.22 | 8.37 | 2.86 |
| Glasgow* | 53.08 | 32.90 | 10.87 | 3.15 |
| Eire† | 55.89 | 30.60 | 10.89 | 2.60 |

population, agrees with the ABO distribution of blood donors from these areas (see Table 3). Also, although the population of Northern Ireland at the moment is stable it is made up of two distinct origins – the Irish Gaelic and the Ulster Scot.

Our results show the necessity of using people born in Northern Ireland as a control group when examining the HLA antigen frequency of people with a particular disease. For example, to have used the Bristol blood donor HLA frequency as controls in our study on patients with a Plummer-Vinson stricture would have led us to believe that HLA -B8 was significantly more frequent in the patients than in the controls, whereas this is not the case when we use controls from Northern Ireland (Middleton et al. 1978).

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* Taken from Kopéc.

† Taken from Dawson.

We have compared the variation in HLA antigen frequency in two age groups. There are no significant differences after correction in the groups suggesting that although some HLA antigens are associated with disease these effects neutralise each other in the population. Previous findings have shown that older people have a larger number of HLA specificities than young people (Gerkin et al. 1974, Bender et al 1973). Like ourselves other recent studies have failed to confirm this (Albert et al. 1974, Murcurová et al. 1975). In our study the average number of HLA specificities per person below 36 was 3.387 and the average in the 36–65 age group was 3.309.

Requests to us for tissue typing relatives of prospective platelet recipients have recently increased. It is very difficult to obtain a full house match for these recipients from their relatives. Having a panel of potential platelet donors should make it easier to obtain a perfect match for these platelet recipients.

## SUMMARY

Histocompatibility (HLA) antigen testing of 200 normal donors was performed to provide a baseline for studies on the HLA antigen frequency of patients with diseases. The results were compared with similar results from Bristol, Eire and Glasgow. The Belfast HLA antigen frequencies closely resembled the results from Eire and Glasgow but showed marked differences from Bristol. This finding corresponds to ABO blood group distribution. Our tissue typed blood donors can now be used as platelet donors if required.

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# PSYCHOLOGICAL SCREENING FOR VASECTOMY

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## INTRODUCTION

THE operation of vasectomy has had a very chequered career. It was first carried out on a dog by Sir Astley Cooper in 1823 and he accurately described the effects. In 1899 Harrison carried out a vasectomy to relieve enlargement of the prostate and this indication continued for several years. It has been carried out since the beginning of this century to prevent epididymitis as a complication following prostatectomy. Sharp (1902) started to carry out large numbers of vasectomies to give relief from the 'habit of masturbation' and in 1909 the same enthusiastic doctor started doing eugenic vasectomies in 'defective individuals'. The eugenic movement grew and several of the States of America and some Western European countries passed legislation supporting compulsory sterilisation in certain conditions, and this practice reached major significance in the Nazi philosophy.

Another very dubious use of vasectomy in the early part of this century was for the purpose of rejuvenation and in the twenties and thirties hundreds of publications appeared from all parts of the world supporting this rejuvenation theory and these continued to appear until testosterone was isolated in 1935.

In the fifties and sixties vasectomies were carried out on a very large scale in India in an attempt to control population growth. This strategy by the Indian Government was one of the principal reasons for its downfall and mass vasectomies are no longer carried out in that country.

In the sixties contraceptive vasectomies were started in Western Europe and the U.S.A. The Simon Population Trust encouraged the procedure in England and favourably reported on the psychological and sexual effects of the operation. In 1972 vasectomy became available under the National Health Service. Prior to this date it was only carried out under the Health Service if there were medical indications.

The history of vasectomy is an unhappy one and guide lines must be developed to safeguard those who would later regret it. It will probably be replaced in the future by some more acceptable form of contraceptive, but in the meantime, it is important to exclude those men in whom vasectomy is unlikely to give a satisfactory long-term result.

Most of the papers dealing with the psychological aspects have concentrated on the post-operative effects. The Simon Trust (1969) found a very low incidence of psychological complications while Wolfers (1970) was rather more cautious and found 10 out of 82 respondents indicated some psychological problems arising from the operation and advised screening of applicants. Although reports concerning vasectomy have come from all over the world, none as yet has appeared from Ireland. The present paper is a prospective study of referrals to

a large district general hospital for vasectomy, with special emphasis on screening for unsuitable applicants.

This paper deals with the characteristics of those interviewed and the reasons why vasectomy was deferred or refused in some instances. A later report will deal with the post-vasectomy effects.

## Methodology:

The patients were referred by general practitioners and were interviewed at a large district general hospital. Some of the men came from outside the normal catchment area of this hospital as the surgeon involved was interested in doing vasectomies. The men were requested to bring their wives with them and this was done in all cases. The husband was interviewed first and the wife immediately afterwards. This method was used firstly in an attempt to ascertain the true state of the marital relationship and secondly the sexual activity and response of each partner. Thirdly it acted as a check on the accuracy of the information, and in particular to ascertain from the wife if her husband had any sexual problems. A fourth point was to ascertain if there was a discrepancy between the partners in their assessment of the frequency and enjoyment of intercourse. Only on a few occasions were the couple seen together, for example, if it was considered that vasectomy was contra-indicated, or if the author had a doubt that both partners wanted a permanent irreversible method of contraception. In cases where it was considered that vasectomy was contra-indicated the reason was usually explained to the couple, but under certain circumstances to only one partner. The general practitioner was notified of the decision and it was left to him to advise or arrange for alternative methods of contraception. It is possible that some may have sought and had vasectomy elsewhere. The surgeon then saw the couple together and briefly explained the operation and the post-operative routine. Generally the vasectomies were carried out under local anaesthetic as an out patient. The couples are presently being followed-up and the findings will be the subject of a further study.

At the interview by the psychiatrist a questionnaire dealing with social, marital, health, sex, contraception, and reason for decision was filled in. The time spent on each varied considerably and in those where there seemed to be some doubts, a considerably longer period of time was taken, and in some cases a second interview was arranged.

All couples were seen under the National Health Service.

## Results:

There were 286 couples interviewed. Two men did not wish to bring their wives and these two are not included in the study. All the couples were married; three of the men and two of the women had been married previously. The age range for the men was 23 years to 49 years (mean age 32.9 years). The age range for females was 22 years to 45 years (mean age 30.5 years).

The number of children was usually small, the range being from one child to nine children (mean 2.7 children), but only one couple had more than six children. The age of the youngest child ranged widely from the unborn child to a young adult of 24 years (the mean age of the youngest child was just under two years). Six women were pregnant when interviewed and, if this was the first or second pregnancy, vasectomy was postponed for approximately one year.

As regards Social Class, according to the Classification of the Registrar General, there were fewer in Social Group I and V compared to the population distribution (Social group I 3.5%; population 10%. Social Group V 6 %; population 22%). The couples were seen over the period 1973-1977 and it was found that the social group varied with time. In the first two years 25 per cent were in Social Group I and II while in the years 1976 and 1977 this figure had dropped to 16 per cent. The couples were very largely protestant, namely 97 per cent while the expected figure according to the Belfast census of 1971 would be 70 per cent.

The length of time the couple had been married varied widely from 5 years to 25 years. The average length of time married was 9.3 years. Enquiries were made from each partner concerning the marital relationship and specifically if there had been any episodes of violence, separations or infidelity. It was considered that the answers given were a considerable under-representation of marital problems. Only twelve couples admitted to serious marital difficulties and in half of these couples vasectomy was refused. One couple proceeded to have a major marital 'row' when informed that vasectomy was contra-indicated.

The commonest problem relating to the couples sexual relationships was a fear of further pregnancies in the wives interviewed. This problem was mentioned spontaneously by 154 (53 per cent) women, and in most of these women this fear caused a strong inhibition of the sexual activity. Detailed questioning about impotence and premature ejaculation only discovered twelve men with these problems, nine of whom were refused vasectomy. When the wife was interviewed she was asked specifically if her husband had any sexual problems and in five of these cases the information came from the wife.

As regards the frequency of sexual intercourse, there was a wide variation from 'never now' to 'daily'. The mean for males was between two and three times per week and the mean for females was three times per week. The wives tended to estimate rather higher frequencies than their husbands. For example, 37 per cent of men gave a frequency of three or more times per week, while 48 per cent of females estimated this frequency. To the question of enjoyment of sexual relationships most men gave a positive response but many of the women stated that a fear of further pregnancies spoilt their sexual life.

As regards the contraceptive used, the majority of couples used the pill or the condom. There were 138 women currently taking the pill of whom 112 were satisfied but had read or been advised about possible long-term effects. In the later part of 1976 more women were seen who had been on the pill for many years and were quite satisfied but had either read about the possibility

of long-term effects or had been advised by their general practitioner to stop the pill. Of the 148 patients who were not currently on the pill, 109 had been on it at some stage and had developed side-effects, or had been advised to stop either because they had been on the pill for many years or had some medical condition making the pill contra-indicated. There were 92 couples currently using the condom, only two of these found it acceptable. Most couples objected to it on aesthetic grounds and many also found it unacceptable because of the higher risk of pregnancy with this method. Many of the couples interviewed had used the condom previously. Although widely used it would seem not a very acceptable method of contraception in this sample of married couples seeking vasectomy. Use of a male method might be above average in the sample as they are presenting with a request for a permanent state of male infertility. Few women used either an intra-uterine device (8) or a diaphragn (5). The former had been tried by some women and most had experienced menstrual disturbances. The diaphragm was generally not acceptable on aesthetic grounds. Coitus interuptus was practiced by 15 couples and six other couples did not appear to be using any method of contraception. In this sample the couples placed great stress on a highly safe method of contraception. This would probably explain the low usage of certain types of contraceptive methods. Those who had tried several methods of contraception and found all unacceptable were questioned especially carefully as it was considered that this might be indicative of a poor outcome of vasectomy.

A history of nervous illness, sufficient to require the help of a psychiatrist, was found in 23 of the females and 11 of the males. Twelve females had a history of post-natal depression. Four men were considered to have a problem with alcohol and two of them had frequent episodes of impotence. There were no schizophrenics in this study. The females showed a fairly high incidence of serious chronic physical illness (Table I). Only seven males (2.5 per cent) showed serious chronic physical illness. The women also showed a high incidence of obstetrical and gynaecological problems and these involved 54 women (19 per cent). Several other women gave a history of deep venous thrombosis and almost a fifth had varicose veins.

The couples were asked why they had decided to request a vasectomy and, apart from the obvious essential reasons that their families were complete and that the male wished to be permanently sterile, a wide variety of supporting reasons was offered, such as:

(1) Being 'easier' for a male as not an 'internal' operation and could be carried out as an out-patient under local anaesthesia.

(2) The fact that the wife 'had been through enough'. By this was often meant a history of caesarean sections or miscarriages or being ill physically.

(3) That other methods were not totally reliable.

The husband often said his wife would be pleased to be sterilized but male sterilization had practical advantages.

Vasectomy was refused in 26 cases (9 per cent). In 21 of these the decision was made at the initial interview and in five at a second interview. In some of

TABLE I

*Health of the Wives*

| *Serious Physical Illness* | | *History of Gynaecological Illness* | | *History of Psychiatric Illness* | |
|---|---|---|---|---|---|
| Osteo-arthritis | 1 | Caesarian Section | 18 | Neurotic Illness | 11 |
| Osteosarcoma | 1 | Miscarriages | 13 | Post-natal depression | 12 |
| Renal pathology | 2 | Termination of Pregnancy | 4 | | — |
| Hypertension | 5 | Difficult deliveries | 9 | | 23 |
| Rheumatic Heart Disease | 4 | Repair operation | 2 | | |
| Blind and cleft palate | 1 | Frequent D. & C. | 1 | | |
| Epilepsy | 2 | Ovarian cyst | 1 | *History of Vascular Disease* | |
| Gall bladder disease | 2 | Ectopic pregnancy | 1 | Deep venous thrombosis | 5 |
| Thyroid disease | 1 | Pre-eclamptic toxaemia | 4 | Varicose Veins | 14 |
| Carcinoma of breast | 1 | Wife sterilised | 1 | | — |
| Coeliac disease | 1 | | — | | 19 |
| Asthma | 4 | | 54 | | |
| History of Cerebral Haemorrhage | 1 | | | | |
| Severe burns | 1 | | | | |
| Coarctation of the Aorta | 1 | | | | |
| | — | | | | |
| | 28 | | | | |

these couples there was more than one reason, such as a combination of male sexual difficulties and an unstable marriage, but the principal reasons are given in Table II.

TABLE II

*Reasons for Refusal*

| | |
|---|---|
| Episodes of Impotence | 8 |
| Premature Ejaculation | 3 |
| Unstable Marriage | 6 |
| Husband having strong doubts concerning potency | 4 |
| Wife uncertain about further children | 2 |
| Wife seriously ill physically | 2 |
| Wife menopausal | 1 |
| | — |
| | 26 |

Vasectomy was deferred in 11 couples (4 per cent). The period of postponement was about one year. The reasons for deferment are given in Table III.

TABLE III

*Reasons for Deferment*

| | |
|---|---|
| Wife young with 1st or 2nd child under 1 year | 6 |
| First child very young with congenital heart disease | 1 |
| Neurotic uncertain couple | 1 |
| Wife pregnant and rather uncertain | 1 |
| Wished to 'think it over' | 1 |
| Some evidence of an unstable marriage | 1 |
| | 11 |

## DISCUSSION

The typical couple who presented in Belfast requesting a vasectomy was aged in their early thirties, having been married about nine years and having two or three children. They were in the middle and upper social groups, protestants, and most had been well informed. Most had been using some contraceptive method in a responsible fashion for some years.

When the study was commenced there was an opinion from one of the Medical Defence Unions that it might be inadvisable to sterilize a male under thirty years of age. With the passage of time this seemed to be a very cautious approach and many men in the latter half of their twenties who have two or three children and a stable marriage would seem to be suitable for the proceedure, if there are no contra-indications. Young women who are pregnant with their second child when interviewed present a problem because of the high infant mortality rate under one year of age, and most of these young mothers were deferred for a year.

The majority of those interviewed had already received counselling either from their general practitioner, or at a family planning clinic. It was not the role of the author or his surgical colleague to advocate vasectomy, or in those refused to recommend other contraceptive measures, but immediate referral back to the general practitioner or family planning clinic was arranged. It seemed unreasonable to the author to refuse or defer a young responsible couple purely on the grounds of age without offering some alternative help.

Few older men requested a vasectomy, and only 43 (14 per cent) were in their forties. The idea of rejuvenation by vasectomy, described by Steinback (1940), no longer exists and none of the men interviewed enquired about this possibility. The men in their forties had wives who had been on the pill for ten or more years and had been advised to find some alternative method of contraception. Generally there was not a wide discrepancy between the ages of the husband and wife. A wide discrepancy would probably have made one cautious about proceeding with a vasectomy. One couple was refused vasectomy as the wife was menopausal.

In Northern Ireland, although unemployment and bad housing are serious problems, one could not suggest that over-population is a major problem and in fact the population in Ireland generally has fallen very considerably in the last 150 years. Those who present for vasectomy do not have big families, the average being 2.7 children. Vasectomy would have very little effect on population trends. In those with large and problem families in Social Group V a vasectomy would probably be unacceptable and where vasectomy has been introduced as a means of controlling population growth, such as India, it has been a failure.

The age of the youngest child showed a wide range. The fact that those whose youngest child was in the teens or early twenties, would mention a dissatisfaction with their present contraceptive methods was mainly due to the recent report concerning the possible long-term effects of the contraceptive pill. (Royal Coll. of Gen. Practitioners 1977) (Vessey, M.P., McPherson K., Johnson B. 1977)

Those in Social Group V were under-represented. This is probably due to a non-acceptance of male sterilization among workingclass men.

The large proportion using the condom as current contraceptive was surprising, especially when the vast majority found it an unpleasant method and not particularly reliable. The possible explanation in this pre-vasectomy group is that there is more than average emphasis on male methods of contraception. The very low use of the intra-uterine device and diaphragm would support this view. The recent reports concerning the long-term effects of the contraceptive pill have increased the demand for vasectomies and this increase is likely to continue until some other safe and acceptable contraceptive method becomes available.

As regards the sexual and marital relationships of those interviewed, it would seem very likely that the problems encountered were an under-estimation. Apart from much more prolonged interviews over a period of time, this is a problem of methodology to which there is no simple solution. Possibly those obviously unsuitable for vasectomy were not referred, so some initial screening had already been carried out by the general practitioner.

The sexual habits do not necessarily reflect those of the community but the wide range of frequency of sexual intercourse and the average incidence of between two and three times per week are in keeping with the Kinsey figures for America. (Kinsey et al 1948 and 1953). The very high incidence of fear of pregnancy initially is surprising but on reflection, this must be one of the main motivating factors in bringing the couple to seek vasectomy. Nevertheless, it is rather surprising, when fear of pregnancy was such a prominent feature among the females, that female sterilization had not been sought earlier. The difference in estimation in the frequency of sexual intercourse between the sexes was a small but significant difference for which of course there could be two explanations and there is no way of ascertaining retrospectively which sex is estimating correctly. Of course, one must accept that in any individual the answers are very approximate, but the tendency for the wives to estimate higher was a consistent pattern throughout.

There has been much written about the reasons for deciding on a vasectomy. The fact that the male wishes to be permanently sterilzeid is an essential reason and also that both partners wish for no further children. It has been stated that the health of the wife should not be a factor (Wolfers 1974), but in this study the health of the wife was often a major reason for choosing a vasectomy and, as can be seen, there was a considerable incidence of morbidity among the females. It would seem to the author that, provided the primary desire to be permanently sterile is present, the health of the wife is a logical and reasonable consideration. The practical advantages of male sterilization compared to female sterilization as suggested by most of the men seemed sensible both to the couples themselves and to the economics of the health service.

The main aim in this study was to screen those seeking vasectomy, to exclude those whom the author considered would not respond well and would be more likely to develop complications. Pre-existing sexual problems in the male such as impotence and ejaculatory difficulties seemed definite contra-indications as it is likely that these problems would worsen with the passage of time and that the vasectomy would be blamed. Also the man with these problems has constant doubts and anxieties about his potency and these are likely to be increased by vasectomy. The man who has had only a few episodes of impotence probably when excess alcohol has been taken, may be suitable for vasectomy. How he and his wife feel about the episodes of impotence are the most important guiding factors. An unstable marriage is a contra-indication for obvious reasons and the husband having a vasectomy may exacerbate the marital discord, despite the partners' claim that it might settle their problems.

A few of the couples interviewed had not received sufficient counselling from their general practitioner, or at the family planning clinic and had not fully considered the implications of the procedure; these were either refused or deferred. If the wife is unlikely to survive a serious illness vasectomy would seem to be contra-indicated for her husband. Deferment was mainly on the grounds of age or not having fully considered all the implications. Jackson and others (1970) also deferred a number on the grounds of age but in her study no mention is made of refusal on grounds of sexual or marital problems.

An American paper by Uhlman (1974) lists reasons for refusing a vasectomy. A high percentage were regarded as too young but some reasons were listed which do not appear in the present series such as 'unmarried' and 'spouse unwilling to sign the consent form'. It would appear that the aims of the American Society for Voluntary Sterilization have had some impact. The aim of their organisation is vasectomy on demand for anyone over the age of twenty-one. To the author this would appear to be very unwise and if a policy such as this was adopted, vasectomy would once again become a highly controversial issue.

Contra-indications listed by Hymes (1977) are: a) Disagreement with the wife over the advisability; b) Consent to the operation on the basis of another person's urging; c) When sterilization appears to be an attempt to save an already failing marriage. These appear fairly obvious and probably reflect more social pressure in the U.S.A. to have a vasectomy. Hynes also states that prior psychiatric treatment does not carry a poor psychological prognosis. Certainly

in the present series those with a history of psychiatric illness were not refused, unless this illness led to definite sexual problems.


## Summary

A total of 286 men who presented for vasectomy were interviewed, and their wives were then interviewed separately. The age range was from 23 - 49 years. The number of children tended to be small, the mean being 2.7 children per couple. The length of time the couple was married varied widely from 5 - 25 years. In the screening interview special reference was made to emotional and sexual difficulties in the marriage. The contraceptive history and sexual practice of the couples is described. Serious chronic physical illness was reported in 10 per cent of the wives and 19 per cent had a history of obstetrical and gynaecological problems. The reasons for the couple deciding to have a vasectomy are described. Vasectomy was refused in 26 men and in another 11 cases the vasectomy was deferred, the main contra-indications being sexual difficulties and an unstable marriage. These results are discussed.



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# ACQUIRED BONE DISEASE IN SMALL PRETERM INFANTS — A POTENTIALLY FATAL DISORDER

by

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BETTER neonatal care has improved survival of infants less than 1.0 kg birth weight (Stewart et al, 1977). One of the challenges in managing very low birth weight (VLBW) babies is that of providing optimal nutrition (Shaw, 1973), given the constraints upon absorption (Grand, Watkins and Torti, 1976) and subsequent metabolism (Rosenberg and Scriver, 1974). Our aim is to highlight the development of bone disease in these infants, despite prophylaxis with vitamins, including Vitamin D and other essential trace elements.

## PATIENTS AND METHODS

*Clinical details*

Fourteen VLBW infants have been recognised with acquired bone disease, 13 since 1974 and one in 1969. Five mothers had ante-partum haemorrhage or severe pre-eclampsia, four had multiple pregnancy (one triplets) and six others went spontaneously into premature labour. Gestational maturity at birth varied from 27 to 32 weeks. This was measured according to Dubowitz, Dubowitz and Goldberg (1970) and confirmed in eight infants by radiological assessment of the degree of calcification of the molar teeth cusps (Kuhns, Sherman and Poznanski, 1972). Birth weights were 0.64 to 1.45 kg. Six infants fell belowe the tenth percentile for gestational maturity (Gairdner and Pearson, 1971). Two babies were asphyxiated at birth, while three others developed idiopathic respiratory distress syndrome. Patient 8 had severe rhesus disease.

Each of the infants had received vitamin supplements from the first week of life. Patients 3 and 6 were given Vitamin D 10 $\mu$g, patient 2, 20$\mu$g and the rest, 30 $\mu$g daily. Patients 2, 3 and 6 were nourished on evaporated milk (Carnation), patients 8 and 13 on SMA Gold Cap and the rest on Cow & Gate Premium. The copper content of reconstituted feeds was 35-40 $\mu$g/dl and the daily intake about 50-60 $\mu$g/kg therefore. None of the expectant mothers had been nutritionally deprived and although no formal dietary assesment was undertaken, all except the mother of patient 4 received dietetic counselling.

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This paper was presented at the Royal Society of Medicine (Paediatric Section) meeting in the Royal Belfast Hospital for Sick Children on Saturday, 1st July, 1978.

Bone disease was recognised between 5 and 12 weeks after birth. In eight infants this took the form of gradually increasing dyspnoea with sub-costal recession and was associated with apnoeic episodes, cyanosis and bradycardia. In patient 13 this appeared to be associated with a viral bronchiolitis. The lighter the infant the more severe their illness and the two who died were lightest of all. Six others were asymptomatic and were detected between 1975 and 1977, because of increased surveillance of VLBW infants.

Clinical features of rickets were few. An abnormally large or full anterior fontanelle was noted in two and in only one of these was there obvious expansion of the wrists. None had evidence of a rachitic rosary, although early radiological changes of rickets were already present.

## LABORATORY RESULTS

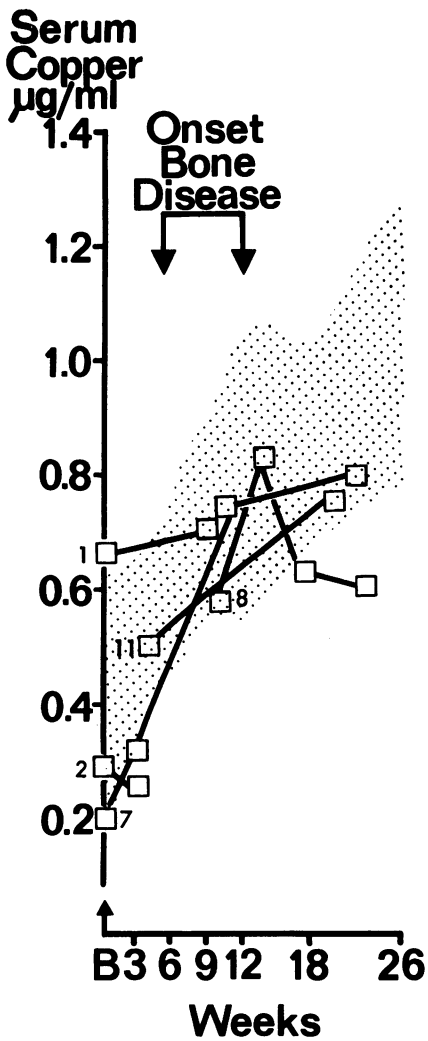
Tests were carried out at the time radiological bone disease was found. Serum alkaline phosphatase activity showed a consistent increase (Table 1). Serum

TABLE 1: BIOCHEMICAL DETAILS

| *Patient* | *Total Maturity weeks* [a] | *Alkaline Phosphatase u/l* [b] | *Calcium mmol/l* | *Magnesium mmol/l* | *Phosphate mmol/l* | *25-OHD$_3$* [c] *ng/ml* | *Urinary aminoacids* |
|---|---|---|---|---|---|---|---|
| 1 | 35 | 297 | 2.48 | 0.74 | 2.50 | 30.05 | Threonine increased |
| 2 | 36 | 47 KAU[d] | 1.40 | 1.13 | 2.40 | 19.5 | Tyrosine increased |
| 3 | 37 | 55 KAU | 1.80 | 0.57 | 1.30 | ND[e] | Generalised increase |
| 4 | 38 | 235 | 2.29 | 0.96 | 2.17 | ND | Threonine increased |
| 5 | 35 | 41 KAU | 2.00 | 0.93 | 2.50 | ND | Threonine increased |
| 6 | 44 | 60 KAU | 1.68 | 0.85 | 1.20 | ND | Generalised increase |
| 7 | 37 | 67 KAU | 2.24 | 0.80 | 2.30 | ND | Threonine increased |
| 8 | 37 | 700 | 1.67 | ND | 1.70 | 16.5 | Generalised increase |
| 9 | 34 | 43 KAU | 2.10 | 0.73 | 2.20 | ND | Normal |
| 10 | 35 | 338 | 2.39 | ND | 2.02 | ND | Normal |
| 11 | 38 | 250 | 2.25 | ND | 1.70 | 34.5 | Normal |
| 12 | 36 | 230 | 2.26 | 0.72 | 1.60 | ND | ND |
| 13 | 39 | 438 | 2.19 | ND | 1.80 | 17.5 | Normal |
| 14 | 37 | 295 | 1.85 | 0.75 | 1.80 | 20.0 | Normal |

a Gestational maturity plus post-natal age at onset of bone disease.
b Alkaline phosphatase – normal range at this age 56-190 u/l.
c 25-OHD$_3$ – lower limits in adults for January, March, June and September are 16, 12, 18 and 25 ng/ml, respectively.
d King Armstrong Units.
e Not determined.

calcium and inorganic phosphate levels were variable. Three infants had biochemical evidence of secondary hyperparathyroidism. Patient 8 had a serum parathormone concentration of 1.8 μg/l (range in normal adults 0.3-0.73 μg/l); this decreased to normal over four weeks following treatment with 0.1 μg/kg/day of 1 α-hydroxyvitamin D (1α-$OHD_3$) (Glasgow and Reid, 1977). Two others had hypophosphataemia and generalised aminoaciduria which were corrected




*Serial copper determinations in the sera of five infants shown in relation to the range (M ± SD) for normal preterm infants (stippled) of mean gestational age 33 weeks.*

following larger doses of Vitamin D. Dr. Angela Fairney, St. Mary's Hospital Medical School, London, using a modification of the method of Haddad and Chyu (Haddad and Chyu, 1971) kindly measured 25-hydroxyvitamin $D_3$ (25-$OHD_3$) for us. The plasma concentration in four babies were within or just above the normal range in adults according to season.

Serum copper concentrations were measured by atomic absorption spectrophotometry (McMaster, 1977). The levels are shown in relation to normal values for preterm infants whose gestational age at birth was 33 weeks (Halliday, 1977). In four infants the copper levels fell within the normal range at the time bone disease was diagnosed (Fig). Although none of the infants was frankly icteric, four were subclinically jaundiced, three of whom had a mildly elevated direct-reacting bilirubin level. Plasma proteins, full blood count and red cell morphology were normal in each case.

## RADIOLOGY

Marked skeletal demineralisation affecting the skull and axial skeleton in particular, was present in all babies (Table 2). In the skull the fine details of the inner ear bones were clearly etched and the sutures poorly defined. More pronounced skeletal changes were found in those with respiratory symptoms. Four of these infants had a fine layer of periosteal new bone along the inferior aspect of the mandible, in two of whom this extended onto the ascending rami (Thomas and Glasgow, 1978).

Pulmonary abnormalities reflecting symptomatic bone disease were present in eight infants. In seven of these the lungs were markedly over-inflated with linear strands radiating out from the hili and small patches of consolidation and collapse. The pattern was such that an initial diagnosis of Mikity-Wilson syndrome was suspected and this was supported in patient 3 by the presence of apparent cystic changes in the right lower zone (Glasgow and Thomas, 1977). Patients 7, 9 and 14 with asymptomatic bone disease, had cardiomegaly and pulmonary plethora due to intracardiac left to right shunts.

The findings in the long bones were less pronounced, although in the majority rachitic changes of variable degree were present at the wrist. These consisted of demineralisation, loss of clarity and slight cupping of the metaphyses of the lower radius and ulna. In only four infants was there definite metaphyseal splaying. Flaring of the anterior ends of the ribs was present in six children. Rickets were seen at the inferior scapular angles in patients 3 and 6.

Fractures were present in five patients; infants 5, 6, and 14 had several fractures of the lateral arcs of the ribs on the left side, and patient 3 had multiple rib and long bone fractures in various stages of healing.

TABLE 2: RADIOLOGICAL FINDINGS IN RELATION TO AGE OF ONSET OF DISEASE

| *Patient* | *Age at onset bone disease (wk)* | *Skeletal changes* | *Lung changes* |
|---|---|---|---|
| 1 | 6 | D,R. P | O,L,C, |
| 2 | 6 | D,R, P | O,L,C, |
| 3 | 9 | D,R,F,P | O,L,C,Cy |
| 4 | 9 | D,R | O,L,C, |
| 5 | 5 | D,R,F | O,L,C, |
| 6 | 12 | D,R,F | C |
| 7 | 7 | D,R | |
| 8 | 10 | D,R | O,L,C, |
| 9 | 6 | D,R | |
| 10 | 5 | D,R, P | |
| 11 | 10 | D,R,F | |
| 12 | 7 | D,R | |
| 13 | 10 | D,R | O,L,C |
| 14 | 7 | D,R,F | |

D, demineralisation; R, rickets; F, fractures; P, periosteal new bone; O, over-inflation; L, linear strands; C, collapse/consolidation; Cy, cysts.

## MANAGEMENT

Vitamin D therapy was given in daily doses varying between 20-125 $\mu$g to Nos. 1, 2, 4-7 and 9-12; one patient received two injections of 500 $\mu$g at an interval of three weeks. Over the subsequent 3-5 weeks as skeletal healing took place in the symptomatic infants, respiration gradually returned to normal. In number 8 the level of 25-$OHD_3$, initially 16.5 ng/ml, increased threefold following therapy with 0.2 $\mu$g of 1$\alpha$-$OHD_3$ daily for three weeks (Glasgow and Reid, 1977). In numbers 1 and 2 however, the respiratory difficulties became particularly marked and the apnoeic episodes frequent and protracted leading to profound bradycardia. Each was managed in a Greogry Head Box with constant positive airways pressure. This resulted in an initial improvement (number 1) but progressive ventilatory failure with increasingly frequent apnoea led to her demise at nine weeks of age. Patient 2 died at the same age following intestinal obstruction due to paralytic ileus (Glasgow and Thomas, 1977).

*Necropsy* (*Patient* 1)

The body weighed 2.0 kg. Abnormal findings were confined to the lungs and bones. The lungs showed generalised thickening of alveolar walls with increase in interstitial fibrous tissue. There were small patches of bronchopneumonia and intra-alveolar fibrosis.

Bone (right femur) was examined by Dr. H. A. Ellis, Royal Victoria Infirmary, Newcastle upon Tyne. Both decalcified and plastic embedded, undecalcified sections were examined. Endochondral ossification was normal. The blood vessels and connective tissue invading the mineralised cartilage were excessive and there was an increase in chondroclastic and osteoclastic activity. The trabeculae were fewer than normal and those at the periphery were not being incorporated into cortical bone. The metaphyseal cortex was thin because resorption was still occurring. Formation of osteoid seemed to be proceeding normally. There was considerable woven osteoid around the diaphysis, and some reduction in lamellar bone formation. No definite mineralisation defect was present. The overall picture was that of osteopaenia somewhat reminiscent of Vitamin C, copper or manganese deficiency.

Necropsy findings in patient 2 have been published previously (Glasgow and Thomas, 1977).

## DISCUSSION

Fourteen VLBW infants are described with acquired metabolic bone disease. All but one were seen from 1974 to 1977 in a high risk Maternity Hospital where the annual delivery rate is about 2,500; in addition approximately 170 babies are admitted annually from peripheral hospitals, of which about one-third are preterm.

Because of improved perinatal care and reduced neonatal mortality, the occurrence of bone disease may be increasing in infants of this gestational maturity. It seems likely however, that it often goes unrecognised because of the paucity of clinical signs. Hence diagnosis depends largely upon knowledge of its existence, coupled with careful radiological and laboratory surveillance. X-ray findings of demineralisation and rickets are uniformly present, although not always of marked degree. Biochemical features usually consist of an elevated alkaline phosphatase activity with more variable reductions of inorganic phosphate, calcium or magnesium. The combination of aminoaciduria and hypophosphataemia indicate hyperparathyroidism (Fraser, Kooh and Scriver, 1967). Raised levels of parathormone were documented in one patient and this responds to specific therapy with drugs, such as $1\alpha$-$OHD_3$, which correct the abnormality in calcium metabolism and heal bone disease (Glasgow and Reid, 1977).

Pure Vitamin D deficiency seems unlikely to be the entire explanation in every patient. The vitamin intake was satisfactory; in only two infants was this less than $20\mu g$ daily. The serum levels of 25-$OHD_3$ from four of our babies and in two similar infants of Davies, Hughes and Moore (1978) were within the normal range and, although this does not exclude a disorder of Vitamin D metabolism, it suggests that larger doses of Vitamin D are unlikely to be prophylactic, or the use of 25-$OHD_3$, therapeutic. Whether a defect is present in renal $1\alpha$-hydroxylation must await further study, nonetheless we have found treatment with $1\alpha$-$OHD_3$ to be efficacious (Glasgow and Reid, 1977).

An infant born very prematurely is already nutritionally deprived, since it is during the last trimester that the fetus acquires much of its mineral content, be it iron, copper or calcium (80 per cent) (McCance and Widdowson, 1961). In those with disturbed placental function as in six of our infants, calcium transport to the baby may be impaired (Khattab and Forfar, 1971). After birth accumulation of nutrients by the VLBW infant is often sub-optimal. Calcium assimilation, for example, is only about 40 per cent of that during late gestation (Shaw, 1976). Therefore such babies acquire about one-twelfth of the term infant's calcium load.

With regard to Vitamin D, the work of Hillman et al (1977) showed no difference in cord blood 25-$OHD_3$ levels between preterm and mature babies. None, however, was less than 1,500 g. Earlier work by this group tended to show that absorption of 25-$OHD_3$ by preterm infants was normal, but that 25-hydroxylation was probably impaired (Hillman and Haddad, 1975). The finding of normal 25-$OHD_3$ values in four babies however, would not support this view. Furthermore the absence of an obvious calcification abnormality on bone histology has led us to seek other aetiological factors which may account for the disorder.

Assuming the histological findings in the femur to be representative of the skeleton as a whole, they suggested a defect in bone matrix. On the other hand there was no radiological support for defects like scurvy or osteogenesis imperfecta. The idea that a trace element, such as copper, may be deficient in VLBW infants with bone disease has been suggested by Griscom, Craig and Neuhauser (1971). The hepatic copper level in their one baby who died was abnormally low and in another infant respiratory difficulty, similar to that in six of our patients, was thought radiologically to resemble the Mikity-Wilson syndrome. Moreover, Hambidge (1976) states that copper deficiency in prematures may be associated with osteoporosis, costochondral beading, muscular hypotonia and apnoea and it is now known their copper retention is low (Dauncey, Shaw and Urman, 1977). Copper deficiency however, was clearly not present in four of our infants by comparison with the range defined in normal premature babies (Halliday, 1977). In any event, about half of our patients had radiologically changes closely resembling those associated with classical nutritional rickets, which contrasts with the findings of Griscom et al (1971). None of our babies showed any haematological or medullary changes, apart from the mild anaemia of prematurity, while those with proven copper deficiency have sideroblastic anaemia with cytochemical and cytological abnormalities in the erythroid precursors associated with myeloid hypolasia (Al-Rashid and Spangler, 1971; Ashkenazi et al, 1973).

We have been impressed by the proportion of these infants born in the winter months of the past three years, a period during which all infants at risk, especially those less than 1.0 kg, have been carefully scrutinized. During winter, solar radiation, the prime source of Vitamin D, is less than in summer (Coblentz, 1947) and this results in significantly lower levels of 25-$OHD_3$ in the adult (McLaughlin et al, 1974). Since maternal blood concentrations largely determine those in the infant's circulation at birth (Rosen et al, 1974), winter born babies are likely to have lower 25-$OHD_3$ levels. It may be noteworthy therefore that only three of our 12 infants were born in summer or autumn. On the other hand

an abnormality in 1$\alpha$-hydroxylation would not be expected to conform to a seasonal expression.

It would appear in the current state of knowledge, that no single explanation can account for all the clinical and laboratory abnormalities in each infant. Various facets of the syndrome may be caused by several nutritional deficiencies, some of which influence the expression of others. Nonetheless, an abnormality in renal 1$\alpha$-hydroxylation is under further investigation.

Finally, our most severely affected babies each had lung changes which were similar to those described in the early stages of the Mikity-Wilson syndrome (Mikity, Hodgman and Tatter, 1967). While the pathogenesis of this disorder is not yet understood, it may be significant that the population at risk, age of onset and clinical presentation, early X-ray changes and natural history of that condition are identical to those of our infants with a disorder primarily of the musculo-skeletal system (Glasgow and Thomas, 1977). Pulmonary function studies in infants with this potentially fatal disorder should be carried out.

## SUMMARY

Fourteen very low birth weight infants, 12 born since early 1974, developed bone disease during the first three months of life, in spite of apparently adequate nutrition including prophylaxis with Vitamin D. In eight the bone disease, possibly linked to muscle weakness, was associated with secondary respiratory distress and apnoea, in six of whom the radiological features closely resembled those seen in the syndrome of pulmonary dysmaturity (Mikity-Wilson). The infants who were lightest of all died at nine weeks of age. Blood biochemistry was variable but the plasma 25-hydroxyvitamin D, in four infants, was within the normal range indicating that pure Vitamin D deficiency is not aetiological, that 25-$OHD_3$ is unlikely to be therapeutic and suggesting that an abnormality of renal 1$\alpha$hydroxylation may be present. Greater scrutiny of the overall population is urged, and in particular, infants of mothers with placetal insufficiency, multiple pregnancies of those born in the winter months, since it is these infants who seem most to be at risk of developing bone disease.

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# THE USE OF IMMUNOFLUORESCENT TECHNIQUES IN DERMATOLOGY

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IN 1975 the Department of Pathology established an immunofluorescence laboratory to aid diagnosis in dermatology.

The purpose of this paper is to show (1) the use and limitations of the techniques involved in immunofluorescent procedures, (2) to describe the skin diseases in which immunofluorescence is of diagnostic or therapeutic value and (3) to review our experience over the past two years. There are many skin diseases in which diagnosis can be difficult at a histopathological level, let alone for the clinician. Immunofluorescence is particularly of value in establishing the diagnosis in the members of the bullous skin diseases, e.g. pemphigus, pemphigoid, dermatitis herpetiformis and benign mucous membrane pemphigoid. In classical pemphigus with a representative, early lesion, the typical features usually are present but not infrequently the diagnosis can be exceedingly difficult, particularly with old lesions, and especially if they have become secondarily infected. In such instances immunofluorescent studies can be crucial to establish the correct diagnosis. Bullous pemphigoid, dermatitis herpetiformis and benign mucous membrane pemphigoid have essentially similar microscopic features — they are all typified by the presence of a sub-epidermal vesicle. Although distinguishing features do exist, they are not always present and, thus, immunofluorescence can often resolve the problem. Immunofluorescent studies are essential in patients suffering from discoid and systemic lupus erythematosus. They are occasionally of value in establishing the diagnosis of a vasculitis.

## Technical Methods

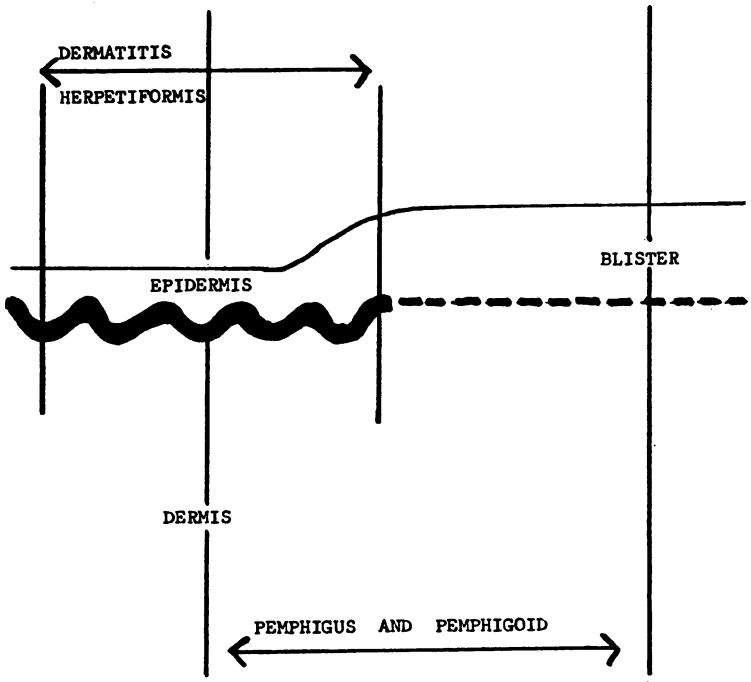
Fluorescence occurs when an object is irradiated with light of a particular (shorter) wavelength and emits light of a longer wavelength. This results in a colour change. A fluorochrome is a substance which possesses the ability to fluoresce. A variety of fluorochromes are used, e.g. fluoroscein and rhodamine. Thus, if one irradiates fluoroscein with blue light it emits light of an apple-green colour. To perform immunofluorescence an antibody is 'tagged' with a fluorochrome. The fluorochrome-labelled antibody may be reactive against immunoglobulins, complement, or other components. On addition of the fluorochrome-labelled antibody to its appropriate antigen, it becomes fixed. This can be detected by observing the colour change when the specimen is viewed under light of the correct wavelength.

There are essentially two types of test used in an immunofluorescence laboratory. One of these is for skin biopsies, the other for examining serum samples. However, before describing these, it seems appropriate to discuss the method of taking biopsies, and their transportation.

Ideally, a technician from the laboratory should be present at the time of taking the biopsy. It is essential that the clinician be aware of the correct site from which to take the biopsy in each of the various diseases commonly studied (Fig. 1).

FIG. 1

*Suitable sites for biopsy. Stippled line represents the basement membrane region.*




It is of great importance that biopsies taken from patients with bullous pemphigoid and pemphigus include both a portion of a blister (preferably a whole blister, if this is possible) with adjacent univolved skin. This has the advantage that both light microscopy and immunofluorescent studies can be performed on one specimen. In dermatitis herpetiformis the biopsy should be taken from uninvolved skin adjacent to a lesion and *not* the lesion itself. If routine histopathological examination is also required, then the biopsy should include both blister and normal skin, the normal skin being separated and sent for immunofluorescent examination. Immediately after the specimen has been taken from the patient it should be snap-frozen in an appropriate cooling mixture. A variety of techniques are available, but we find the use of iso-pentane pre-cooled in liquid nitrogen satisfactory. Following this the specimen is transferred to a

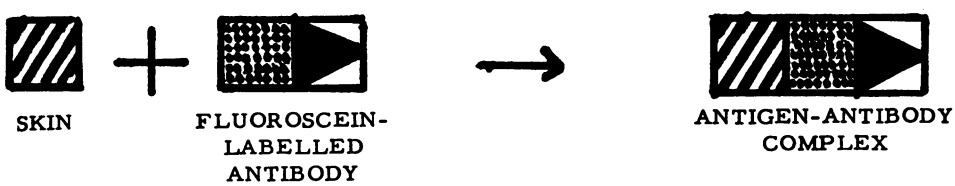
cryostat for sectioning. Where laboratory facilities are limited, or when the technician cannot attend, the specimen may be wrapped in aluminium foil or parafilm and frozen in liquid nitrogen. The specimen can then be transported to the laboratory.

Serum samples (*without anti-coagulant*) can be collected in the usual manner and submitted to the laboratory.

Skin biopsies are most often examined by the direct immunofluorescent technique (Fig. 2), the purpose of this being to demonstrate the presence and location of in vivo bound substances such as immunoglobulins and complement.

FIG. 2

Fig. II




*The direct immunofluorescent test.*

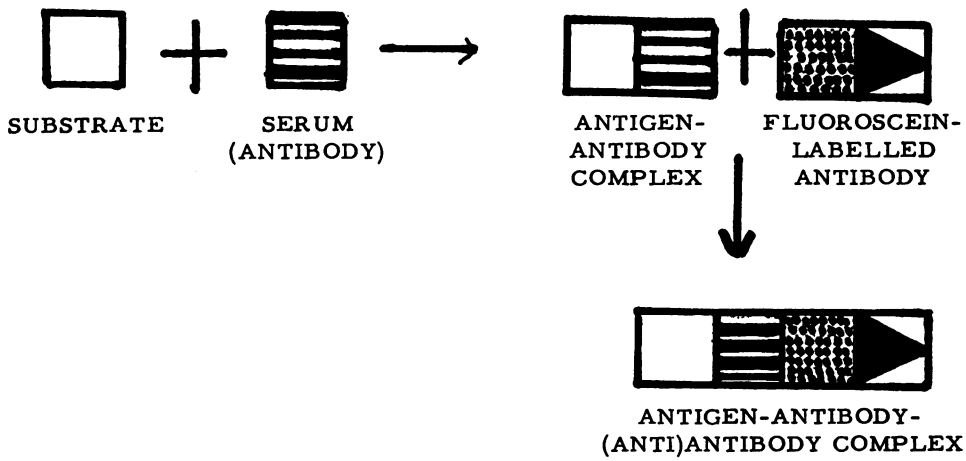
Fluoroscein-labelled anti-human immunoglobulin, etc., is added to a suitably prepared tissue section and the specimen is examined under blue light. If the anti-human immunoglobulin has been 'fixed'. its presence will be identified by fluorescence.

Serum samples are examined by the indirect immunofluorescent technique (Fig. 3), the purpose of this test being the detection of circulating antibodies.

To perform the test, the patient's serum is added to a variety of substrates (tissues); if the appropriate antibody is present it will 'fix' to its corresponding antigen in the substrate. Fluoroscein-labelled anti-human immunoglobulin is then added and the section is examined under blue light.

FIG. 3

Fig. III




*The indirect immunofluorescent test.*

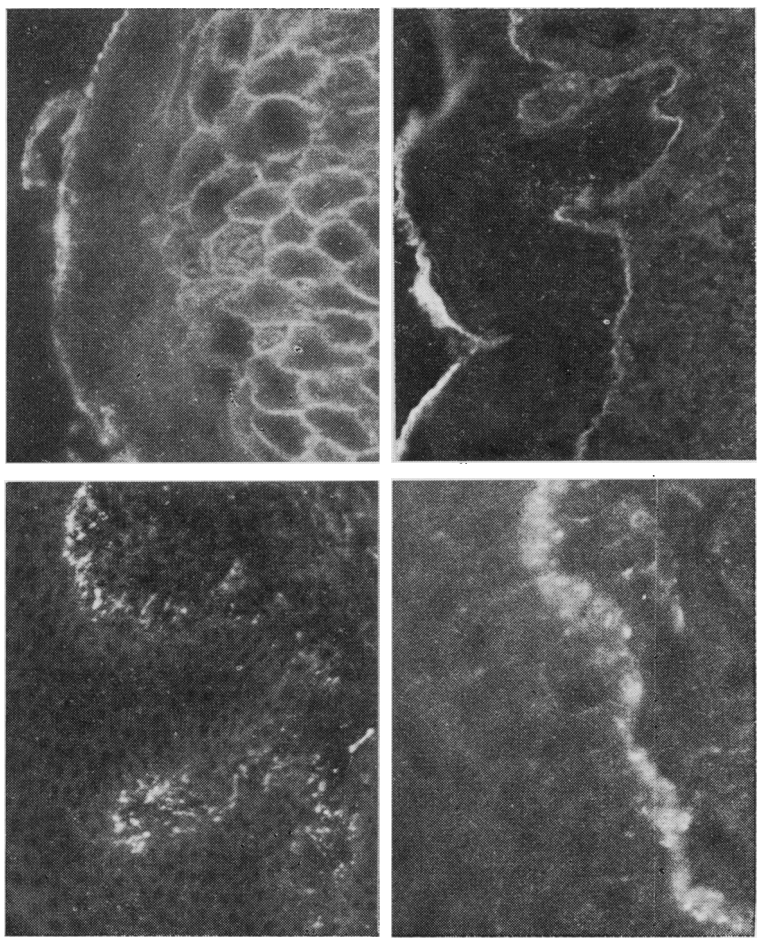
## DISEASES STUDIED

(TABLE 1)

*Immunofluorescent findings in the more commonly investigated skin diseases.*

| *Disease* | *Skin* | *Serum* |
|---|---|---|
| PEMPHIGUS (variants) | Intercellular staining of squamous epithelium | Anti-intercellular substance antibody |
| BULLOUS PEMPHIGOID | Linear basement membrane staining | Anti-basement membrane antibody |
| DERMATITIS HERPETIFORMIS | IgA in dermal papillae | ? anti-reticulin antibody |
| BENIGN MUCOUS MEMBRANE PEMPHIGOID | Linear basement membrane staining | Low titre anti-basement membrane antibody |
| SYSTEMIC LUPUS ERYTHEMATOSUS | Granular staining at basement membrane (lesion and normal skin) | Anti-nuclear factor, etc. |
| DISCOID LUPUS ERYTHEMATOSUS | Granular staining at basement membrane (lesion only) | May contain anti-nuclear factor |

| | | |
|---|---|---|
| SYSTEMIC SCLEROSIS<br>MIXED CONNECTIVE TISSUE DISEASE | Negative<br>IgM, rarely IgG at basement membrane or within blood vessels | Anti-nuclear factor<br>Anti-ribonucleoprotein, antibody to 'extractable' nuclear antigen |
| VASCULITIDES | May find immunoglobulin and complement | Negative |



FIGS. 4 to 7

FIG. 4 *(Top left). Pemphigus vulgaris. 'Fish-net' staining around prickle cells* x 250.

FIG. 5 *(Top right). Bullous pemphigoid. Linear staining at basement membrane region* x 100.

FIG. 6 *(Lower left). Dermatitis herpetiformis. Positive staining in the dermal papillae* x 100.

FIG. 7 *(Lower right). Systemic lupus erythematosus. Positive granular staining at basement membrane region* x 250.

### *Pemphigus*

Pemphigus vulgaris has long been known to be an immunologically mediated disease (Beutner and Jordon, 1964). Immunoglobulins and complement are found in the inter-cellular region of the squamous epithelium (Fig. 4). The much rarer pemphigus erythematosus is characterised by immunoglobulins and complement in a granular distribution at the epidermo-dermal junction in addition to the changes mentioned above. Pemphigus foliaceus shows features similar to pemphigus vulgaris.

Examination of the serum from a patient with pemphigus can virtually always be shown to contain an antibody (usually IgG), which reacts with the intercellular region of squamous epithelium. Circulating antibodies can sometimes be difficult to detect and repeat samples may be necessary. A source of possible confusion may arise with the pemphigus-like antibodies that are known to develop on occasion in people with severe burns (Thivolet and Beyvin, 1968).

The presence and titre of anti-intercellular antibody have been shown to be of prognostic value in patients with pemphigus (Beutner, Chorzelski and Jordon, 1970). An individual change in titre is not sufficient for adjustment of steroid dosage, but an increasing titre is certainly suggestive of impending relapse and, thus, possibly an indication for altering treatment dosages. Repeat tests should be performed perhaps weekly whilst the patient is in relapse, and every three or six months when in remission.

### *Bullous Pemphigoid*

This interesting disease can be a problem both clinically and histologically. It is, therefore, fortunate that pemphigoid is characterised by the presence of a specific (as far as is known) antibody (Fig. 5) active against the basement membrane region of squamous epithelium (Beutner, Jordon and Chorzelski, 1968). Unfortunately, there does not seem to be much correlation between titres of basement membrane antibody and the severity of the disease process.

### *Benign Mucous Membrane Pemphigoid*

Recent studies (Hudson and Black, 1975) have shown that this disease has features similar to bullous pemphigoid. IgG and complement (more rarely IgA) are found at the basement membrane region of the biopsy. Although usually in low titre, circulating antibodies have been detected against the basement membrane zone.

### *Dermatitis Herpetiformis*

Immunofluorescent examination of the biopsy typically shows the presence of granular IgA in the dermal papillae (Fig. 6). Complement may also be demonstrated in a similar location. Rarely they may be found at the basement membrane region, and are occasionally linear. It is to be emphasised that the IgA deposits may be patchy in distribution and, therefore, repeat biopsies occasionally are necessary to establish the diagnosis.

Examination of the serum in patients with dermatitis herpetiformis may reveal a variety of antibodies. These include anti-reticulin antibody, anti-gastric parietal cell antibody, anti-nuclear factor and thyroid microsomal antibody. Of these, anti-reticulin antibody is of most significance.

### *Systemic and Discoid Lupus Erythematosus*

Immunological investigations are obviously of great importance in both the above conditions.

Examination of a skin biopsy can be of diagnostic value in both discoid and systemic lupus. It shows granular deposits of immunoglobulins (IgG and/or IgM) and complement at the epidermodermal junction (Fig. 7). This is of particular importance in the diagnosis of systemic lupus, in that these deposits are found in clinically normal (sun-exposed) skin as well as in the lesion itself. Cases of so-called transitional lupus may show deposits in normal skin. It is worthwhile remembering that false negative results can occur in patients on steroid therapy. Some workers (Dantzig, Mauro, Rayhanzadeh and Rudofsky, 1975) have shown that there is a high correlation between positive cutaneous immunofluorescence and the more severe forms of lupus nephritis.

### *Scleroderma*

Examination of skin biopsies from patients with scleroderma and morphoea are disappointingly negative. Examination of the serum in cases of scleroderma frequently reveals an anti-nuclear antibody, often of the speckled or nucleolar type. In morphoea the serum is usually free from such antibodies.

However, in the less common mixed connective tissue disease (mesenchymal, inflammatory scleroderma) recent studies (Winkelmann, Carapeto and Jordon, 1977) have shown that immunofluorescence may have some part to play in diagnosis. Immunoglobulins (IgM, rarely IgG) and complement were described at the basement membrane or within blood vessels. Serological investigation is said to reval the presence of antibodies to ribonucleoprotein and 'extractable' nuclear antigen.

### *Vasculitides*

A variety of primary vascular inflammatory diseases exist and many of these involve cutaneous vessels, e.g. allergic vasculitis, polyarteritis nodosa. If immunofluorescent tests are to be performed, the biopsy should be taken from an early lesion. Direct immunofluorescence may reval immunoglobulin and complement in and around blood vessels. However, interpretation of these biopsies is often exceedingly difficult.

## Results

During the period May 1975 to May 1977 specimens were received from 170 patients. These included 337 skin biopsies and 379 serum samples. The submitted material included a wide range of conditions (Table 2).

(TABLE 2)

*Range of diseases investigated.*

| *Disease* | *No. of cases* | *Disease* | *No. of cases* |
|---|---|---|---|
| Dermatitis herpetiformis | 34 | Urticaria | 7 |
| Bullous phemphigoid | 15 | Darier's disease | 1 |
| Pemphigus (variants) | 7 | Erythema elevatum diutinum | 1 |
| Cicatricial pemphigoid | 2 | Jessner's lymphocytic infiltrate | 1 |
| Lupus erythematosus (discoid & systemic) | 11 | Acne rosacea | 1 |
| Vasculitis | 10 | Photosensitivity | 2 |
| Lichen planus | 2 | Necrobiosis lipoidica diabeticorum | 1 |
| Psoriasis | 2 | Bechet's syndrome | 1 |
| Herpes gestationis | 2 | Familial annular erythema | 1 |
| Scleroderma | 2 | Lupus vulgaris | 1 |
| Subcorneal pustular dermatosis | 2 | Balanitis | 1 |
| Dermatitis (variants) | 13 | Folliculitis | 1 |
| Purpura | 3 | Pityriasis rosea | 1 |
| Pruritis | 5 | Verruca vulgaris | 1 |
| Hailey-Hailey disease | 1 | Untraceable | 40 |
| Total | | 172 | |

Dermatitis herpetiformis was the most commonly encountered disease, material being examined from a total of 34 patients (Tables 3 and 4). Skin biopsies were shown to contain IgA with or without complement in the dermal papillae, or less commonly along the basement membrane in 23 (67%) patients. Examination

(TABLE 3)

*Dermatitis herpetiformis skin biopsies — Results.*

| *No. of cases* | *Direct immunofluorescence of skin biopsy* |
|---|---|
| 11 | IgA in DP* |
| 7 | IgA + C** in DP |
| 2 | Granular IgA at BM† |
| 3 | Linear IgA at BM |
| 11 | Negative |
| 34 | Total |

*DP — dermal papillae; **C — complement
†BM — basement membrane

(TABLE 4)

*Dermatitis Herpetiformis Serum — Results*

| *No. of cases* | *Indirect immunofluorescent examination* |
|---|---|
| 4 | Anti-reticulin antibody |
| 4 | Anti-gastric parietal cell antibody |
| 1 | Anti-nuclear factor |
| 1 | Anti-intercellular substance antibody |
| 24 | No antibody |
| 34 | Total |

of the serum disclosed a variety of antibodies, including anti-reticulin and anti-gastric parietal cell antibodies.

Speciments were received from 15 patients with bullous pemphigoid (Table 5). In all cases in which immunofluorescent studies were performed on skin biopsies, immunoglobulins and/or complement were found deposited in a linear fashion

(TABLE 5)

*Pemphigoid – Skin Biopsies Results*

| *No. of cases* | *Direct immunofluorescence of skin biopsy* |
|---|---|
| 1 | Linear IgG at BM |
| 6 | Linear IgG + C at BM |
| 1 | Linear IgG ÷ IgM + C at BM |
| 1 | Linear IgM at BM |
| 1 | Linear C at BM |
| 5 | Not performed |
| 15 | Total |

along the basement membrane. The serum in all cases contained an anti-basement membrane antibody of the IgG sub-class.

Oral mucosa and serum were examined from two patients with cicatricial pemphigoid. In each case IgG and complement were demonstrated as a linear deposition along the basement membrane of the mucosa. Antibodies were not detected in their sera.

Pemphigus is an exceedingly rare disease and we were fortunate in being able to study seven cases. Of these, six patients had skin biopsies performed

(TABLE 6)

*Pemphigus – Skin Biopsies Results*

| *No. of cases* | *Direct immunofluorescent of skin biopsy* |
|---|---|
| 3 | IgG in ICR†† |
| 1 | IgA in ICR |
| 1 | IgG + C in ICR |
| 1 | IgG + IgM in ICR |
| 1 | Not examined |
| 7 | Total |

†† ICR – intercellular region

(Table 6). Examination of the serum in all patients revealed an antibody (IgG in six cases, IgA in one) of the pemphigus type.

We investigated specimens from eleven patients with lupus erythematosus (Table 7). Of these, nine were of the discoid type and two of the systemic type. In all cases immunoglobulins and/or complement were detected as a granular

(TABLE 7)

*Lupus Erythematosus – Skin Biopsies Results*

| *No. of cases* | *Direct immunofluorescence of skin biopsy* |
|---|---|
| 2 | Granular IgG ÷ C at BM |
| 1 | Granular IgG + IgA ÷ C at BM |
| 1 | Granular C at BM |
| 2 | Granular IgG ÷ IgM + C at BM |
| 1 | Granular IggG + IgM at BM |
| 3 | Granular IgM at BM |
| 1 | Granular IgM ÷ C at BM |
| 2 | Negative (uninvolved skin) |
| 13 | Total |

deposit at the basement of the membrane region of the skin. Skin biopsies from unaffected skin in the two patients suspected to be suffering from systemic lupus erythematosus were negative.

Skin biopsies from ten patients suspected of suffering from a vasculitis were examined (Table 8). In eight of these immunoglobulins and/or complement were detected outlining the dermal blood vessels.

(TABLE 8)

*Vasculitis – Skin Biopsies Results*

| *No. of cases* | *Direct immunofluorescence of skin biopsy* |
|---|---|
| 1 | IgA + C outlining BV§ |
| 1 | IgA outlining BV |
| 3 | C outlining BV |
| 1 | IgM + C outlining BV |
| 1 | IgG, IgM + C outlining BV |
| 1 | IgG + C outlining BV |
| 2 | Negative |
| 10 | Total |

§BV – blood vessels

Two patients suffered from herpes gestationis. Skin biopsies from both were examined by the direct immunofluorescent technique. In both, IgG and complement were detected as a granular, almost linear deposition along the basement membrane region. Examination of the sera failed to reveal any antibodies.

Immunofluorescent examination of the skin from two patients with lichen planus was performed. Characteristic fluorescent bodies were identified in the papillary dermis on treating the sections with fluoroscein-labelled anti-IgG, anti-IgM and anti-complement.

Significant fluorescent findings were not found in any of the other cases.

## CONCLUSIONS

Our experience over a two year period has confirmed the value of immunofluorescence in diagnostic dermatology. Thus, immunofluorescence may establish a diagnosis in cases where there is a doubt,, and can on occasion be of value in assessing treatment regimes. There are, however, several points which must be emphasised.Firstly, the biopsy must be taken from the correct site (Fig 1), otherwise the possibility of false negative results arise. Secondly, an adequate clinical history with information of current treatment is essential, since an increasing number of drugs are being associated with a variety of auto-antibodies, e.g. pemphigus-type antibodies in patients taking rifampicin (Gange et al., 1976). Thirdly, in patients suspected to be suffering from dermatitis herpetiformis there is, unfortunately, a known (albiet low) tendency for a false negative result. The laboratory, therefore, must examine diligently a large number of sections in order to detect the IgA deposits. On occasion a repeat biopsy will be necessary.

To date we have not, to our knowledge, experienced either false positive or false negative results in either pemphigus or pemphigoid cases.

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# ANNUAL REPORT FOR 1976 OF THE BELFAST POISONS INFORMATION SERVICE

by

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The Casualty Department of the Royal Victoria Hospital has continued to make available information about potential poisons to doctors in Northern Ireland. When the basic information is not sufficient, the enquirers are referred to a panel of experts who do their best to help. The basic information used by the Service is provided by Dr. Goulding, of the Poisons Information Service, New Cross Hospital, London, and is supplemented by information derived from various specialist reference books. However, the work of the service would be simplified if all Casualty Departments and Health Centres carried a short text-book on the treatment of poisoning (such as 'The Treatment of Common Acute Poisonings' by Henry Matthew and A. A. H. Lawson) and two official handbooks in their current editions:

1. Poisonous Chemicals used on Farms and Gardens. Notes for the guidance of medical practitioners issued by the Department of Health and Social Services (DHSS) and revised inserts issued from time to time.
2. Approved Products for Farmers and Growers. Issued every three years by the Department of Agriculture, Fisheries and Food.

A total of 1578 enquiries was made in 1976 which was an increase of 354 on 1975. The total number of enquiries for each year from 1970 to 1976 is shown in Figure 1. With the exception of 1972 there has been a progressive increase in the number of enquiries each year. The increase from 1975 to 1976 was the biggest single increase between consecutive years. A breakdown of the enquiries relating to children and those relating to adults showed that the increase affected both groups (Table 1).

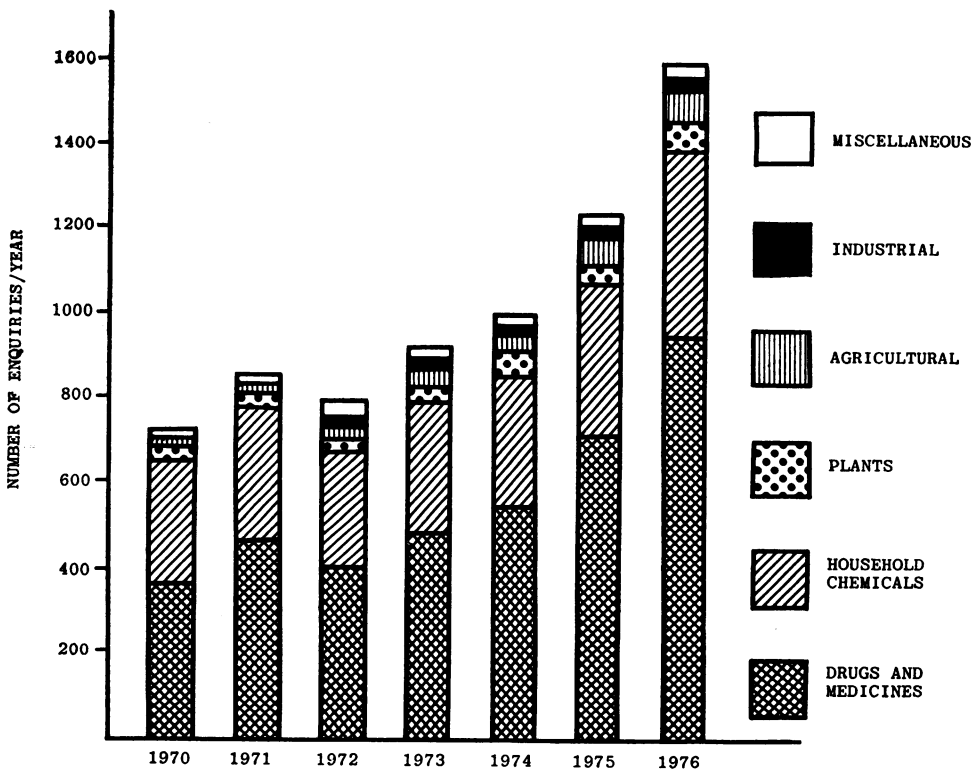
TABLE 1: NUMBER OF ENQUIRIES ABOUT ADULTS AND CHILDREN

(Figures in brackets are percentages for each year)

| | 1976 | 1975 | 1974 | 1973 |
|---|---|---|---|---|
| Children | 923 (58) | 736 (60) | 628 (68) | 579 (63) |
| Adults | 552 (35) | 436 (30) | 271 (27) | 265 (29) |
| Age unknown | 103 ( 7) | 52 ( 4) | 94 ( 9) | 78 ( 8) |
| Total | 1,578 | 1,224 | 993 | 922 |

Division of the enquiries for the years 1970–1976 into five main groups is also shown in Figure 1. In all years drugs and medicines account for the greatest number of enquiries and in 1976 for 939 enquiries (60 per cent in total). There

FIG. 1

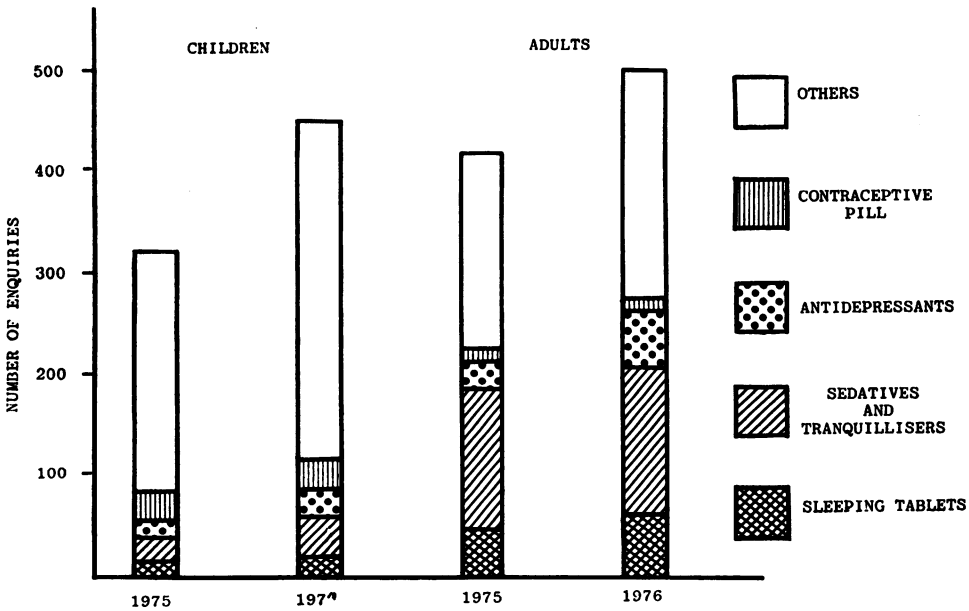



were increases in enquiries about all categories of products – drugs and medicines up by 24 per cent, household substances by 20 per cent, plants by 40 per cent and agricultural products by 15 per cent. The total number of enquiries about the last two groups remained small.

The number of enquiries about drugs and medicines for children and adults in 1975 and 1976 are shown in Figure 2.. The analysis showed an increase in the total number of enquiries in both groups from 1975 to 1976 but this increase was greater in the children group. The enquiries for children relate to a wide variety of drugs and indicate that children will try out indiscriminately any tablet that they find lying around. The four largest single groups of drugs about

which enquiries relating to children have been received are shown (Figure 2). These groups probably reflect the drugs most commonly used by their mothers

FIG. 2




with the exception of tricyclic anti-depressants where out of 28 reported cases, 19 involved poisoning with liquid preparations used in the treatment of enuresis.

All enquiries concerning the taking of drugs have been categorised according to drug group and whether they have been taken by adults or children. The total number of prescriptions issued for each of these drug groups was calculated using the annual drug frequency tables which list all the coded drugs giving the total number of prescriptions and the total number of tablets issued for every drug. The number of prescriptions was then related to the actual number of reported incidents in each group and expressed as number of enquiries per 100,000 prescriptions. Tables 2 and 3 show the drug enquiries for adults per children.

In adults 50 per cent of enquiries were for three groups of drugs – anti-depressants, sedatives and tranquillisers and sleeping tablets (Fibure 2). When these enquiries are related to the number of prescriptions written a value for the number of enquiries per 100,000 prescriptions can be obtained and these results are given in Table 2. These show the much greater frequency with which enquiries are made about drugs having an effect on the central nervous system. It is probably that many, if not most, of these enquiries relate to self-poisoning

TABLE 2: ADULTS AND DRUG ENQUIRIES

| *Drug* | *No. of Enquiries* (per cent in brackets) | | *No. of Enquiries per* 100,000 *scripts* |
|---|---|---|---|
| Barbituates | 45 | ( 9) | 26 |
| Other sleepers | 57 | (11) | 18 |
| Benzodiazepines | 57 | (11) | 10 |
| Other tranquillisers | 60 | (12) | 28 |
| Antidepressants | 57 | (11) | 23 |
| MAOI inhibitors | 3 | (–) | 98 |
| Oral contraceptives | 2 | (–) | 1 |
| Others | 221 | (44) | 2 |
| Total | 502 | (100) | 4 |

TABLE 3: CHILDREN AND DRUG ENQUIRIES

| *Drug* | *No. of Enquiries* (per cent in brackets) | | *No. of Enquiries per* 100,000 *scripts* |
|---|---|---|---|
| Barbituates | 8 | ( 2) | 5 |
| Other sleepers | 10 | 2) | 3 |
| Benzodiazepines | 23 | ( 5) | 4 |
| Other tranquillisers | 20 | ( 4) | 9 |
| Antidepressants | 28 | ( 6) | 11 |
| MAOI inhibitors | – | | – |
| Oral contraceptives | 24 | ( 5) | 17 |
| Others | 236 | (75) | 3 |
| Total | 449 | (100) | 4 |

(Ghodse 1976) but it is most unlikely that these figures indicate the number of self-poisoning cases which occurred in the province in 1976. The use of these groups of drugs for self-poisoning may arise either from a belief that such drugs would be effective or that they have been prescribed for patients with an unstable personality. Further analysis of the enquiries for adults show a male to female ration of 1 to 1.56. In 20 per cent of cases more than one drug was involved.

The reasons for the increase in number of enquiries is not known but the following factors should be considered in any discussion:

(i) the relationship between the actual incidence of poisoning or inappropriate drugs and the number of enquiries to the Poison Information Centre has never been established. Thus the increase in number of

enquiries may result either from an increase in the number of poisonings occurring in the province or from an increase in the number of enquiries with no change in the number of poisonings.

(ii) there was an increase in 1976 in the number of prescriptions dispensed and therefore an increase in the number of drugs consumed.

(iii) the increase in enquiries about poisoning in children, if it reflects an increase in actual poisoning, may indicate greater carelessness with drugs and household chemicals by parents.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# BOOK REVIEWS

MEDICAL ACID-BASE BALANCE – the basic principles. By Michael L. G. Gardner. (Pp. 125, figures 7. £3.95). London: Brailliere Tindall. 1978.

THIS little book is an honest attempt by an experienced clinical biochemist to explain the principles of acid-base balance to medical students, and to postgraduates who must needs refresh their memory. There are few clinicians whose field of practice covers all aspects of the possible acid-base disturbances – most of us adapt to our sector of knowledge and focus on a few useful landmarks. I found the book relatively unhelpful in revealing the foundations of those particular landmarks visible to me but it was helpful in coming back to first principles for the whole subject. It is a pity that more direct clinical practice is not included, such as a house physician's practical guide towards correction of acid-base imbalance. Diabetic ketoacidosis, the major metabolic acidosis with considerable respiratory and renal components, is not mentioned at all in the index and I could find the words only once in the text. On the other hand I learnt a lot about the difficulties of measuring plasma bicarbonate.

The chief value of the book, to either an informed medical student or an interested postgraduate will be in the discussions in the appendices of the several recent techniques for determination of pH, $pCO_2$ and $pO_2$. The several complex monograms and other aids to calculation are handled from an unbiased viewpoint. These sections are practical and informative, and helpful to the clinician in his contact with laboratory staff. The mathematical theoretician will like the numerous formulae and the logical structure of the book : I would prefer preclinical medical students to learn this subject from a more practical standpoint, but for a source to consult with regard to basic principles this book is more useful than the average pre-clinical textbook.

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IT used to be that people interested in cellular aspects of immunology thought only of lymphocytes - the other cells were just there for fun. The macrophage was then considered to be worthy of serious attention with the result that it has enjoyed a dramatic rise in status. The eosinophil is now getting the same treatment with, it is to be hoped, the same result.

The literature on the eosinophil is vast. In the preface to this book the authors refer to a review published in 1914 which cited almost 3,000 references. That this and much subsequent work has contributed so little to our understanding of the eosinophil is largely due to the fact that techniques available to study haematogenous cells were inappropriate to the fundamental problems of their origins and functions. The best way to study cell function is to use methods which measure functions - methods which study structure and distribution of highly mobile cell populations in histological 'stills' cannot by their very nature get into these problems in any depth. Since the 1960's many such methods have been developed and much of the rapid expansion of knowledge in immunology and haematology has been due to their application. The authors of this book have been chosen to emphasize these aspects of their subject.

The chief virtues of the book are its brevity and its honesty. The authors do not attempt to cover up ignorance with either a smoke-screen of speculation or an ill-digested catalogue of observations. The book is set out in five sections dealing with structure and behaviour, changes in numbers, participation in phenomena of immunity, hormonal influences, and clinical observations. The chapters are concise and well referenced (not just to the most recent literature) and they highlight not only areas of progress but also areas of ignorance.

The book is printed clearly, the subject matter well set out and it has an adequate index. The black-and-white photographs are not brilliantly clear but suffice for their purpose. It is probably not a book that many individual doctors would wish to purchase but as a point of reference it should be useful to those in both laboratory and clinical medicine whose problems occasionally bring them face-to-face with the eosinophil.

*T.A.McN.*

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IT cannot be claimed that the widespread use of abbreviations has facilitated easy reading of either papers or case notes and often they cause both annoyance and misunderstanding. Most should only have a limited use within a speciality and the meaning of many is totally different in another speciality. This book lists more than thirteen thousand abbreviations and well illustrates this diversity of meaning. The abbreviation M is given 36 different meanings. However, we must live with abbreviations, though it is to be hoped that many listed here will forever escape our notice.

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J.E.M.

## USE AND INTERPRETATION OF RENAL BIOPSY. By G. E. Striker, L. J. Quadracci and R. E. Cutler. (Pp xiii+347; illustrated. £17.50). Philadelphia, London and Toronto: Saunders and Eastbourne: Holt-Saunders, 1978.

THIS book is the eighth in a series of monographs on major problems in pathology. It reviews the subject of renal biopsy as it concerns clinicians and pathologists. It has an interesting content of historical material as background. There is a section on the clinical evaluation of patients with renal disease which would be of relevance to those studying for MRCP examinations. The book is generously illustrated throughout its 26 chapters with line diagrams and photographs of light, immunofluorescence and electron microscopy. A moderate list of references is given at the end of each chapter though there is no direct referrel to these in the text.

Diseases of renal glomeruli, tubules, interstitium and vessels are analysed. The authors make a deliberate effort to avoid any controversial points of classification of glomerular disease, sticking to purely descriptive tersm. The omission of acute bacterial pyelonephritis from the text is unusual when other tubulo-interstitial diseases are considered in detail. Nine well-illustrated chapters deal with renal diseases associated with systemic syndromes and these would be useful for reference purposes. The final section, on renal transplantation, has seven references all dealing with recurrent glomerulonephritis. This amplifies the importance of a relatively rare occurence and unfortunately does not refer the reader to some of the interesting literature on the nature and diagnosis of transplant rejection.

Whilst this book ocntains much valuable material its price of £17.50 may restrict its appeal particularly since several other excellent textbooks of renal disease exist.

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The ophthalmic manifestations of diabetes, thyroid disease, hypertension, rheumatic disorders, and certain genetic abnormalities are briefly and clearly described with a current explanation of their physical signs and a review of their pertinent therapeutic modalities.

Ophthlamic aspects of some central nervous system abnormalities are presented with special reference to papilloedema and disorders of ocular motility, and a small section is devoted to the electrophysiological evaluation of visual functions. A valuable account of the ocular side effects of systematically administered drugs is given and some useful pointers are provided for the evaluation of the optic disc in glaucoma.

Most of the chapters are very brief with few illustrations, and much detail is omitted in a text of this size. A few inaccuracies and occasional syntactical errors are present, but on the whole this volume makes easy reading, is full of useful clinical points and up-to-date ophthalmological information, and should be helpful reading for the physician, general practitioner, medical student and junior trainee ophthalmologist.

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I particularly like the section on infectious diseases and immunological disorders. As one would expect of a North American text book it is by far the largest section, due largely, I believe, to the vast clinical load of very ill infectious disease patients typically found in an American hospital and which, for some reason, is infrequently found in the British scene. The next ihapter is a splendid one on immunological disorders and has a fine bibliography.

The chapter on pulmonary hypertension and oedema is well written but the section on the adult respiratory distress syndrome is superb and leaves no one in any doubt about the importance of this relatively recently described condition and the contribution that pulmonary physiology has made to understanding its patho-physiology. What can one say about radiology? Outside of specialist text books on this subject I have never seen such a collection of magnificent X-rays.

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The author in the first chapter discusses the normal anatomy, and there follows a comprehensive review of the radiological techniques developed in the investigation of the liver. It perhaps reflects Dr. McNulty's extensive experience with traditional procedures that the techniques of percutaneous transhepatic cholangiography, selective arteriography and the various venographic procedures are comprehensively reviewed, including such highly specialised techniques as percutaneous transhepatic portal vein phlebography.

The techniques of isotope and gray-scale ultra sound scanning and computed tomography are reviewed to a limited extent. Due to the rapid progress in these techniques it is inevitable that any monograph will be overtaken by events. In discussion of the various disease entities undue emphasis is placed on invasive techniques, for example, in the investigation of mass lesions of the liver, and gall bladder enlargement, the angiographic changes are described in detail, while C.T. and ultra sound are superficially covered.

The disease processse are clearly set out with chapters on congenital, traumatic, inflammatory, vascular, and neoplastic disorders, and this leads to repetition but is useful for reference purposes. The bibliography is comprehensive and the reproduction of the radiograph is of a high standard.
Dr. McNulty, a graduate of Queen's University, is a recognised authority on the radiography of liver disease. This book is an excellent source of reference, not only to the radiologist, but to any specialist with an interest in liver disease.

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The development and structure and the physiology of the organ are briefly dealt with in single chapters. There is merit in not confusing the pathologist by considerations of the widely varied anatomy of the placenta in different animals, but today, when many are far too quick to extrapolate obscrvations made in animals to man, some warning of these really enormous differences might still be useful in a book which will become a definitive and authoritative text.

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There are no less than 333 ilusttrations in this remarkably comprehensive atlas. The majority illustrate a wide spectrum of the echocardiographic abnormalities encountered in clinical practice. Seventy tracings illustrating echocardiographic abnormalities of the mitral valve are included. Notworthy among these is the series illustrating mitral valve prolapse. Another 53 photographs give a comprehensive overview of the usefulness of echocardiography in abnormalities of the left ventricle, and especially in the diagnosis of the cardiomyopathies. The chapter on pericardial disease is very helpful regarding effusions but not regarding constrictive pericarditis.

The final chapter correlates echocardiographic, phonocardiographic and other graphic representations of cardiac activity. It illustrates the insight which echocardiography has given into the genesis of heart sounds and murmurs, and emphasizes the value of routinely recording the phonocardiogram during echocardiography.

This atlas does not push back the frontiers of knowledge relating to its subject, but it does usefully bring together in one compact volume a large collection of superb examples of the echocardiographer's art. It should certainly be bought by every cardiologist who has anything to do with echocardiograms. Most cardiac units will want to have one copy beside their recording apparatus and another at the elbow of the cardiologist reporting on the tracings.

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## MULTIPLE CHOICE QUESTIONS IN HUMAN PHYSIOLOGY. By I. C. Roddie and W. F. M. Wallace. Second Edition. (Pp. x+349. £5.00) London Lloyd-Luke. 1977.

THE value of this book, not only for undergraduate students of medicinie but for those preparing for the basic science part of fellowship and other higher examinations, was emphasised in a review seven years ago. Questions and answers in both basic and applied physiology are included and an increasingly wide field is covered. Students who have tested their knowledge by study of this book should be both informed and given confidence. Perhaps regular study of a few pages a day would stimulate their seniors to orientate to the changes in knowledge in the basic sciences and stimulate further reading.

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M.E.S.

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THE value of this book, not only for undergraduate students of medicinie but for those preparing for the basic science part of fellowship and other higher examinations, was emphasised in a review seven years ago. Questions and answers in both basic and applied physiology are included and an increasingly wide field is covered. Students who have tested their knowledge by study of this book should be both informed and given confidence. Perhaps regular study of a few pages a day would stimulate their seniors to orientate to the changes in knowledge in the basic sciences and stimulate further reading.

## VIRAL DISEASES OF THE FETUS AND NEWBORN. By J. B. Hanshaw and J. A. Dudgeon (Pp. xvi+356, Illustrated. £14.00) Philadelphia, London and Toronto. Saunders and Eastbourne. Holt-Saunders. 1978.

THIS is volume XVII in the excellent series "Major Problems in Clinical Pediatrics" and the problems of viral infections in the fetus and newborn are indeed becoming evident as major ones causing both fetal and neonatal death and morbidity with symptoms, such as nerve deafness, which may only become apparent years later.

Both authors are eminent workers in microbiology and both are also active in clinical practice and have contributed extensively from both the laboratory and the bedside. The more extensive chapters are those dealing with rubella by Professor Dudgeon from London, who explores all aspects including mass immunization and the late handicaps which are often insufficiently appreciated, and the chapter on congenital cytomegalovirus where many extensive studies are integrated by Dr. Hanshaw who has himself contributed so much to this. Other chapters deal with the growing problem, especially in America, of herpes simplex, and with infections by the enteroviruses, and with varicella-zoster, smallpox and vaccinia, hepatitis and other agents. Valuable chapters on the pathology of the placenta and on the development of immune mechanisms are contributed by W. A. Blanc and by W. C. Marshall.

This is a completely authoritative work very fully documented and, even if only some are prepared to read it in detail, all should use it to make themselves aware of the growing importance of such infections in practice.

J.E.M.

## CLINICAL MANAGEMENT OF HEAD, NECK AND TMJ PAIN AND DYSFUNCTION. A Multi-Disciplinary Approach to Diagnosis and Treatment. Edited by Harold Gelb, D.M.D. (Pp xviii+547; illustrated. £29.75). Philadelphia, London and Toronto: Saunders and Eastbourne: Holt-Saunders.

THE appearance of this new book on the subject of Head, Neck and TMJ Dysfunction represents a welcome and overdue accumulation of information on a topic which has long troubled the medical and dental profession.

The book, which contains contributions from 19 authors, is systematically laid out and quite beautifully illustrated. Although extremely lengthy, particularly in respect of some of the treatments prescribed for various conditions, the book maintains a high and even standard of writing throughout the chapters. It is unfortunate that so few of the references listed after each chapter are of European or British origin.

In his foreword Professor Harold Gelb states: "We have attempted to overcome certain shortcomings of the traditional health care orientation by crossing specialty and professional boundaries" - in this respect he has achieved a fair measure of success for the multidisciplinary approach covers many aspects of diagnosis and treatment planning.

It is unlikely that this book will be bought by many British doctors or dentists, but as an excellent attempt to cover an extremely difficult subject it deserves a place in most medical libraries.

J.G.McG.

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J.G.McG.

## PRINCIPLES OF FAMILY MEDICINE. By Robert E. Rakel (Pp. viii+536. £12.00) Philadelphia, London and Toronto: W. & B. Saunders, 1977.

A SPATE of textbooks on general practice have recently appeared and have outlined the content and the role of the general practitioner. The terms 'general practitioner' and 'family doctor' are used synonymously, yet this book undoubtedly suggests that the study of family structure and dynamics, and the impact of illness upon the family, adds a new dimension to general practice and justifies the decision in America to change the name of the academic discipline. The socio-behavioural influences of family life on illness are less emphasised in undergraduate education in most British medical schools. These chapters should be useful to all involved in teaching and to students at all levels of education, and to practising clinicians. The book is well written, comprehensive and easy to assimilate. The author quotes widely from World literature on various academic and organisational aspects of primary care and the principles should be applicable in gencral practice in all the developed countries.

The book acclaims general practice/family medicine as a specialty in its own right. The author integrates elementary principles very skillfully, whilst the varying emphasis on internal medicine and socio-behavioural aspects of care in different countries, is revealed. In America there is still confusion of role between family practitioners, general internists and paediatricians.

The trend in America towards a system of comprehensive primary care is evident with the provision of continuing care to individuals and their families through G.P.s working with other health professionals in a team. Time however has to be made available to practice sound preventive and anticipatory medicine. The book describes the expansion of nurse practitioners and physicians' assistants in America. This development appears to conflict with a G.P.'s claim to handle all undifferentiated illness. Nurse management protocols call for physician involvement only when serious problems exist. These tend to be biased towards internal medicine. However, the chapter on the primary care team provides an authoritative reference for all students and for general practitioners who wish to reflect on ways and means of controlling their excessive work load.

The book deals effectively with preventive clinical medicine and injects a sense of realism into a neglected area of medicine. The value of screening proceedures is discussed and yearly check-ups and practical measures are defined to deal with selected clinical problems at selected intervals.

Communication and interpersonal relationships between doctor and patient are discussed effectively and with great understanding; also, up-to-date concepts on the development of efficient record systems with a problem orientated format and applicable anywhere in general practice. The pro formas on family charting and profiles show how far the American centres of excellence are ahead in these fields due to their greater economic resources. These final chapters highlight the major deficiencies of record keeping in the National Health Service in Britain. The author portrays the need to make available to each general practitioner easily retrievable data about the significant features of each patient and his family unit.

This is an excellant book which should be compulsory reading for all senior undergraduates and for all doctors who are undergoing vocational training for general practice. It should be available in all medical libraries as a reference source for all practising clinicians. The author is to be congratulated on a fine achievement. It is a hard-cover book of some 536 pages and is good value for money.

*W.G.I.*

## GYNAECOLOGICAL AND OBSTETRIC UROLOGY. By H. J. Buchshaum and J. D. Schmidt. (Pp. 461 illustrated. £24) Philadelphia, London and Toronto: W. B. Saunders, 1978.

IN their introduction to this new book, the contributing editors, former colleagues at the University of Iowa where the urology and gynaecology operating theatres were adjacent and shared a common scrub up, remind their readers that from a close association in embryonic life the two systems maintain a close relationship thereafter. Nevertheless the specialist training in these disciplines on both sides of the Atlantic frequently does not take adequate notice of how diseases of one system may affect the other.

In an attempt to remedy this defect the editors have gathered together a host of contributors (twenty-nine, several of whom are international authorities) from both specialities with the obstetrician/gynaecologists outnumbering urologists by a factor of two. They were faced at the outset with a problem that does not occur in a standard single author textbook when the subject is tackled from start to finish. Significant developments, and there have been many in the past two decades, have to be selected and a rehash of texts published elsewhere has to be avoided. The choice existed between providing superficial coverage of many topics or extensive information on a few. In this they have in the main been successful, although there is some overlap and repitition particularly in the section on urinary incontinence where methods of patient assesment are repeated in several chapters as well as being discussd in the opening section in the chapter on the urological examination. Nevertheless, this repitition does not detract from the quality of the presentation.

The first section deals with the anatomy, physiology and examination of the female genitourinary tract, and the chapter by Lapides and Diokon on the physiology of micturition not only describes this clearly, but also details the evaluation of bladder function in a simple and logical manner.

The section on urinary incontinence has a particularly important contribution in this common and troublesome disorder. His rational approach to classification and treatment is borne out in the results of his personal series where a cure rate of 96 per cent was achieved in a group of 341 patients followed up for from 5 to 18 years.

In the section on the genitourinary tract in pregnancy there are two good review type chapters, one by Robertson on the alterations in renal function during pregnancy and the renal changes in toxaemia and the other an excellent summary of present thoughts on asymptomatic bacteria by Cunningham and Whalley. To bring the section right up to date there is a stimulating chapter on the gynaecological and obstetric problems which occured in 75 renal allograph receipients.

The standard of illustration is high throughout with many excellent and clear line drawings and radiographs.

In conclusion, this is a book which covers the subject thoroughly though the style is uneven and there is repetition. Its cost will discourage many, but it will be a valuable book of reference in departmental and postgraduate centre libraries where it will perhaps be appreciated more by those at the "sharp end" than those who are entering the speciality.

*G.A.M.*